

# EAU Guidelines on Renal Cell Carcinoma

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# 1. INTRODUCTION

## 1.1 Aims and scope

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

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

## 1.2 Panel composition

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

## 1.3 Acknowledgement

The RCC Guidelines Panel is most grateful for the long-standing methodological and scientific support provided by Prof.Dr. O. Hes (pathologist, Pilzen, Czech Republic) for two sections of this document: Histological diagnosis and Other renal tumours [1]\*.

## 1.4 Available publications

A quick reference document (Pocket Guidelines) is available presenting the main findings of the RCC Guidelines. This is an abridged version which may require consultation together with the full text version. All documents can be accessed on the EAU website: <http://uroweb.org/guideline/renal-cell-carcinoma/>.

## 1.5 Publication history and summary of changes

### 1.5.1 Publication history

The EAU RCC Guidelines were first published in 2000. This 2023 RCC Guidelines document presents a substantial update of the 2022 publication.

### 1.5.2 Summary of changes

All chapters of the 2023 RCC Guidelines have been updated, based on the 2022 version of the Guidelines. References have been added throughout the document.

New data have been included in the following sections, resulting in updates and changes in evidence summaries and recommendations:

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

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

Recommendation	Strength rating
Do not routinely screen any population for primary RCC.	Weak

#### 3.6 Summary of evidence and recommendations for the management of other renal tumours

Summary of evidence	LE
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
Recent histological work up and results of active surveillance of Bosniak III cysts shows low risk of malignant potential/course.	2

\* †Deceased, July 2022.

Recommendations	Strength rating
Offer AS to patients with biopsy-proven oncocytoma or other oncocytic renal tumours as an acceptable alternative to surgery or ablation.	Weak
Offer systemic therapy (everolimus) to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak

7.2.4.1 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

Recommendation	Strength rating
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

7.2.5.5 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	LE
Adjuvant pembrolizumab defined by the inclusion criteria of the trial* after nephrectomy improves DFS.	1b
Adjuvant PD-L1 inhibition with atezolizumab 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
The lack of biomarker data is hindering progress in this field. Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	4

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

Recommendation	Strength rating
Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.	Strong
Inform patients about the potential risk of overtreatment and immune-related side effects if adjuvant therapy is considered.	Strong
Offer adjuvant pembrolizumab to ccRCC patients, preferably within 12–16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial: <ul style="list-style-type: none"> <li>• Intermediate-high risk: <ul style="list-style-type: none"> <li>• pT2, grade 4 or sarcomatoid, N0, M0</li> <li>• pT3, any grade, N0, M0</li> </ul> </li> <li>• High risk: <ul style="list-style-type: none"> <li>• pT4, any grade, N0, M0</li> <li>• any pT, any grade, N+, M0</li> </ul> </li> <li>• M1 no evidence of disease (NED): <ul style="list-style-type: none"> <li>• NED after resection of oligometastatic sites <math>\leq</math> 1 year from nephrectomy</li> </ul> </li> </ul>	Weak

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

Summary of evidence	LE
Patients with MSKCC or IMDC poor risk do not benefit from CN.	1a

Recommendation	Strength rating
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak

#### 7.4.4.1.2 Summary of evidence and recommendations for immunotherapy in cc-mRCC

Summary of evidence	LE
<i>Sequencing systemic therapy</i>	
Nivolumab plus ipilimumab was associated with 46% grade 3–4 toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade 3–5 toxicity ranging between 61–72% and 1% of treatment-related deaths.	1b

Recommendations	Strength rating
<i>Treatment-naïve patients</i>	
Offer treatment with PD1 combinations in centres with experience.	Weak
Offer either nivolumab plus ipilimumab, pembrolizumab plus axitinib, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naïve patients with IMDC intermediate- or poor-risk disease.	Strong
Offer either pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to treatment-naïve patients with IMDC favourable risk.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable risk.	Weak
Offer sunitinib or pazopanib to treatment-naïve cc-mRCC patients with any IMDC risk 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.	Weak
<i>Sequencing systemic therapy</i>	
Sequence systemic therapy in treating mRCC.	Strong
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
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer nivolumab or cabozantinib to those patients who received first-line VEGF targeted therapy alone.	Strong

#### 7.4.4.2.1 Summary of evidence and recommendation for targeted therapy in non-clear-cell metastatic 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

#### 7.4.4.3.1 Summary of evidence and recommendations for targeted therapy in papillary metastatic RCC

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

## 2. METHODS

### 2.1 Data identification

For the 2023 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive scoping search was performed, which was limited to studies representing high certainty of evidence (i.e., systematic reviews with or without meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only for therapeutic interventions, and systematic reviews and prospective studies with well-defined reference



standards for diagnostic accuracy studies) published in the English language. In case no higher level data exists for a particular topic, lower level evidence was considered for inclusion. The search was restricted to articles published between May 28<sup>th</sup>, 2021 and May 24<sup>th</sup>, 2022. Databases covered included Medline, EMBASE, and the Cochrane Library. After de-duplication, a total of 1,810 unique records were identified, retrieved and screened for relevance.

A total of 59 new references have been included in the 2023 RCC Guidelines publication. A search strategy is published online: <https://uroweb.org/guidelines/renal-cell-carcinoma/publications-appendices>.

For each recommendation within the guidelines there is an accompanying online strength rating form which includes the assessment of the benefit to harms ratio and patients' preferences for each recommendation. The strength rating forms draws on the guiding principles of the GRADE methodology but do not purport to be GRADE [2, 3]. Each strength rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation; references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation.

The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Specific chapters were updated by way of systematic reviews, commissioned and undertaken by the Panel, based on prioritised topics or questions. These reviews were performed using standard Cochrane systematic review methodology: <https://www.cochranelibrary.com/about/about-cochrane-reviews>.

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

## **2.2 Review**

All publications ensuing from systematic reviews have been peer reviewed. The 2021 print of the RCC Guidelines was peer-reviewed prior to publication.

## **2.3 Future goals**

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.

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

- What is the best treatment option for  $\geq$  T2 tumours?
- Adjuvant targeted therapy for RCC at high risk for recurrence;
- Systematic review of prevalence of intraperitoneal recurrences following robotic/laparoscopic partial nephrectomy;

- Systematic review of individual, unit and hospital surgical volume for radical and partial nephrectomy and their impact on outcomes;
- RECUR database analysis of recurrent disease/follow-up.

## 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

### 3.1 Epidemiology

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [6, 7]. In 2020, there were an estimated 431,288 new cases of RCC globally, of which 138,611 in Europe [8]. The higher incidence in Europe and North America is hypothesized to be due to a higher prevalence of small renal masses (SRMs) in settings where abdominal imaging is more ubiquitous. In 2020, Lithuania reported the highest overall rate of RCC, followed by Czechia, with estimated age-standardised rates (ASRs) of 14.5/100,000 and 14.42/100,000, respectively. A person living in Czechia has a 2.83% risk of developing RCC [7, 8]. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe. In 2022, worldwide mortality from RCC was 179,368 deaths (115,600 men and 63,768 women), with a calculated global ASR rate of 1.8/100,000 [8].

In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilising or declining thereafter [9]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [6, 7].

Renal cell carcinoma is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics [10]. There is a 1.5–2.0:1 predominance in men over women with a higher incidence in the older population [7, 8, 11].

### 3.2 Aetiology

Established risk factors include lifestyle factors such as smoking (hazard ratio [HR]: 1.23–1.58), obesity (HR: 1.71), BMI (> 35 vs. < 25), and hypertension (HR: 1.70) [7, 8, 11, 12]. 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 carcinoma (chRCC) to 61.9% in those with collecting duct/medullary carcinoma [13]. In a recent systematic review diabetes was also found to be detrimental [14]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. 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 [7, 8, 14–18]. A number of other factors have been suggested to be associated with higher or lower risk of RCC, including specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [11]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [7, 8, 11, 12]. Genetic risk factors are known to play a role in the development of RCC (see Section 3.5.6 - Hereditary kidney tumours).

### 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. 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 [19–21]. Targeting of high-risk patient groups e.g., those with end-stage renal disease (ESRD) which is associated with a 10-fold increased risk of developing RCC may also be a valid approach (see Section 3.5.2) [22]. There is currently no evidence to support primary screening in the general population. However, the panel recommends genetic screening in subgroups of patients with a family history (see Section 5.5).

### 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 any population 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 5<sup>th</sup> edition of the World Health Organization (WHO) classification of urogenital tumours published in 2022 [23, 24]. The 5<sup>th</sup> edition presents standard morphologic diagnostic criteria, combined with immunohistochemistry and relevant molecular tests was significantly revised as compared to the 2016 classification [10]. 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, *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 [10, 25] (LE: 2b). The 5-year OS for non-metastatic (including N1) chromophobe, papillary, clear-cell and collecting duct RCC is 91%, 82%, 81% and 44%, respectively [26]. 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. Multilocular cystic renal neoplasm of low malignant potential is a new subtype of cRCC 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 [23, 27].

Histological diagnosis includes, besides RCC type; evaluation of 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 [10, 23].

**Table 3.1 World Health Organization classification of renal tumours 2022** [23, 24]

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
	<i>TFE3</i> -rearranged RCCs
	<i>TFEB</i> -altered RCC ( <i>TFEB</i> -rearranged RCC and <i>TFEB</i> amplified RCC)
	<i>ELOC</i> (formerly <i>TCEB1</i> )-mutated RCC
	Fumarate hydratase-deficient RCC
	Succinate dehydrogenase-deficient RCC
	<i>ALK</i> -rearranged RCCs
	<i>SMARCB1</i> -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
	Epithelioid 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
	Congenital mesoblastic nephroma
	Rhabdoid tumour of kidney
	Clear cell sarcoma of kidney
5. Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Paediatric cystic nephroma
	Cystic partially differentiated nephroblastoma
	Nephroblastoma
6. Miscellaneous tumours	
Germ cell tumours of the kidney	

### 3.4.1 Clear-cell RCC

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found. The loss of von Hippel-Lindau protein function contributes to tumour initiation, progression, and metastases. The 3p locus harbours additional ccRCC tumour suppressor genes (*UTX*, *JARID1C*, *SETD2*, *PBRM1*, *BAP1*) [23]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC, but this difference disappears after adjustment for stage and grade [28, 29]. 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 tumor devoid of any expansile solid growth, with clear cells lining with 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 [23, 24]. Nephron-sparing surgery (NSS) is sufficient, if technically feasible [30].

### 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 [23, 24]. Papillary RCC has traditionally been subdivided into two types; Type I and II pRCC [10]. 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 “oncocyctic 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, formally 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 (12.5%), probably due to the fragility of the tumour papillae [31].

### 3.4.3 **Chromophobe RCC**

Chromophobe RCC is now grouped in “oncocyctic and chromophobe tumours”. Most chrRCCs are discovered incidentally in asymptomatic patients [23, 24]. Overall, chrRCC 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 PTEN (see Section 3.5.6 for further information) [23, 24]. 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 [23, 24]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [23, 24]. The prognosis is relatively good, with high 5-year recurrence-free survival (RFS), and 10-year CSS [32]. The five- and 10-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 chrRCC is rare. For completely excised lesions < pT2a without coagulative necrosis or sarcomatoid features, the prognosis is excellent [33].

## 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 is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

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

Renal medullary carcinoma (RMC) (referred to as *SMARCB1*-deficient renal medullary carcinoma in the 2022 WHO Classification) is a very rare tumour, comprising < 0.5% of all RCCs [34], 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. It is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [35, 36] and most patients (~67%) will present with metastatic disease [35, 37]. 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” [23].

### 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 [27, 38]. 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 [23].

### 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 [23].

### 3.5.4 **Renal oncocytoma**

Oncocytoma is a benign tumour representing 3–7% of all solid renal tumours and its incidence increases to 18% when tumours < 4 cm are considered [10, 39]. The diagnostic accuracy of imaging modalities (CT, magnetic resonance imaging [MRI]) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [10, 39]. However, the new imaging technology <sup>99m</sup>Tc-sestamibi (SestaMIBI, MIBI) SPECT/CT has shown promising initial results for the differentiation between benign and low-grade RCC [40]. 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) [23, 24], other RCCs (12.5%), and other benign lesions (4.2%) [41]. 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 < 14 mm [42–44]. Preliminary data show that active surveillance (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 [45, 46].

### 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 3.5.6), 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) [23].

### 3.5.6 **Hereditary kidney tumours**

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (age 46 years or younger) of all RCC tumours [47]. Hereditary kidney tumours are found in the following entities: VHL syndrome; hereditary pRCC; Birt–Hogg–Dubé syndrome; Fumarate hydratase-deficient RCC (FHD-RCC), previously called hereditary leiomyomatosis and RCC (HLRCC); tuberous sclerosis; germline succinate dehydrogenase (SDH) mutation; non-polyposis colorectal cancer syndrome; hyperparathyroidism–jaw tumour syndrome; phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS); constitutional chromosome 3 translocation; familial non-syndromic ccRCC and BAP1-associated RCC [48]. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [49–52].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [53, 54]. In most hereditary RCCs nephron-sparing approaches are recommended. The exceptions are FHD-RCC and 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 [55, 56]. Active surveillance for VHL,



SDH and FHD-RCC 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 [56]. Multidisciplinary and co-ordinated care should be offered, where appropriate [57]. In FHD-RCC, renal screening in relatives has shown benefit in detecting early-stage RCCs [58], with HLRCC RCCs appearing to have unique molecular profiles.

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 [59].

A recent phase II trial demonstrated clinical activity of an oral HIF-2 $\alpha$  (hypoxia-inducible factor) inhibitor MK-6482 (belzutifan) in VHL patients [60]. Additional information on treatment of VHL can be found in Section 7.4.4.5.1.

### 3.5.7 **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 [61]. 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 [62]. 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 [10, 49, 63]. 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 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 [49, 63]. Epithelioid AMLs are potentially malignant with a variable proportion of cases with aggressive behaviour [64]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2022 [23, 24]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [65]. Subtypes of AML are oncocytic AML and AML with epithelial cysts [23].

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

#### 3.5.7.1 *Treatment of angiomyolipoma*

Active surveillance is the most appropriate option for most AMLs (48%). In a group of patients on AS, only 11% of AMLs showed growth, and spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [65, 66] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4-cm cut-off should not per se trigger active treatment [65]. 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 [65].

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

In patients diagnosed with tuberous sclerosis, size reduction of often bilateral AMLs can be induced by inhibiting the mTOR pathway using everolimus, as demonstrated in RCTs [67, 68]. 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 [69].

**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 <i>SMARCB1</i> 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 [23, 24, 29].	High, very aggressive. Median survival 30 months [70].	Surgery. Response to targeted therapies is poor [71].
Clear-cell papillary renal cell tumour	Patient with ACKD, 100 times greater risk compared with general population [24].	Indolent	Surgery, NSS, discuss active surveillance.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle. < 1% of renal neoplasm. Female predilection (3–4:1) [24].	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.
<i>TFE3</i> re-arranged RCC	Gene fusions involving <i>TFE3</i> 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.
<i>TFEB</i> re-arranged RCC	Gene fusions involving the <i>TFEB</i> transcription factor, typically via a t(6;11)(p21;q12) translocation resulting in a <i>MALAT1-TFEB</i> gene fusion. Formerly translocation RCC t(6;11). Less common than <i>TFE3</i> -re-arranged RCC. Appr. 100 cases in the literature [24].	More indolent than the <i>TFE3</i> -rearranged RCC, with fewer than 10% of cases resulting in patient death.	Surgery. Systemic therapy in metastatic disease.
<i>ELOC</i> (formerly <i>TCBE1</i> )-mutated RCC	Twenty cases described in literature. Typically T1.	Indolent. Only 2 metastatic cases described.	NSS.
Fumarate hydratase-deficient RCC	Formerly hereditary leiomyomatosis and RCC-associated RCC. Alterations in the <i>FH</i> gene. Autosomal dominant. 21–30% lifetime risk of RCC [58]. Cutaneous leiomyomas, female uterine leiomyoma or leiomyosarcoma. More common in males. Median age 44 years [23, 27, 72].	Often aggressive.	Immediate surgery. No data about treatment of metastatic disease. Genetic counselling in the family. Imaging screening in relatives [58].



Succinate dehydrogenase-deficient RCC (SDH-deficient RCC)	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 ( <i>ALK</i> ) at chromosome 2 <i>p</i> 23. Appr. 40 cases described.	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 lesions - mixed epithelial and stromal tumour 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.

### 3.5.8 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 [73]. Bosniak IV cysts are mostly (83%) malignant tumours with pseudo-cystic changes only [74]. 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%;  $\kappa$  [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity ( $\kappa$  = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS ( $\kappa$  = 0.95) [75]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44–0.58) in Bosniak III and 0.89 (0.83–0.92) in Bosniak IV cysts, respectively. In a systematic review, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% of these showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [73]. The updated Bosniak classification strengthens the classification and includes also MRI [76] and even CEUS diagnostic criteria [77].

The most common histological types for Bosniak III cysts is ccRCC with pseudo-cystic changes and low malignant potential [78, 79]; multilocular cystic renal neoplasm of low malignant potential [MCRNLMP], 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 [73, 76, 80, 81].

### 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.	1b
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
Recent 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: <ul style="list-style-type: none"> <li>• large tumours (a recommended threshold of intervention does not exist);</li> <li>• females of childbearing age;</li> <li>• patients in whom follow-up or access to emergency care may be inadequate;</li> <li>• persistent pain or acute or repeated bleeding episodes.</li> </ul>	Weak
Offer systemic therapy (everolimus) to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation.	Weak

## 4. STAGING AND CLASSIFICATION SYSTEMS

### 4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [82]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single- and multi-institution studies [83, 84]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer;
- The value of size stratification of T2 tumours has been questioned [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 [84];
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [90, 91] (LE: 4).

The TNM classification should not be considered the only criterion for clinical decision-making, but a patient's condition, comorbidities and wishes are of fundamental importance to select the most optimal treatment. A new RCC EAU staging classification was proposed in 2022 [92].

**Table 4.1: 2017 TNM classification system [82]**

<b>T - Primary tumour</b>			
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)		
<b>N - Regional Lymph Nodes</b>			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
<b>M - Distant metastasis</b>			
M0	No distant metastasis		
M1	Distant metastasis		
<b>pTNM stage grouping</b>			
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), 8<sup>th</sup> Edn. 2017 [93].

## 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 [94-96]. These systems include assessment of tumour size, exophytic/endophytic properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole location.

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

# 5. DIAGNOSTIC EVALUATION

## 5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. The majority of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [97] (LE: 3). In a recent prospective observational cohort study, 60% of patients overall, 87% of

patients with stage Ia renal tumours and 36% of patients with stage III or IV disease presented incidentally [98]. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6–10%) and correlates with aggressive histology, advanced disease, and poorer outcomes [98-100] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [101] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [102] (LE: 3).

### 5.1.1 **Physical examination**

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

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

### 5.1.2 **Laboratory findings**

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium [103], 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 [104, 105] (LE: 2b):

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

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

## 5.2 **Imaging investigations**

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [97] (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 [106] (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 [107] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [108-111] (LE: 3). Abdominal CT provides information on [112]:

- function and morphology of the contralateral kidney [113] (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 [114, 115]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [116-119] (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 [120-123] (LE: 3). In MRI, especially high-resolution T2-weighted images provide a superior delineation of the uppermost tumour thrombus, as the inflow of the enhanced blood may be reduced due to extensive occlusive tumour thrombus growth in the inferior vena

cava. The T2-weighted image with its intrinsic contrast allows a good delineation [123].

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [123, 124] (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 [125]. Recently, the use of multiparametric MRI (mpMRI) to diagnose ccRCC via a clear cell likelihood score (ccLS) in SRMs was reported [126]. 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 [127], and ccLS was found to be an independent prognostic factor for identifying ccRCC. The system is promising and deserves further validation.

For the diagnosis of complex renal cysts (Bosniak IIF–III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%;  $\kappa = 0.11$ ); MRI, due to a higher sensitivity for enhancement, showed a 71% sensitivity and 91% specificity ( $\kappa = 0.64$ ). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% ( $\kappa = 0.95$ ) [75].

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 [128].

A recent systematic review and meta-analysis [129] 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, and high risks of confounding.

### 5.2.3 **Other investigations**

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision-making [104, 105] (LE: 2a). Positron-emission tomography (PET) is not recommended [116, 130] (LE: 1b).

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

Chest CT is accurate for chest staging [90, 91, 131–133] (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 [134, 135]. 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 thrombocytopenia, 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 [131, 136, 137] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [136, 138, 139] (LE: 3). A recent prospective comparative blinded study involving 92 consecutive mRCC patients treated with first-line 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) [140].

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 2001–2019 [141]. 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 IMDC intermediate risk and 26% were favourable risk. A majority (86%) of the patients had  $\geq 2$  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 [142, 143] (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 [76]; however, it requires further validation. The management of cystic renal tumours is also discussed in Section 3.4.7.

**Table 5.1: Bosniak classification of renal cysts [142]**

<b>Bosniak category</b>	<b>Features</b>	<b>Work-up</b>
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intra-renal, non-enhancing, high attenuation renal lesions $\geq$ 3 cm. Generally well-margined.	Follow-up, up to five years. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or AS – see Chapter 7. Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

## 5.3 **Renal tumour biopsy**

### 5.3.1 **Indications and rationale**

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable medical and surgical treatment strategy in the setting of metastatic disease [144-149] (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 [150]. 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 [151].

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) [144, 147, 152] (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 [147, 153] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [144, 148, 154] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [144, 148] (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 [152, 155, 156] (LE: 2a). A systematic review and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel, including 57 publications and a total of 5,228 patients. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [152]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [144, 147, 153] (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 [152] (LE: 2b). However, 0–22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [145-149, 153, 154, 157] (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%) [144, 158-160].

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 [152].

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) [152] (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 [144, 147, 161, 162] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [163] (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 [164].

### 5.3.4 **Morbidity**

Overall, percutaneous biopsies have a low morbidity [152]. 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 [165]. 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 [165].

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 [152].

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 [166].

### 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 [167]. 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 [168] (see Section 3.4.4. - 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 3.4.4). 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 [47]. 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 [47, 169-177].

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
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 positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2a

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, 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 [178, 179] (Table 4.1).

### 6.3 Histological factors

Histological factors include tumour grade, RCC subtype, lymphovascular invasion, tumour necrosis, and invasion of the collecting system [180, 181]. Tumour grade is considered one of the most important histological prognostic factors. Fuhrman nuclear grade [182] has now been replaced by the WHO/ISUP grading classification [183]. This relies solely on nucleolar prominence for grade 1–3 tumours, allowing for less inter-observer variation [184]. 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 [185]. 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 [186]. The percentage of the sarcomatoid component appears to be prognostic as well, with a larger percentage of involvement being associated with worse survival. However, there is no agreement on the optimal prognostic cut-off for sub-classifying sarcomatoid changes [187, 188]. 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 [189]. Both the WHO/ISUP and chRCC grading systems need to be validated for prognostic systems and nomograms [183].

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 [190, 191] (Table 6.1). However, prognostic information provided by the RCC type is lost when stratified according to tumour stage [191, 192] (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 [193]. 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 [194]. Some studies suggest poorer survival for type 2 than type 1 [195], but this association is often lost in the multivariable analysis [196]. A meta-analysis did not show a significant survival difference between both types [197, 198].

Renal cell carcinoma with Xp11.2 translocation has a poor prognosis [199]. 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 [200-202] (LE: 2b). Surgically excised malignant complex cystic masses contain ccRCC in the majority of cases, and more than 80% are pT1. In a recent series, 5-year CSS was 98% [203]. 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 [142]**

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

CSS = cancer-specific survival.

In all RCC types, prognosis worsens with stage and histopathological grade (Table 6.2). The 5-year 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 [204, 205]. 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 [206].

**Table 6.2: Cancer-specific survival by stage [15]**

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, C-reactive protein (CRP) [207], albumin, and various indices deriving from these factors such as the neutrophil-to-lymphocyte ratio (NLR) [102, 208-213] (LE: 3). As a marker of systemic inflammatory response, a high pre-operative NLR has been associated with poor prognosis [214], 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 [215-217]. This association is linear with regards to cancer-specific mortality (CSM), while obese RCC patients show increasing all-cause mortality with increasing BMI [218]. There is also evolving evidence on the prognostic value of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation [213, 219, 220].

## 6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CAIX), VEGF, HIF, Ki67 (proliferation), p53, p21 [221], PTEN (phosphatase and tensin homolog) cell cycle [222], E-cadherin, osteopontin [223] CD44 (cell adhesion) [224, 225], CXCR4 [226], PD-L1 [227], miRNA, SNPs, gene mutations, and gene methylations have been investigated (LE: 3) [28]. 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 [207, 227, 228]. 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 [229]. In IMmotion151 (NCT02420821), a T effector/IFN- $\gamma$ -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 [230]. In CheckMate 214 (NCT02231749), a higher angiogenesis gene signature score was associated with better overall response rates and PFS for sunitinib, while a lower angiogenesis score was associated with higher ORR in those treated with nivolumab plus ipilimumab. Progression-free survival  $\geq$  18 months was more often seen in patients with higher expression of Hallmark inflammatory response and Hallmark epithelial mesenchymal transition gene sets [213].

Urinary and plasma Kidney-Injury Molecule-1 (KIM-1) has been identified as a potential diagnostic and prognostic marker. KIM-1 concentrations were found to predict RCC up to five years prior to diagnosis and were associated with a shorter survival time [231]. KIM-1 is a glycoprotein marker of acute proximal tubular injury and therefore mainly expressed in RCC derived from the proximal tubules such as ccRCC and pRCC [232]. 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 [233-235]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [234]. Loss of chromosome 9p and 14q have been consistently shown to be associated with poorer survival [236-238]. 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 [237]. Additionally, a 16-gene signature was shown to predict disease-free survival (DFS) in patients with non-metastatic RCC [239]. 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 [240-247]. These models are more accurate than TNM stage or grade alone for predicting clinically relevant oncological outcomes (LE: 3). Before being adopted, new prognostic models should be evaluated and compared to current prognostic models with regards to discrimination, calibration and net benefit. In metastatic disease, risk groups assigned by the Memorial Sloan Kettering Cancer Center (MSKCC) (primarily created in the pre-targeted therapy era, and validated in patients receiving targeted therapy) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (initially created in the targeted therapy era) differ in 23% of cases [248]. 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. The discrimination of the IMDC model may be improved by addition of a seventh variable, namely presence of brain, bone, and/or liver metastases [249]. IMDC intermediate-risk disease may also be sub-classified according to presence of bone metastasis or by platelet count [250, 251]. There is no conclusive evidence that one prognostic model is more accurate than another. Tables 6.3 and 6.4 summarise the current most relevant prognostic models.

## 6.7 Summary of evidence and recommendations for prognostic factors

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

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

**Table 6.3: Prognostic models for localised RCC**

Prognostic model	Subtype*	Risk factors/prognostic factors
UISS** [252]	All	<ol style="list-style-type: none"> <li>1. ECOG PS</li> <li>2. T classification</li> <li>3. N classification (N+ classified as metastatic)</li> <li>4. Grade</li> </ol> <p>T1N0M0G1–2, ECOG PS 0: low-risk disease  T3N0M0G2–4, ECOG PS ≥ 1 OR T4N0M0: high-risk disease  Any other N0M0: intermediate-risk disease</p>
Leibovich score/model 2003 [243]	CC	<ol style="list-style-type: none"> <li>1. T classification (pT1a: 0, pT1b: 1, pT2:3, pT3-4: 4 points)</li> <li>2. N classification (pNx/N0: 0, pN+: 2 points)</li> <li>3. Tumour size (&lt; 10 cm: 0, ≥ 10 cm: 1 point)</li> <li>4. Grade (G1-2: 0, G3: 1, G4: 3 points)</li> <li>5. Tumour necrosis (absent: 0, present: 1 point)</li> </ol> <p>0–2 points: low-risk disease  3–5 points: intermediate-risk disease  6 or more points: high-risk disease</p>
Leibovich score/model 2018 [253]	CC, P, CH	<p><u>ccRCC</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• No risk groups/prognostic groups.</li> </ul> <p><u>pRCC</u></p> <ul style="list-style-type: none"> <li>• Low risk (group 1): grade 1–2, no fat invasion, no tumour thrombus.</li> <li>• Intermediate risk (group 2): grade 3, no fat invasion, no tumour thrombus.</li> <li>• High risk (group 3): grade 4 or fat invasion or any level tumour thrombus.</li> </ul> <p><u>chRCC</u></p> <ul style="list-style-type: none"> <li>• Low risk (group 1): no fat invasion, no sarcomatoid differentiation, no nodal involvement.</li> <li>• Intermediate risk (group 2): fat invasion and no sarcomatoid differentiation and no nodal involvement.</li> <li>• High risk (group 3): sarcomatoid differentiation or nodal involvement.</li> </ul>
VENUSS score/model*** [196, 254]	P	<ol style="list-style-type: none"> <li>1. T classification (pT1: 0, pT2: 1, pT3–4: 2 points)</li> <li>2. N classification (pNx/pN0: 0, pN1: 3 points)</li> <li>3. Tumour size (≤ 4 cm: 0, &gt; 4 cm: 2 points)</li> <li>4. Grade (G1/2: 0, G3/4: 2 points)</li> <li>5. Tumour thrombus (absent: 0, present: 2 points)</li> </ol> <p>0–2 points: low-risk disease  3–5 points: intermediate-risk disease  6 or more points: high-risk disease</p>
GRANT score/model**** [255]	All	<ol style="list-style-type: none"> <li>1. Age &gt; 60 years</li> <li>2. T classification = T3b, pT3c or pT4</li> <li>3. N classification = pN1</li> <li>4. (Fuhrman) grade = G3 or G4</li> </ol> <p>0–1 factors: favourable-risk disease  2 or more factors: unfavourable-risk disease</p>

\* 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-integrated-staging-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 [256]**	All	<ol style="list-style-type: none"> <li>1. Karnofsky PS [257]* &lt; 80%</li> <li>2. Interval from diagnosis to systemic treatment &lt; 1 year</li> <li>3. Haemoglobin &lt; lower limit of normal</li> <li>4. Corrected calcium &gt;10 mg/dL/&gt; 2.5 mmol/L</li> <li>5. LDH &gt; 1.5x upper limit of normal</li> </ol> <p>0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–5 factors: poor-risk disease</p>
IMDC [258]***	All	<ol style="list-style-type: none"> <li>1. Karnofsky PS [257]* &lt; 80%</li> <li>2. Interval from diagnosis to treatment &lt; 1 year</li> <li>3. Haemoglobin &lt; lower limit of normal</li> <li>4. Corrected calcium &gt; upper limit of normal (i.e., &gt; 10.2 mg/dL)</li> <li>5. Neutrophil count &gt; upper limit of normal (i.e., &gt; 7.0×10<sup>9</sup>/L)</li> <li>6. Platelet count &gt; upper limit of normal (i.e., &gt; 400,000)</li> </ol> <p>0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–6 factors: poor-risk disease</p>

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 Treatment of localised RCC

#### 7.1.1 Introduction

Sections 7.1.2 and 7.2.4.2 are underpinned by a systematic review which includes all relevant published literature comparing surgical management of localised RCC (T1–2N0M0). Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Historically, surgery has been the benchmark for the treatment of localised RCC.

#### 7.1.2 Surgical treatment

##### 7.1.2.1 Nephron-sparing surgery versus radical nephrectomy in localised RCC

###### 7.1.2.1.1 T1 RCC

###### Outcome 1: Cancer-specific survival

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [259, 260]. 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]) [261].

### 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 [259, 262-266]. When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [263, 267] 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 [268, 269]. An analysis of the U.S. Medicare database [270] could not demonstrate an OS benefit for patients  $\geq 75$  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. Shuch *et al.*, compared patients who underwent PN for RCC with a non-cancer healthy control group via a retrospective database analysis; showing an OS benefit for the cancer cohort [271]. 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 [261]. 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 [266]. 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) [272]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD which requires haemodialysis. Huang *et al.*, found that 26% of patients with newly diagnosed RCC had an GFR  $\leq 60$  mL/min, even though their baseline serum creatinine levels were in the normal range [105].

### 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 [273].

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 [273, 274].

In view of the above, and since oncological safety (CSS and RFS) of PN, so far, has been found non-differing from RN outcomes, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term PN potentially limits the incidence of cardiovascular disorders and development of ESRD and the need for haemodialysis. Irrespective of the available data, in frail patients, treatment decisions should be individualised, weighing the risks and benefits of PN vs. RN, the increased risk of peri-operative complications, and the risk of developing or worsening of CKD post-operatively.

#### 7.1.2.1.2 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 [275]. 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 [275]. A recent multicentre study compared the survival outcomes in patients with larger ( $\geq 7$  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 ( $p = 0.04$ ) [276]. 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 [277], 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 [278]. 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.



### 7.1.2.1.3 T3 RCC

A recent 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 [279].

### 7.1.2.2 Associated procedures

#### 7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN with, or without, ipsilateral adrenalectomy [280]. 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 [280].

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

The indication for LN dissection (LND) together with PN or RN is still controversial [281]. 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+) [282]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [283]. 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 [284]. 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 [283, 285-287]. 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 [288]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of 10 for the number of nodes dissected resulted in a 10% absolute increase in DSS.

In addition, in a larger cohort of 1,983 patients, Capitanio *et al.*, demonstrated that eLND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [289]. As to morbidity related to eLND, a recent retrospective propensity score analysis from a large single-centre database showed that eLND is not associated with an increased risk of Clavien grade  $\geq 3$  complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [290].

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 [282]. 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 [283, 291, 292]. At least fifteen LNs should be removed [289, 293]. Sentinel LND is an investigational technique [294, 295].

#### 7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [296, 297]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [298, 299]. These indications will be revisited in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

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

Summary of evidence	LE
The oncological outcome in terms of OS following PN equals that of RN in patients with c/p T1 RCC.	1b
Retrospective studies suggest that oncological outcomes are similar following PN vs. RN in patients with larger ( $\geq 7$ 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.	2b
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

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

#### 7.1.3.1 *Radical nephrectomy techniques*

##### 7.1.3.1.1 Open versus laparoscopic or robotic approach

No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A cohort study [300] and a number of retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher stage disease and locally more advanced tumours [301-303]. A retrospective comparative study with data retrieved from a national database studying the OS of open vs. minimally-invasive RN (laparoscopic RN or RARN) 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 [304]. Based on a systematic review, less morbidity was found for laparoscopic vs. open RN [259].

Data from one RCT [275] and two NRS [305, 306] 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 [306]. No difference in the number of patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all three studies [302, 305, 306]. Surgical complication rates were low with very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [305].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal  $\geq$  T2 tumours. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of hospital stay, and convalescence, compared to those who underwent open RN [303, 306, 307]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [303, 306, 307] (LE: 2b). Another multicentre propensity matched analysis compared laparoscopic- and open surgery for pT3a RCC, showing no significant difference in 3-year RFS between groups [308]. The best approach for laparoscopic RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [309, 310] and one quasi-randomised study [283]. Quality of life variables were similar for both approaches. Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [311] and one database review and estimated 5-year OS, CSS, and RFS rates were comparable [312]. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN cohort [311, 312]. However, the sample size was small.



#### 7.1.3.1.2 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 [313]. A recent systematic review 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 [314]. A systematic review reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause CSM [315].

#### 7.1.3.1.3 Laparoscopic single port versus laparoscopic multi-port approach

Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [316, 317].

#### 7.1.3.2 *Partial nephrectomy techniques*

##### 7.1.3.2.1 Open versus laparoscopic approach

Studies comparing laparoscopic and open PN found no difference in PFS [318-321] and OS [320, 321] 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 [308]. 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 [308]. The mean estimated blood loss was found to be lower with the laparoscopic approach [318, 320, 322], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [318, 320]. Operative time is generally longer with the laparoscopic approach [319, 321] and warm ischaemia time is shorter with the open approach [318, 320, 322, 323]. The results for GFR decline are debatable, a RCT reported greater 3–12 month kidney function reduction in the open group [324] whilst in a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [321], but not after 3.6 years follow-up. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [323]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [325]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [326]. 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 [327].

##### 7.1.3.2.2 Open versus robotic approach

One study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate- early- and short-term complications, variation in creatinine levels and pathologic margins were similar between groups [328].

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 [329].

OPERA, a prospective RCT comparing open (OPN) vs. robotic partial nephrectomy (RAPN) in intermediate/high complexity renal tumours (RENAL Score  $\geq 7$ ) prematurely closed due to poor accrual. Considering these limitations, the clinical impact of robotic PN is still controversial.

##### 7.1.3.2.3 Open versus hand-assisted approach

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN vs. open PN patients, but there was no significant difference in high Clavien grade complications. Three months after the operation, GFR was lower in the HALPN than in the open PN group [330].

##### 7.1.3.2.4 Open versus laparoscopic versus robotic approaches

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, after five years of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [331].

##### 7.1.3.2.5 Laparoscopic versus robotic approach

Another study included the 50 last patients having undergone laparoscopic and robotic PN for T1–T2 renal tumours by two different surgeons with an experience of over 200 procedures each in laparoscopic and

robotic PN and RAPN, respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between RAPN and LPN when performed by highly experienced surgeons [332].

A meta-analysis, including a series of NSS with variable methodological quality compared the peri-operative outcomes of robot-assisted- and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of hospital stay. No significant differences were observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins (PSMs) [333].

A recent 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 [334].

#### 7.1.3.2.6 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 [335]. In terms of peri-operative complications, retroperitoneal and transperitoneal PN have similar outcomes [335].

A recent systematic review assessed the outcomes of retroperitoneal vs. transperitoneal RAPN. Seventeen studies, published between 2013 and 2021, were retrieved; none of which a RCT. Among the 6,266 patients included 2,261 (36.1%) and 4,005 (63.9%) underwent retroperitoneal vs. transperitoneal RAPN, respectively. Both retroperitoneal and transperitoneal RAPN offered similar surgical outcomes, while retroperitoneal RAPN was associated with shorter surgical time and length of hospital stay [336].

#### 7.1.3.2.7 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 [326]. 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 [327].

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 localised renal masses [337].

#### 7.1.3.2.8 Surgical volume

In a recent analysis of 8,753 patients who underwent PN, an inverse non-linear relationship of hospital volume with morbidity of PN was observed, with a plateauing seen at 35 to 40 cases per year overall, and 18 to 20 cases for the robotic approach [338]. A retrospective study of a U.S. National Cancer Database looked at the prognostic impact of hospital volume and the outcomes of robot-assisted PN including 18,724 cases. This study shows that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower PSM rates [339]. A French study, including 1,222 RAPN patients, has shown that hospital volume is the main predictive factor of Trifecta achievement (no complications, warm ischaemia time  $< 25$  min, and negative surgical margins) after adjustment for other variables, including surgeon volume [340]. 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 [341].

#### 7.1.3.2.9 Pre-operative embolisation prior to partial nephrectomy

A systematic review and meta-analysis of 270 patients demonstrated significantly reduced blood loss in patients with selective renal artery embolisation ( $n = 222$ ;  $154 \pm 22.6$  mL vs.  $n = 48$ ;  $353.4 \pm 69.6$  mL) prior to PN [342].

#### 7.1.3.3 Positive surgical margins on histopathological specimens

A PSM is encountered in about 2–8% of PNs [333]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [343, 344]. Most trials showed that intra-operative

frozen section analysis had no influence on the risk of definite PSMs [345]. 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) [346–349].

The majority of retrospective analyses reported so far indicated that PSMs do not translate into a higher risk of metastases or a decreased CSS [347, 348]. 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 [350]. 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 5-year OS rate in pT3a tumours (PSM: 69% vs. NSM: 90.9 %) [351].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy [352]. Local tumour bed recurrences were found in 16% in patients with PSMs compared with 3% in those with negative margins [346]. 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 [347, 353]. On the other hand, protection from recurrence is not ensured by negative surgical margins [354].

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

Summary of evidence	LE
Laparoscopic RN has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1–T2a tumours are equivalent for laparoscopic- and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon’s expertise and skills.	2b
Robot-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Partial nephrectomy is associated with a higher percentage of PSMs compared to RN.	3
Transperitoneal and retroperitoneal laparoscopic PN do not differ in 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
Radical nephrectomy after PSMs can result in over-treatment in many cases.	3

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally-invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally-invasive surgery if this approach may compromise oncological-functional- and peri-operative outcomes.	Strong
Intensify follow-up in patients with a positive surgical margin, especially in upstaged pT3a patients.	Weak

#### 7.1.4 Therapeutic approaches as alternatives to surgery

##### 7.1.4.1 Active surveillance and watchful waiting

Elderly and comorbid patients with incidental SRMs have a low RCC-specific mortality and significant competing-cause mortality [355, 356]. 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 [357]. 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 [270, 358, 359]. 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 [358]. Analyses of older patients (> 75 years) failed to show the same benefit in CSM for surgical treatment [360–362].

### *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 [363, 364]. A systematic review of eighteen AS cohorts comprising 2,066 patient (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 [365]. 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  $\geq 4$  cm, and four (6.7%) by both criteria. Six patients developed metastases, and all were of ccRCC histology [366].

### *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 [355]. 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 [367].

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 [368, 369].

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 [368]. In the previously mentioned large systematic review 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) [365].

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 [357, 363, 364, 370–373].

### *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 [374].

#### *7.1.4.2 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,  $p = 0.0003$ ) [366].

#### *7.1.4.3 Tumour ablation*

##### *7.1.4.3.1 Role of renal mass biopsy*

A RMB is required prior to tumour ablation (TA) (see Sections 5.3 - Renal tumour biopsy and 5.4 - Summary of evidence and recommendations for the diagnostic assessment of RCC). Historically, up to 45% of patients underwent TA of a benign or non-diagnostic mass [375, 376]. 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) [377]. A RMB in a separate session reduces over-treatment significantly, with 80% of patients with benign lesions opting not to proceed with TA [376]. Additionally, there is some evidence that the oncological outcome following TA differs according to RCC subtype which should therefore be

factored into the decision-making process. In a series of 229 patients with cT1a tumours (mean size 2.5 cm) treated with RFA, the 5-year DFS rate was 90% for ccRCC and 100% for pRCC (80 months: 100% vs. 87%,  $p = 0.04$ ) [378]. In another series, the total TA effectiveness rate was 90.9% for ccRCC and 100% for pRCC [379]. 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 [380]. Furthermore, patients with high-grade RCC or metastasis may choose different treatments over TA. Finally, patients without biopsy or a non-diagnostic biopsy are often assumed to have RCC and will undergo potentially unnecessary radiological follow-up or further treatment.

#### 7.1.4.3.2 Cryoablation

Cryoablation is performed using either a percutaneous- or a laparoscopic-assisted approach, with technical success rates of  $> 95\%$  [381]. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [382-384]. 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 [383]. A shorter average length of hospital stay was found with the percutaneous technique [383-385]. A systematic review including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [386]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

Oncological outcomes after cryoablation have generally been favourable for cT1a tumours. In a recently published series of 308 patients with cT1a and cT1b tumours undergoing percutaneous cryoablation, local recurrence was seen in 7.7% of cT1a tumours vs. 34.5% of cT1b tumours. On multivariable regression, the risk of disease progression increased by 32% with each 1 cm increase in tumour size (HR: 1.32,  $p < 0.001$ ). Mean decline in eGFR was 11.7 mL/min/1.73 m<sup>2</sup> [387]. In another large series of 220 patients with biopsy-proven cT1 RCC, 5-year local RFS was 93.9%, while metastasis-free survival approached 94.4% [381]. A series of 134 patients with T1 RCC (median tumour size 2.8 cm) submitted to percutaneous cryoablation yielded a 10-year DSF of 94% [388].

For cT1b tumours, local tumour control rates drop significantly. One study showed local tumour control in only 60.3% at three years [389]. In another series, the PFS rate was 66.7% at twelve months [390]. Furthermore, recent analyses demonstrated 5-year CSM rates of 7.6–9% [391, 392]. On multivariable analysis, cryoablation of cT1b tumours was associated with a 2.5-fold increased risk of death from RCC compared with PN [391].

Recurrence after initial cryoablation is often managed with re-cryoablation, but only 45% of patients remain disease-free at two years [393].

#### 7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Several studies compared patients with cT1a tumours treated by laparoscopic or percutaneous RFA [394-397]. 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 [398]. This is generally managed by re-RFA, approaching overall total technical success rates  $> 95\%$  with one or more sessions [399].

Long-term outcomes with over five years of follow-up following RFA have been reported. In recent studies, the 5-year OS rate was 73–79% [398, 399], due to patient selection. Oncological outcomes for cT1a tumours have been favourable. In a recent study, the 10-year DFS rate was 82%, but there was a significant drop to 68% for tumours  $> 3$  cm [399]. In series focusing on clinical T1b tumours (4.1–7.0 cm), the 5-year DFS rate was 74.5% to 81% [398, 400]. Oncological outcomes appear to be worse than after surgery, but comparative data are severely biased (see Section 7.1.4.3.4). In general, most disease recurrences occur locally and recurrences beyond five years are rare [399, 400].

#### 7.1.4.3.4 Tumour ablation versus surgery

The Guideline Panel performed a protocol-driven systematic review of comparative studies (including  $> 50$  patients) of TA with PN for T1N0M0 renal masses [401]. 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 systematic review, TA as treatment for T1 renal masses was found to be safe in terms of complications and adverse events (AEs), but its long-term oncological effectiveness compared with PN remained unclear. The primary reason for the persisting uncertainty was related to the nature of the available data; most studies were retrospective observational studies with poorly matched controls, or single-arm case series with short follow-up. Many studies were poorly described and lacked a clear comparator.



There was also considerable methodological heterogeneity. Another major limitation was the absence of clearly defined primary outcome measures. Even when a clear endpoint such as OS was reported, data were difficult to interpret because of the varying length and type of follow-up amongst studies. The Panel also appraised the published systematic reviews based on the AMSTAR 2 tool which showed “Critically Low” or “Low” ratings [401].

Tumour ablation has been demonstrated to be associated with good long-term survival in several single-arm non-comparative studies [402, 403]. 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 [268, 391, 392, 404, 405]. However, there appears to be no clinically significant difference in 5-year CSM between TA and AS [359].

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.

#### 7.1.4.3.5 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours. Patients usually receive 26 Gy in a single fraction, three fractions of 14 Gy or five fractions of 6 Gy [406, 407]. In a systematic review of non-comparative single-arm studies with a median follow-up range of 5.8–79.2 months, the local control rate was 97.2% and the mean change in eGFR was 7.7 mL/min/1.73 m<sup>2</sup>. Grade 3 or 4 toxicities occurred in 1.5% of patients. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [407]. Even though early results of SABR are encouraging, more evidence from RCTs is needed [408].

#### 7.1.4.3.6 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 5-year local progression rate was 3.2%, while 4.3% developed distant metastases [409]. Results appear to be favourable for cT1b tumours as well [410]. 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 [411].

#### 7.1.4.3.7 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.

#### 7.1.4.3.8 Summary of evidence and recommendations for therapeutic approaches as alternative to surgery

Summary of evidence	LE
Most population-based analyses show a significantly lower CSM 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

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

## 7.2 Treatment of locally advanced RCC

### 7.2.1 Introduction

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

### 7.2.2 Role of lymph node invasion in locally-advanced RCC

In locally-advanced RCC, the role of LND is still controversial. The only available RCT demonstrated no survival benefit for patients undergoing LND but this trial mainly included organ-confined disease cases [282]. In the setting of locally-advanced disease, several retrospective papers and systematic reviews addressed the topic with contradictory results. Bhindi *et al.*, could not confirm any survival benefit in patients at high risk of progression treated with LND [412]. More recently, Luo *et al.*, reported a systematic review and meta-analyses showing a survival benefit in patients with locally-advanced disease treated with LND [413]. More specifically, thirteen studies on patients with LND and non-LND were identified and included in the analysis. In the subgroup of locally-advanced RCC (cT3–T4NxM0), LND showed a significantly better OS rate in patients who had undergone LND compared to those without LND (HR: 0.73, 95% CI: 0.60–0.90,  $p = 0.003$ ).

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

In case of cN-, the probability of finding pathologically-confirmed LN metastases ranges between 0 and 25%, depending mainly on primary tumour size and the presence of distant metastases [414]. In case of clinically-negative LNs (cN-) at imaging, removal of LNs is justified only if visible or palpable during surgery [415], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [284, 412]. Whether to extend the LND also to retroperitoneal areas without cN+ remains controversial [283].

#### 7.2.2.2 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) up to 54.5% in case of locally-advanced disease. In cN+, removal of visible and palpable nodes during LND is always justified [415], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [284, 412].

### 7.2.3 Management of RCC with venous tumour thrombus

Tumour thrombus formation in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [416, 417].

In two of the largest published studies a higher OS was different in patients with a level of thrombus in the renal vein and inferior caval vein and survival was also not associated with tumour size, grade, perinephric fat extension, sarcomatoid features, Eastern Cooperative Oncology Group PS and regional- and distant metastases in multivariate analysis [416, 417]. 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 (open vs. laparoscopic vs. robotic) and approach for each case should be selected based on the extent of tumour thrombus.

A systematic review was undertaken on the management of venous tumour thrombus in non-metastatic RCC, with a high risk of bias across all studies [418, 419]. Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [418].

The surgical method selected depended on the level of tumour thrombus and the grade of occlusion of the IVC [418]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

A systematic review comparing robot-assisted laparoscopic- and open tumour thrombectomy at all levels found lower transfusion rates and overall complication rates for the minimally-invasive approach, however major complication rates were similar to those in open thrombectomy. The optimal patient selection for the different approaches remains unclear [419].

A feasibility study with neoadjuvant axitinib to reduce the thrombus was positive, but larger studies are needed before its use can be routinely implemented into clinical practice [420].

#### 7.2.4 Management of locally-advanced unresectable RCC

The management of locally-advanced unresectable RCC should be based around systemic therapy [421]. 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 [298, 299, 422, 423].

##### 7.2.4.1 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

#### 7.2.5 Neoadjuvant and adjuvant therapy

Neoadjuvant therapy is currently under investigation and available in clinical trials. There is currently no evidence from a systematic review (including ten retrospective studies and two RCTs) that adjuvant radiation therapy increases survival [424]. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [425-429] (LE: 1b). A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carbonic anhydrase IX (CAIX) (ARISER Study) [430].

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, several RCTs comparing VEGFR-TKI vs. placebo have been published [431-438]. 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 [439].

##### 7.2.5.1 PD-1 Inhibition: Keynote-564

The Keynote-564 trial is the first trial to report positive primary endpoint data on DFS [440, 441]. Keynote-564 evaluated pembrolizumab (17 cycles of 3-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  $\leq$  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. placebo (HR: 0.68, 95% CI: 0.53–0.87,  $p = 0.001$ ). The estimated 24-month DFS rate was 77% vs. 68% 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 showed a non-statistically significant trend towards a benefit in the pembrolizumab arm (HR: 0.54, 95% CI: 0.30–0.96,  $p = 0.0164$ ). Follow-up was short and few OS events occurred (2-year OS rate of 97% [pembrolizumab] vs. 94% [placebo]). Grade 3–5 all-cause AEs 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.

##### 7.2.5.2 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 [442]. IMmotion010 evaluated atezolizumab 1200 mg (once every 3 weeks for 16 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,  $\geq 12$  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  $\geq 1\%$  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 AEs 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 AEs.

#### 7.2.5.3 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) [443]. 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 12 cycles or 6 months plus ipilimumab 1 mg/kg Q6W for 4 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 AE grade  $\geq 3$  were 29% in the nivolumab plus ipilimumab group and 2% in the placebo group with 4 deaths (1%) considered related to combination therapy. The high AE profile may have contributed to the lack of efficacy and patient retention. The results of the nivolumab arm are awaited.

#### 7.2.5.4 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 [444]. Patients with clinical stage  $\geq T2$  or T any N+ RCC or patients with selected oligometastatic disease were included if they had no evidence of disease within 12 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 DSMC. The OS was not statistically different (HR: 1.48; 95% CI: 0.89–2.48;  $p = 0.93$ ), although not mature. Grade 3–4 AEs occurred in 20% (nivolumab arm) and 6% (control arm) of patients, respectively. Fifteen (4%) patients died in the nivolumab arm and 18 (4%) in the surgery alone arm.

Following the application of the EAU Guidelines modified GRADE assessment the panel reached consensus and issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk (defined as per study) operable ccRCC until final OS data are available [445]. 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 [453]. 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 (STRAC) [443, 446]. The Panel took the following evidence limitations into account when deciding to make to a weak recommendation for adjuvant pembrolizumab:

- A high proportion of patients, cured by surgery, are receiving unnecessary, and potentially harmful treatment.
- The tolerability profile is acceptable but grade 3–5 AEs were higher with 14.7% in the pembrolizumab arm vs. the placebo arm (occurring in approximately one-third of patients, all cause). Approximately 18% of patients required treatment discontinuation early for AEs which gives a broad indicator of tolerability. There is a significant risk of life-changing toxicity.
- Other ICI trials have not shown consistent results.
- Biomarker analysis to predict outcome and AEs are not available.
- Final OS data are not yet available.

The results of IMmotion010, CheckMate 914 and PROSPER need to be discussed with patients [442-444]. 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 [446].

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. 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.

**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
<b>Keynote-564</b> <b>NCT03142334</b> Median follow-up of 30.1 mo. [440]	994	PEMBRO 200 mg IV Q3W (17 cycles) vs. placebo	DFS in the ITT by IR	<b>Intermediate-high:</b> pT2 grade 4 or sarcomatoid; pT3 any grade <b>High:</b> pT4 any grade, pN1 <b>M1 NED:</b> cM0 after resection of oligometastatic disease < 12 mo.	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE)  HR: 0.63 (95% CI: 0.50–0.80) p < 0.002  DFS at 24 mo.: PEMBRO: 78.3% PLACEBO: 67.3%	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE)  HR: 0.52 (95% CI: 0.31–0.86) not significant  alive at 30 mo.: PEMBRO: 95.7% PLACEBO: 91.4%
<b>IMmotion010</b> <b>NCT03024996</b> Median follow-up of 44.7 mo. [442]	778	ATEZO 1200 mg IV Q3W (16 cycles or 1 yr.) vs. placebo	DFS in the ITT by IR	<b>By TNM:</b> 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
<b>CheckMate 914</b> <b>NCT03138512</b> Median follow-up of 37.0 mo. [443]	816	NIVO 240 mg IV Q2W (× 12 cycles) + IPI 1 mg/kg IV Q6W (× 4 cycles vs. placebo)	DFS in the ITT by BICR	<b>By TNM:</b> 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

<b>PROSPER</b> <b>NCT03055013</b> Median follow-up: NR [444]	779	Neoadjuvant NIVO 240 mg IV Q2W (x 2 cycles) followed by adjuvant NIVO 240 mg Q2W for 3 mo. and Q4W for 6 mo. vs. observation	RFS in the ITT by IR	<b>By TNM:</b> >= cT2 (7 cm) or cT any cN1	(ITT), RFS: NIVO: NR (NE) Observation: NR (NE)  HR: 0.97 (95% CI: 0.74–1.28) p = 0.43	(ITT) NIVO: NR (NE) Observation: NR (NE)  HR: 1.48 (95% CI: 0.89–2.48) p = 0.93
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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 = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks.

#### 7.2.5.5 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	LE
Adjuvant sorafenib, pazopanib, everolimus, girentuximab, or axitinib does not improve DFS or OS after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved DFS but not OS.	1b
Adjuvant pembrolizumab defined by the inclusion criteria of the trial* after nephrectomy improves DFS.	1b
Adjuvant PD-L1 inhibition with atezolizumab 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
The lack of biomarker data is hindering progress in this field. Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	4

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

Recommendations	Strength rating
Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.	Strong
Inform patients about the potential risk of overtreatment and immune-related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	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: <ul style="list-style-type: none"> <li>• Intermediate-high risk: <ul style="list-style-type: none"> <li>• pT2, grade 4 or sarcomatoid, N0, M0</li> <li>• pT3, any grade, N0, M0</li> </ul> </li> <li>• High risk: <ul style="list-style-type: none"> <li>• pT4, any grade, N0, M0</li> <li>• any pT, any grade, N+, M0</li> </ul> </li> <li>• M1 no evidence of disease (NED): <ul style="list-style-type: none"> <li>• NED after resection of oligometastatic sites ≤ 1 year from nephrectomy</li> </ul> </li> </ul>	Weak

## 7.3 Advanced/metastatic RCC

### 7.3.1 Local therapy of advanced/metastatic RCC

#### 7.3.1.1 Cytoreductive nephrectomy

Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a combined

analysis of two RCTs comparing CN+ IFN-based immunotherapy vs. IFN-based immunotherapy only, increased long-term survival was found in patients treated with CN [447].

However, IFN-based immunotherapy is no longer relevant in contemporary clinical practice. In order to investigate the role and sequence of CN in the era of targeted therapy, a structured literature assessment was performed to identify relevant RCTs and systematic reviews published between July 1<sup>st</sup> - June 30<sup>th</sup> 2019.

Two RCTs [448, 449] and a narrative systematic review were identified [450]. The narrative systematic review included both RCTs and 10 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 [448]. 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 [449]. This confirms previous findings from single-arm phase II studies [450, 451]. 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 [452]. These data are confirmed by CARMENA [448] and upfront pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial [453].

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 recent systematic review evaluating effects of CN demonstrated an OS advantage of CN [450]. 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 [454].

**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 [455]	ipilimumab + nivolumab	187/847 (22%)	84	103	NA	0.63 (0.42–0.94)
CheckMate 9ER [456]	cabozantinib + nivolumab	196/651 (30.1%)	101	95	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Javelin 101 [457]	axitinib + avelumab	179/886 (20.2%)	90	89	0.75 (0.48–1.65)	NA
KEYNOTE-426 [458]	axitinib + pembrolizumab	143/861 (16.6%)	73	70	0.68 (0.45–1.03)	0.57 (0.36–0.89)
CLEAR [459]	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 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.

#### 7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery or with non-resectable disease, embolisation can control symptoms including visible haematuria or flank pain [298, 299, 422] (see recommendations Section 7.1.2.2.4).

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

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy in patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk 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 MSKCC poor-risk patients.	Strong
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak



Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

### 7.3.2 **Local therapy of metastases in metastatic RCC**

A systematic review of the local treatment of metastases from RCC in any organ was undertaken [460]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and AEs. A risk-of-bias assessment was conducted [461]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [462-470]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [470-472], two in the brain [473, 474] and one each in the liver [475] lung [476] and pancreas [477]. Three studies were published as abstracts only [465, 467, 476]. Data were too heterogeneous to meta-analyse. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

#### 7.3.2.1 *Complete versus no/incomplete metastasectomy*

A systematic review, including only eight studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [462-469]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [469]. Non-surgical modalities were not applied. Six studies [463-465, 467-469] 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 [462] showed no significant difference in CSS between complete and no metastasectomy, and one [466] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [476], liver [475], and pancreas [477], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both targeted therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and 5-year OS for metastasectomy vs. no metastasectomy.

More recently, a prospective study evaluated US-guided endoscopic RFA in patients with pancreatic metastases (n = 12). Median size of a single pancreatic metastasis was 17 mm. After 27.7 months of follow-up, the 6- and 12-month focal control rates were 84% and 73%, respectively, although two severe complications occurred. Due to the low numbers of patients in this study, RFA for pancreatic metastases will still remain experimental [478].

#### 7.3.2.2 *Local therapies for RCC bone metastases*

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [472]. Single-dose IGRT ( $\geq 24$  Gy) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [470]. A significantly higher 5-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 stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases to the spine [471]. Pain, ORR, time-to-pain relief and duration of pain relief were similar.

#### 7.3.2.3 *Local therapies for RCC brain metastases*

Two studies on RCC brain metastases were included. A 3-arm study compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT [473]. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus WBRT.

Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS and WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [474]. Several patients in all groups underwent



alternative surgical and non-surgical treatments after initial treatment. One-, two- and 3-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better 2-year local control rate compared with metastasectomy plus conventional radiotherapy.

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 4 or 5 toxicity was observed.

#### 7.3.2.4 *Embolisation of metastases*

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [170]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [171] (see recommendation Section 7.1.2.2.4).

#### 7.3.2.5 *Stereotactic radiotherapy in oligo-recurrent and oligo-progressive metastases*

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 2-year local control rate of 78.3% (95% CI: 72.5–83.0). 1, 2 and 3-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 3 or higher toxicities were reported [480].

Similar results in oligo-progressive mRCC has been reported in a prospective study including 37 patients with IMDC favourable- and intermediate risk where 1-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 BED10 was 72 Gy, corresponding to a SRT dose of 40 Gy in 5 fractions. Median PFS was 9.3 months and there were no reported grade 3 acute or late toxicities [481].

#### 7.3.2.6 *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 by offering adjuvant TKI treatment after metastasectomy did not demonstrate an improvement in RFS. In a recent phase II trial 129 patients were randomised to either pazopanib 800 mg daily vs. placebo for 52 weeks. The primary study endpoint of a 42% DFS improvement from 25% to 45% at three years was not met. Hazard ratio for DFS in pazopanib vs. placebo-treated patients was 0.85 (0.55–1.31),  $p = 0.47$  [172]. A second phase II trial randomised 69 ccRCC patients after metastasectomy and no evidence of disease to either sorafenib (400 mg twice daily) or observation. The study was terminated early due to slow accrual and the availability of new agents and multimodal treatment options, including surgery or a locoregional approach. The primary endpoint of RFS was not reached with a RFS of 21 months in the sorafenib arms vs. 37 months in the observation arm ( $p = 0.404$ ) [173], which also did not change after a longer median follow-up period of 42 months [173].

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) [440, 441]. A metachronous interval of < 1 year for recurrences following surgery with curative intent is a poor prognostic factor by IMDC classification [256, 482]. Systemic therapy based on immune combinations has stronger levels of evidence than surgery in this intermediate/advanced disease setting [483]. Also, TKI-driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [172, 173].

Results for single-agent pembrolizumab post-surgery for metastatic disease are therefore difficult to interpret due to the small subgroup. Nevertheless, the DFS HR of 0.29 (95% CI: 0.12–0.69) 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%) [484, 485].

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 [442]. This result underscores the need for caution in the treatment of the M1 NED subgroup.

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

Summary of evidence	LE
Retrospective comparative studies consistently 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 16 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 mRCC 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

## 7.4 Systemic therapy for advanced/metastatic RCC

### 7.4.1 Chemotherapy

Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered to patients with collecting duct or medullary carcinoma [174].

#### 7.4.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

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

### 7.4.2 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 [486-488]. This process substantially contributes to the development and progression of RCC. Several targeting drugs for the treatment of mRCC are approved in both the USA and Europe.

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

In major trials leading to registration of the approved targeted agents, patients were stratified according to the IMDC risk model (Table 7.3) [258].

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

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

\* Based on [258]; # based on [482].

CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; n = number of patients; OS = overall survival; yr = year.

#### 7.4.2.1 Tyrosine kinase inhibitors

##### 7.4.2.1.1 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- $\alpha$ . Overall survival was greater in patients treated with sunitinib (26.4 months) vs. IFN- $\alpha$  (21.8 months) despite crossover [489].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [490]. 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 [491, 492].

##### 7.4.2.1.2 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 [493].

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 [494]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%,  $p < 0.05$ ) due to symptomatic toxicity [495]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

##### 7.4.2.1.3 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) [496].

The overall median PFS was greater for axitinib than sorafenib. Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months) after progression on sunitinib. Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [497]. 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 [498]. As a result of this study, axitinib is not approved for first-line therapy.

##### 7.4.2.1.4 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 [226]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [499, 500]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58, 95% CI: 0.45–0.75) [499] (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 3 or 4 AEs 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 [501,

502]. Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66, 95% CI: 0.46 to 0.95; one-sided  $p = 0.012$ ). Objective response rate was 46% (95% CI: 34–57) for cabozantinib vs. 18% (95% CI: 10–28) for sunitinib. All-causality grade 3 or 4 AEs were similar for cabozantinib and sunitinib. No difference in OS was seen. Due to limitations of the statistical analyses within this trial, the evidence is inferior over existing choices.

#### 7.4.2.1.5 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 (PDGFR $\alpha$ ), re-arranged during transfection (RET) and receptor for stem cell factor (KIT). It has recently been investigated in a randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.4.1.1 for discussion of results) [503].

#### 7.4.2.1.6 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 [504, 505]. Tivozanib was approved by the EMA in front-line mRCC. While it was associated with a PFS advantage in both studies, no OS advantage was seen. In view of the choice of sorafenib as the control arm in the front-line trial, the Panel considers there is too much uncertainty, and too many attractive alternatives, to support its use in this front-line setting.

#### 7.4.2.2 Monoclonal VEGF antibody

Bevacizumab is a humanised monoclonal antibody. Initial first-line treatment in combination with IFN- $\alpha$  has been superseded by more effective therapies [506–508]. Bevacizumab in combination with atezolizumab has not been approved for treatment of mRCC (see Section 7.4.3.2) [509].

#### 7.4.2.3 mTOR inhibitors

##### 7.4.2.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [510]. Its use has been superseded as front-line treatment option.

##### 7.4.2.3.2 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) [511]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [511].

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

#### 7.4.2.4 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
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 EMA approved, but the evidence is still considered inferior over existing choices 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
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-naïve vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

### 7.4.3 Immunotherapy

#### 7.4.3.1 Immune checkpoint inhibitors

##### 7.4.3.1.1 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 [512]. Immune checkpoint inhibitor monotherapy has been investigated as second- and third-line therapy. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy for mRCC with a clear cell component (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 AEs with nivolumab than with everolimus [513]. Nivolumab has superior OS to everolimus (HR: 0.73, 95% CI: 0.57–0.93,  $p < 0.002$ ) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus with a 5-year OS probability of 26% vs. 18% [514] (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-naïve patients. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95% CI: 0.82–1.71) which did not justify further assessment of atezolizumab as single agent as first-line treatment option in this group of patients, despite high complete response rates in the biomarker-positive population [515]. 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) [516]. 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 [517, 518].

##### 7.4.3.2 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 [455] and a paradigm shift in the treatment of mRCC [519]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete response rates (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve the pre-defined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29–0.41).

A recent update with 60-month data shows ongoing benefits for the immune combination with independently assessed complete response rates of 11% and a HR for OS in the IMDC intermediate- and poor-risk group of 0.68 (0.58–0.81) [520]. However, this complete response rate has not been consistent across trials for this combination (the Cosmic313 study showed complete response rates of 3% [521]).

In CheckMate 214 the 60-months OS probability was 43% for ipilimumab plus nivolumab vs. 31% for sunitinib, respectively [522]. In this update the IMDC good-risk group did not continue to perform better with sunitinib although this effect occurs due to a late overlap of the Kaplan-Meier curves (HR for OS: 0.94 [95% CI: 0.65–1.37]) [522]. Nivolumab plus ipilimumab was associated with 46% grade 3–4 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.

The frequency of steroid use has generated controversy and further analysis, as well as real world data, are required. For these reasons the Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The KEYNOTE-426 trial (NCT02853331) reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naive cc-mRCC patients [523]. 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 [524]. Treatment-related AEs ( $\geq$  grade 3) occurred in 63% of patients receiving axitinib and pembrolizumab vs. 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms [523].

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 [525]. 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 AEs ( $\geq$  grade 3) occurred in 61% of patients receiving cabozantinib and nivolumab vs. 51% of patients receiving sunitinib. Treatment-related deaths occurred in one patient in the nivolumab/cabozantinib arm and in two patients in the sunitinib arm. With an extended follow-up with median 32.9 months the median OS was 37.7 months in the nivolumab plus cabozantinib patients vs. 34.3 months (29.0–not estimable) in the sunitinib treated patients (HR: 0.70 [95% CI: 0.55–0.90,  $p = 0.0043$ ). The updated median PFS was 16.6 months (12.8–19.8) vs. 8.3 months (7.0–9.7; HR 0.56 [95% CI: 0.4–0.68],  $p < 0.0001$  [526].

The randomised phase III trial CLEAR (Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma) was published [527]. 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. Efficacy was observed across all IMDC risk groups, independently of PD-L1 status. Treatment-related AEs of grade 3 and higher with lenvatinib plus pembrolizumab were 72%. Treatment-related death occurred in four patients in the lenvatinib plus pembrolizumab arm and in one patient in the sunitinib arm.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [457]. 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 [528]. 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],  $p = 0.27$ ) [509, 529]. Therefore, these combinations cannot currently be recommended.

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 [521]. 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 has yet to be reported. Objective response was 43% vs. 36% in the triplet vs. the control arm with a complete response rate of 3% in both arms. Treatment-related AEs of  $\geq$  grade 3 with cabozantinib plus nivolumab plus ipilimumab were 73% vs. 41% in the nivolumab plus ipilimumab control arm. The use of high-dose steroids ( $\geq$  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 AE was 12% vs. 5% in the control arm.

Although the primary endpoint of PFS was met, objective response rates of the triplet combination are modest as known for TKI + IO doublets. Treatment-related AEs 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
<b>KEYNOTE-426</b> <b>NCT02853331</b> Median follow-up 42.8 months [523, 524, 530]	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	<b>IMDC</b> FAV 31% IMD 56% POOR 13%  <b>MSKCC</b> Not determined	(ITT) PEMBRO + AXI: 15.7 (13.6–20.2) SUN: 11.1 (8.9–12.5)  HR: 0.68 (95% CI: 0.58–0.80) p < 0.0001	(ITT) PEMBRO + AXI: 45.7 (43.6–NR) SUN: 40.1 (34.3–44.2)  HR: 0.73 (95% CI: 0.60–0.88) p = 0.001
<b>JAVELIN 101</b> <b>NCT02684006</b> Median follow-up 19 months [457, 528]	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	<b>IMDC</b> FAV 22% IMD 62% POOR 16%  <b>MSKCC</b> FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1–20.7) SUN: 7.0 (5.7–9.6)  HR: 0.62 (95% CI: 0.49–0.78) p < 0.0001	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4–NE)  HR: 0.83 (95% CI: 0.60–1.15) p = 0.1301
<b>IMmotion151</b> <b>NCT02420821</b> Median follow-up 24 months [509, 529]	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	<b>IMDC</b> Not determined  <b>MSKCC</b> 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
<b>Checkmate 214</b> <b>NCT02231749</b> Median follow-up of 60 months [455, 522]	1096	NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W vs. SUN 50 mg PO QD 4/2 wk	PFS and OS in the IMDC intermediate and poor risk population by BICR	<b>IMDC</b> FAV 23% IMD 61% POOR 17%  <b>MSKCC</b> 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

<b>CheckMate 9ER</b> <b>NCT03141177</b> Median follow-up of 23.5 months [525, 526]	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	<b>IMDC</b> FAV 22% IMD 58% POOR 20%  <b>MSKCC</b> Not determined	(ITT) NIVO + CABO: 17.0 (12.6–19.4) SUN: 8.3 (6.9–9.7)  HR: 0.52 (95% CI: 0.43–0.64) p < 0.0001	(ITT) NIVO + CABO: NR (NE) SUN: 29.5 (28.4–NE)  HR: 0.66 (98.9% CI: 0.50–0.87) p = 0.0034
<b>CLEAR</b> <b>NCT02811861</b> Median follow-up of 33.4 months [527, 531]	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	<b>IMDC</b> FAV 31% IMD 59% POOR 9% NE 1%  <b>MSKCC</b> FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO + LEN: 23.9 (20.8–27.7) SUN: 9.2 (6.0–11.0)  HR: 0.39 (95% CI: 0.32–0.49) p > 0.001	(ITT) PEMBRO + LEN: NR (41.5–NE) SUN: NR (38.4–E)  HR: 0.72 (95% CI: 0.55–0.93) p = 0.005
<b>COSMIC-313</b> Median follow-up of 20.2 months [521]	855	NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W + CABO 40 mg 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)	<b>IMDC</b> 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

*ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; 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 = progression-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; 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 [532, 533] (LE: 1).

Patients who stop TKI and IO due to immune-related toxicity can receive single-agent TKI once the AE 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).

#### 7.4.4 Therapeutic strategies

##### 7.4.4.1 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 7.1). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease), remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Figure 7.1).

##### 7.4.4.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [503, 513]. Pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are the new standard of care in front-line therapy. The impact of front-line immune checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or TKI plus IO in a first-line setting are lacking, and available cohorts are limited [534]. Prospective data on tivozanib, cabozantinib and axitinib are available for patients progressing on immunotherapy, but these studies do not focus solely on the front-line setting, involve subset analyses, and are too small for definitive conclusions [513, 535].

Retrospective data on VEGFR-TKI therapy after progression on front-line immune combinations exist but have significant limitations. When considering this data in totality, there is some activity but it is still too early to recommend one VEGFR-TKI over another after immunotherapy/immunotherapy or immunotherapy/VEGFR combination (Figure 7.2) [536, 537]. After the axitinib plus pembrolizumab combination, changing the VEGFR-TKI at progression to cabozantinib or any other TKI not previously used is recommended.

The Panel do not support the use of mTOR inhibitors unless VEGF-targeted therapy is contra-indicated as they have been outperformed by other VEGF-targeted therapies in mRCC [538]. Drug choice in the third-line setting, after ICI 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 [500]. 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 [538]. 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 [503]. As shown in a study which also included patients on ICIs, tivozanib provides PFS superiority over sorafenib in VEGF-refractory disease [539].

##### 7.4.4.1.2 Summary of evidence and recommendations for immunotherapy in cc-mRCC

Summary of evidence	LE
<i>Treatment-naïve patients</i>	
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 ORR benefits compared to sunitinib alone.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC across all IMDC risk groups demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
The combination of nivolumab plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naïve patients with cc-mRCC leads to superior survival compared to sunitinib.	2b
<i>Sequencing systemic therapy</i>	
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 AEs 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 3–4 toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade 3–5 toxicity ranging between 61–72% and 1% of treatment-related deaths.	1b

Recommendations	Strength rating
<i>Treatment-naïve patients</i>	
Offer treatment with PD1 combinations in centres with experience.	Weak
Offer either nivolumab plus ipilimumab, pembrolizumab plus axitinib, or lenvatinib plus pembrolizumab, or nivolumab plus cabozantinib to treatment-naïve patients with IMDC intermediate- or poor-risk disease.	Strong
Offer either pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to treatment-naïve patients with IMDC favourable risk.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable risk.	Weak
Offer sunitinib or pazopanib to treatment-naïve cc-mRCC patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong <sup>a</sup>
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.	Weak
<i>Sequencing systemic therapy</i>	
Sequence systemic therapy in treating mRCC.	Strong
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
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer nivolumab or cabozantinib to 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 multidisciplinary team.	Strong

<sup>a</sup> 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 7.1: Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC**

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

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.

\*pazopanib for intermediate-risk disease only.

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

[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

**Figure 7.2: EAU Guidelines recommendations for later-line therapy**

	Standard of care	Alternative
Prior IO	Any VEGF-targeted therapy that has not been used previously in combination with IO [4]	
Prior TKI	nivolumab [1b] cabozantinib [1b]	axitinib [2b]

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

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

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

[4] = expert opinion.

#### 7.4.4.1.3 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. Bevacizumab/atezolizumab, ipilimumab/nivolumab, axitinib/pembrolizumab and avelumab/axitinib can all be recommended instead of VEGF-targeted therapy alone. These options have OS advantages over sunitinib and superseded VEGF-targeted therapy.

**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)
<b>KEYNOTE-426</b> <b>NCT02853331</b> Median follow-up 12.8 mo. [540]	861	PEMBRO + AXI	51	NR	NR	58.8
		SUN	54	8.4 HR: 0.54 (0.29–1.00)	NR HR: 0.58 (0.21–1.59)	31.5
<b>JAVELIN 101</b> <b>NCT02684006</b> [541, 542]	886	AVE + AXI	47	7.0 (5.3–13.8)	NA	46.8 (32.1–61.9)
		SUN	61	4.0 (2.7–5.7) HR 0.57 (0.33–1.00)		21.3 (11.9–33.7)
<b>IMmotion151</b> <b>NCT02420821</b> Median follow-up 13 to 17 mo. [543]	915	ATEZO + BEV	68	8.3 (5.4, 12.9)	21.7 (15.3, NE)	49 (36–1)
		SUN	74	5.3 (3.3, 6.7) HR: 0.52 (0.34–0.79)	15.4 (10.4, 19.5) 0.64 (0.41, 1.01)	14 (7–23)
<b>Checkmate 214</b> <b>NCT02231749</b> Median follow-up of 30 mo. [544]	1096	NIVO + IPI	60	8.4 (5.2–24.0)	31.2 (23.0–NE)	56.7 (43.2–69.4)
		SUN	52	4.9 (4.0–7.0) HR: 0.61 (0.38–0.97)	13.6 (7.7–20.9) HR: 0.55 (0.33–0.90)	19.2 (9.6–32.5)
<b>CheckMate 9ER</b> <b>NCT03141177</b> Median follow-up 16 mo. [545]	651	NIVO + CABO	34	10.3 (5.6–19.4)	NR (22.8–NE)	55.9 (37.9–72.8)
		SUN	41	4.2 (2.6–8.3) HR: 0.42 (0.23–0.74)	19.7 (8.9–29.5) HR: 0.36 (0.17–0.79)	22.0 (10.6–37.6)
<b>CLEAR</b> <b>NCT02811861</b> Median follow-up 27 mo. [527, 546]	712	PEMBRO + LEN	28	11.1	NE	60.7
		SUN	21	5.5 HR: 0.39 (0.18–0.84)	NE HR: 0.91 (0.32–2.58)	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 = progression-free survival; sRCC = sarcomatoid RCC; SUN = sunitinib.

7.4.4.1.3.1 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 ccRCC with sarcomatoid features.	2a



Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

#### 7.4.4.2 Treatment of patients with non-clear-cell metastatic RCC

No phase III trials of patients with non-cc-mRCC have been reported. Expanded access programmes and subset analyses from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Treatment in non-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib, cabozantinib and pembrolizumab [547-550].

##### 7.4.4.2.1 Summary of evidence and recommendation for targeted therapy in non-clear-cell metastatic 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 systematic review of phase II trials and subgroups of patients.	1a

Recommendation	Strength rating
Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak

#### 7.4.4.3 Papillary metastatic RCC

The most common non-cc subtype is papillary RCC (pRCC). There are small single-arm trials for sunitinib and everolimus [550-554]. Both these agents have been widely given in pRCC, but more recent data suggests cabozantinib and other combinations may be preferable [555, 556].

For pRCC new evidence is available from the SWOG PAMMET randomised phase II trial which compared sunitinib to cabozantinib, crizotinib and savolitinib in 152 patients with papillary mRCC [555]. 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 3 or 4 AEs 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 5 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 [556] as first-line treatment for MET-driven tumours defined as chromosome 7 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  $\geq 3$  AEs 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.

Early evidence for TKI + IO based combination is derived from two phase II studies of lenvatinib plus pembrolizumab and cabozantinib and nivolumab. The Keynote-B61 phase II trial investigated lenvatinib plus pembrolizumab administered to 51 patients with pRCC [557]. The primary endpoint of objective response was 52.9%, with a median follow-up of 8.2 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 48% and a PFS of 12.5 (6.3–15.9) months [558]. Indirect comparisons suggest these data compare favourably with those of VEGFR-TKI therapy 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 [559]. Pembrolizumab can be considered in this setting due to the high unmet need; although the VEGFR TKI + IO combination may be preferable.

Patients with non-cc-mRCC should be referred to a clinical trial, where appropriate.

#### 7.4.4.3.1 Summary of evidence and recommendations for targeted therapy in papillary metastatic RCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Savolitinib improved PFS over sunitinib in patients with MET-driven advanced pRCC.	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 RCT.	Weak
Offer pembrolizumab alone or lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak

#### 7.4.4.4 Treatment of patients with rare tumours

##### 7.4.4.4.1 Renal medullary carcinoma

Renal medullary carcinoma is one of the most aggressive RCCs [29, 194] and most patients (~67%) will present with metastatic disease [29, 31]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter, often within a few weeks.

Despite treatment, median OS is thirteen months in the most recent series [35]. 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 [35, 560]. 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 [561, 562]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including TKIs and mTOR inhibitors [35, 169]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [169]. There are no prospective comparisons between different chemotherapy regimens, but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [35, 36]. High-dose-intensity combination of MVAC has also shown efficacy against RMC [563] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine [36]. 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 [561, 562]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

##### 7.4.4.5 Treatment of hereditary RCC

###### 7.4.4.5.1 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-2 $\alpha$  inhibitor, has been approved by the US Food and Drug Administration (FDA, August 2021) 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 [564]. 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  $\geq$  grade 3 AEs, and seven patients (11.5%) discontinued the treatment. In the treatment with pazopanib for VHL only 52% continued with the treatment after 24 weeks [565]. 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) [566].

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, due to the limited safety data currently available.

## **7.5 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.

### **7.5.1 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 [208, 567].

The prognosis of recurrent disease not due to multifocality is poor, despite salvage nephrectomy [567]. 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 [568, 569].

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [570]. 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.

### **7.5.2 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 3–4 disease. Most patients with local recurrence of RCC are diagnosed by either CT/MRI scans as part of the post-operative follow-up [571]. 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 [571–573].

Isolated local recurrence is associated with worse survival [208, 574]. 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 [575–577]. Among these alternatives, surgical resection with negative margins remains the only therapeutic option shown to be associated with improved survival [574]. Open surgery has been successfully reported in studies [578, 579]. 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 [575]. 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) [580].

The 5-year OS with isolated local recurrence was 60% (95% CI: 0.44–0.73) and 10-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: 10-year OS rate 31% (95% CI: 10.2–55.0) vs. 45% (95% CI: 21.5–65.8; HR: 0.26;  $p = 0.0034$ ) [571]. Metastatic progression was observed in 60 patients (58.8%) after surgery [572]. Patient survival can be linked to the type of treatment received, as shown by Marchioni, *et al.* [573]. In a cohort of 96 patients, 45.8% were metastatic at the time of recurrence; 3-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 ( $p < 0.001$ ).

However, minimally-invasive approaches, including standard and hand-assisted laparoscopic- and robotic approaches for the resection of isolated RCC recurrences have been occasionally reported. Recently, Martini *et al.*, published the largest surgical cohort 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 [581]. Ablative therapies including cryoablation, radiofrequency and microwave ablation, may also have a role in managing recurrent RCC patients, but further validation will be needed [582, 583].

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. Johnson *et al.*, published on 51 planned repeat PNs in 47 patients with locally-recurrent disease, reporting a total of 40 peri-operative complications, with temporary urinary extravasation being the most prevalent [584]. Since local recurrences develop early, with a median time interval of 10–20 months after treatment of the primary tumour [585], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up) even though benefit in terms of cancer control has not yet been demonstrated [586].

Adverse prognostic parameters are a short time interval since treatment of the primary tumour (< 3–12 months) [587], sarcomatoid differentiation of the recurrent lesion and incomplete surgical resection [575]. 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 7.2.5. Neoadjuvant and adjuvant therapy). Local recurrence combined with other metastases is treated as a metastatic RCC.

### 7.5.3 **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. FOLLOW-UP IN RCC

### 8.1 Introduction

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

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- distant metastases;
- cardiovascular events.

There is no consensus on follow-up strategies after RCC treatment, with limited evidence suggesting that more frequent post-operative imaging intervals do not provide any improvement for early detection of recurrence that would lead to improved survival [586]. 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 [588].

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 [192, 589, 590] (LE: 4). One study has shown a survival benefit in patients who were followed within a structured surveillance protocol vs. patients who were not [591]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [591].

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 [592]. For patients with low-stage disease but with a Charlson comorbidity index  $\geq 2$ , the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age.

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 [593]. 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 [593, 594].

Recurrence after PN is rare, but early diagnosis is relevant, as the most effective treatment is surgery [578, 595]. Recurrence in the contralateral kidney is rare (1–2%) and can occur late (median 5–6 years) [596] (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.

## 8.2 Which imaging investigations for which patients, and when?

- The sensitivity of chest radiography and US for detection of small RCC metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in comparative studies including histological evaluation [597-599]. Therefore, follow-up for recurrence detection with chest radiography and US are less sensitive [600].
- 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 [116, 130].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors [588].
- 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 [601].

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 [243, 245, 602, 603]. These models, of which the most utilised are summarised in Chapter 6 - Prognosis, have been compared and validated [604] (LE: 2). Using prognostic variables, several stage-based follow-up regimens have been proposed, although, none propose follow-up strategies after ablative therapies [605, 606]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [240]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [607] (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 [608].

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

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yr (**) (***)	> 5 yr (**) (***)
<b>Low risk of recurrence</b>  For ccRCC: Leibovich Score 0–2  For non-ccRCC: pT1a–T1b pNx–0 M0 and histological grade 1 or 2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-
<b>Intermediate risk of recurrence</b>  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
<b>High risk of recurrence</b>  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 [243]. 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 [244].

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

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

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

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable.	4



After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a 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

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 ccRCC, or the University of California Los Angeles integrated staging system for non-ccRCC.	Weak
Intensify follow-up in patients after NSS 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

## 9. REFERENCES

1. Alaghebandan, R., *et al.* A tribute to Prof. Ondrej Hes, MD, PhD (1968-2022). *Mod Pathol*, 2022. <https://pubmed.ncbi.nlm.nih.gov/36333474/>
2. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 2008. 336: 924. <https://pubmed.ncbi.nlm.nih.gov/18436948/>
3. Guyatt, G.H., *et al.* What is “quality of evidence” and why is it important to clinicians? *BMJ*, 2008. 336: 995. <https://pubmed.ncbi.nlm.nih.gov/18456631/>
4. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. Access date January 2023. <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>
5. Guyatt, G.H., *et al.* Going from evidence to recommendations. *BMJ*, 2008. 336: 1049. <https://pubmed.ncbi.nlm.nih.gov/18467413/>
6. Ferlay, J., *et al.* Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*, 2018. 103: 356. <https://pubmed.ncbi.nlm.nih.gov/30100160/>
7. Capitanio, U., *et al.* Epidemiology of Renal Cell Carcinoma. *Eur Urol*, 2019. 75: 74. <https://pubmed.ncbi.nlm.nih.gov/30243799/>
8. Bukavina, L., *et al.* Epidemiology of Renal Cell Carcinoma: 2022 Update. *Eur Urol*, 2022. 82: 529. <https://pubmed.ncbi.nlm.nih.gov/36100483/>
9. Levi, F., *et al.* The changing pattern of kidney cancer incidence and mortality in Europe. *BJU Int*, 2008. 101: 949. <https://pubmed.ncbi.nlm.nih.gov/18241251/>
10. Moch, H., *et al.* The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*, 2016. 70: 93. <https://pubmed.ncbi.nlm.nih.gov/26935559/>
11. Tahbaz, R., *et al.* Prevention of kidney cancer incidence and recurrence: lifestyle, medication and nutrition. *Curr Opin Urol*, 2018. 28: 62. <https://pubmed.ncbi.nlm.nih.gov/29059103/>
12. Huang, J., *et al.* A Global Trend Analysis of Kidney Cancer Incidence and Mortality and Their Associations with Smoking, Alcohol Consumption, and Metabolic Syndrome. *Eur Urol Focus*, 2022. 8: 200. <https://pubmed.ncbi.nlm.nih.gov/33495133/>

13. Gansler, T., *et al.* Prevalence of Cigarette Smoking among Patients with Different Histologic Types of Kidney Cancer. *Cancer Epidemiol Biomarkers Prev*, 2020. 29: 1406.  
<https://pubmed.ncbi.nlm.nih.gov/32357956/>
14. Al-Bayati, O., *et al.* Systematic review of modifiable risk factors for kidney cancer. *Urol Oncol*, 2019. 37: 359.  
<https://pubmed.ncbi.nlm.nih.gov/30685335/>
15. van de Pol, J.A.A., *et al.* Etiologic heterogeneity of clear-cell and papillary renal cell carcinoma in the Netherlands Cohort Study. *Int J Cancer*, 2021. 148: 67.  
<https://pubmed.ncbi.nlm.nih.gov/32638386/>
16. Jay, R., *et al.* Alcohol consumption and the risk of renal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Urol Oncol*, 2017. 35: 117.  
<https://pubmed.ncbi.nlm.nih.gov/28159493/>
17. Wozniak, M.B., *et al.* Alcohol consumption and the risk of renal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer*, 2015. 137: 1953.  
<https://pubmed.ncbi.nlm.nih.gov/25866035/>
18. Antwi, S.O., *et al.* Alcohol consumption, variability in alcohol dehydrogenase genes and risk of renal cell carcinoma. *Int J Cancer*, 2018. 142: 747.  
<https://pubmed.ncbi.nlm.nih.gov/29023769/>
19. Diana, P., *et al.* Screening programs for renal cell carcinoma: a systematic review by the EAU young academic urologists renal cancer working group. *World J Urol*, 2022.  
<https://pubmed.ncbi.nlm.nih.gov/35362747/>
20. Rossi, S.H., *et al.* Epidemiology and screening for renal cancer. *World J Urol*, 2018. 36: 1341.  
<https://pubmed.ncbi.nlm.nih.gov/29610964/>
21. Usher-Smith, J.A., *et al.* The Yorkshire Kidney Screening Trial (YKST): protocol for a feasibility study of adding non-contrast abdominal CT scanning to screen for kidney cancer and other abdominal pathology within a trial of community-based CT screening for lung cancer. *BMJ Open*, 2022. 12: e063018.  
<https://pubmed.ncbi.nlm.nih.gov/36127097/>
22. Akerlund, J., *et al.* Increased risk for renal cell carcinoma in end stage renal disease - a population-based case-control study. *Scand J Urol*, 2021. 55: 209.  
<https://pubmed.ncbi.nlm.nih.gov/33769206/>
23. WHO Classification of Tumours Editorial Board. Urinary and Male Genital Tumours. In: *WHO Classification of Tumours*, 5th Edition, Volume 8. 2022. ISBN 978-92-832-4512-4.
24. Moch, H., *et al.* The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*, 2022. 82: 458.  
<https://pubmed.ncbi.nlm.nih.gov/35853783/>
25. Moch H, H.P, Ulbright TM, Reuter VE, Eds. WHO Classification of Tumours of the Urinary System and Male Genital Organs, eds. WHO. 2016, Lyon, France.  
<https://pubmed.ncbi.nlm.nih.gov/26996659/>
26. An, J., *et al.* Patient Characteristics and Survival Outcomes of Non-Metastatic, Non-Clear Cell Renal Cell Carcinoma. *Front Oncol*, 2021. 11: 786307.  
<https://pubmed.ncbi.nlm.nih.gov/35083144/>
27. Trpkov, K., *et al.* New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. *Mod Pathol*, 2021. 34: 1392.  
<https://pubmed.ncbi.nlm.nih.gov/33664427/>
28. Klatte, T., *et al.* Prognostic factors and prognostic models for renal cell carcinoma: a literature review. *World J Urol*, 2018. 36: 1943.  
<https://pubmed.ncbi.nlm.nih.gov/29713755/>
29. Keegan, K.A., *et al.* Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. *J Urol*, 2012. 188: 391.  
<https://pubmed.ncbi.nlm.nih.gov/22698625/>
30. Pitra, T., *et al.* A Comprehensive Commentary on the Multilocular Cystic Renal Neoplasm of Low Malignant Potential: A Urologist's Perspective. *Cancers (Basel)*, 2022. 14: 831.  
<https://pubmed.ncbi.nlm.nih.gov/35159098/>
31. Hora, M. Re: Philip S. Macklin, Mark E. Sullivan, Charles R. Tapping, *et al.* Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from a UK Tertiary Referral Centre. *Eur Urol* 2019;75:861-7. *Eur Urol*, 2019. 76: e96.  
<https://pubmed.ncbi.nlm.nih.gov/31255420/>

32. Volpe, A., *et al.* Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. *BJU Int*, 2012. 110: 76.  
<https://pubmed.ncbi.nlm.nih.gov/22044519/>
33. Neves, J.B., *et al.* Pattern, timing and predictors of recurrence after surgical resection of chromophobe renal cell carcinoma. *World J Urol*, 2021. 39: 3823.  
<https://pubmed.ncbi.nlm.nih.gov/33851271/>
34. Amin, M.B., *et al.* Collecting duct carcinoma versus renal medullary carcinoma: an appeal for nosologic and biological clarity. *Am J Surg Pathol*, 2014. 38: 871.  
<https://pubmed.ncbi.nlm.nih.gov/24805860/>
35. Shah, A.Y., *et al.* Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. *BJU Int*, 2017. 120: 782.  
<https://pubmed.ncbi.nlm.nih.gov/27860149/>
36. Iacovelli, R., *et al.* Clinical outcome and prognostic factors in renal medullary carcinoma: A pooled analysis from 18 years of medical literature. *Can Urol Assoc J*, 2015. 9: E172.  
<https://pubmed.ncbi.nlm.nih.gov/26085875/>
37. Alvarez, O., *et al.* Renal medullary carcinoma and sickle cell trait: A systematic review. *Pediatr Blood Cancer*, 2015. 62: 1694.  
<https://pubmed.ncbi.nlm.nih.gov/26053587/>
38. Breda, A., *et al.* Clinical and pathological outcomes of renal cell carcinoma (RCC) in native kidneys of patients with end-stage renal disease: a long-term comparative retrospective study with RCC diagnosed in the general population. *World J Urol*, 2015. 33: 1.  
<https://pubmed.ncbi.nlm.nih.gov/24504760/>
39. Bhatt, N.R., *et al.* Dilemmas in diagnosis and natural history of renal oncocytoma and implications for management. *Can Urol Assoc J*, 2015. 9: E709.  
<https://pubmed.ncbi.nlm.nih.gov/26664505/>
40. Wilson, M.P., *et al.* Diagnostic accuracy of 99mTc-sestamibi SPECT/CT for detecting renal oncocytomas and other benign renal lesions: a systematic review and meta-analysis. *Abdom Radiol (NY)*, 2020. 45: 2532.  
<https://pubmed.ncbi.nlm.nih.gov/32193593/>
41. Patel, H.D., *et al.* Surgical histopathology for suspected oncocytoma on renal mass biopsy: a systematic review and meta-analysis. *BJU Int*, 2017. 119: 661.  
<https://pubmed.ncbi.nlm.nih.gov/28058773/>
42. Liu, S., *et al.* Active surveillance is suitable for intermediate term follow-up of renal oncocytoma diagnosed by percutaneous core biopsy. *BJU Int*, 2016. 118 Suppl 3: 30.  
<https://pubmed.ncbi.nlm.nih.gov/27457972/>
43. Kawaguchi, S., *et al.* Most renal oncocytomas appear to grow: observations of tumor kinetics with active surveillance. *J Urol*, 2011. 186: 1218.  
<https://pubmed.ncbi.nlm.nih.gov/21849182/>
44. Richard, P.O., *et al.* Active Surveillance for Renal Neoplasms with Oncocytic Features is Safe. *J Urol*, 2016. 195: 581.  
<https://pubmed.ncbi.nlm.nih.gov/26388501/>
45. Abdessater, M., *et al.* Renal Oncocytoma: An Algorithm for Diagnosis and Management. *Urology*, 2020. 143: 173.  
<https://pubmed.ncbi.nlm.nih.gov/32512107/>
46. Meagher, M.F., *et al.* Comparison of renal functional outcomes of active surveillance and partial nephrectomy in the management of oncocytoma. *World J Urol*, 2021. 39: 1195.  
<https://pubmed.ncbi.nlm.nih.gov/32556559/>
47. Shuch, B., *et al.* Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. *J Clin Oncol*, 2014. 32: 431.  
<https://pubmed.ncbi.nlm.nih.gov/24378414/>
48. Moch, H., *et al.* Morphological clues to the appropriate recognition of hereditary renal neoplasms. *Semin Diagn Pathol*, 2018. 35: 184.  
<https://pubmed.ncbi.nlm.nih.gov/29454577/>
49. Eble JN, S.G., *et al.* Pathology and genetics of tumours of the urinary system and male genital organs. In: *World Health Organization Classification of Tumours*. S.G. Eble JN, Epstein JI, *et al.*, Eds. 2004, IARC: Lyon, France.
50. Srigley, J.R., *et al.* The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol*, 2013. 37: 1469.  
<https://pubmed.ncbi.nlm.nih.gov/24025519/>

51. Pignot, G., *et al.* Survival analysis of 130 patients with papillary renal cell carcinoma: prognostic utility of type 1 and type 2 subclassification. *Urology*, 2007. 69: 230.  
<https://pubmed.ncbi.nlm.nih.gov/17275070/>
52. Przybycin, C.G., *et al.* Hereditary syndromes with associated renal neoplasia: a practical guide to histologic recognition in renal tumor resection specimens. *Adv Anat Pathol*, 2013. 20: 245.  
<https://pubmed.ncbi.nlm.nih.gov/23752087/>
53. Shuch, B., *et al.* The surgical approach to multifocal renal cancers: hereditary syndromes, ipsilateral multifocality, and bilateral tumors. *Urol Clin North Am*, 2012. 39: 133.  
<https://pubmed.ncbi.nlm.nih.gov/22487757/>
54. Bratslavsky, G., *et al.* Salvage partial nephrectomy for hereditary renal cancer: feasibility and outcomes. *J Urol*, 2008. 179: 67.  
<https://pubmed.ncbi.nlm.nih.gov/17997447/>
55. Chahoud, J., *et al.* Evaluation, diagnosis and surveillance of renal masses in the setting of VHL disease. *World J Urol*, 2021. 39: 2409.  
<https://pubmed.ncbi.nlm.nih.gov/32936333/>
56. VHL Alliance. VHLA Suggested Active Surveillance Guidelines. 2020. Access date January 2023.  
<https://www.vhl.org/>
57. Nielsen, S.M., *et al.* Von Hippel-Lindau Disease: Genetics and Role of Genetic Counseling in a Multiple Neoplasia Syndrome. *J Clin Oncol*, 2016. 34: 2172.  
<https://pubmed.ncbi.nlm.nih.gov/27114602/>
58. Forde, C., *et al.* Hereditary Leiomyomatosis and Renal Cell Cancer: Clinical, Molecular, and Screening Features in a Cohort of 185 Affected Individuals. *Eur Urol Oncol*, 2020. 3: 764.  
<https://pubmed.ncbi.nlm.nih.gov/31831373/>
59. Kauffman, E.C., *et al.* Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. *Nat Rev Urol*, 2014. 11: 465.  
<https://pubmed.ncbi.nlm.nih.gov/25048860/>
60. Jonasch, E., *et al.* Phase II study of the oral HIF-2 inhibitor MK-6482 for Von Hippel-Lindau disease-associated renal cell carcinoma. *J Clin Oncol*, 2020. 38: 5003.  
[https://ascopubs.org/doi/10.1200/JCO.2020.38.15\\_suppl.5003](https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.5003)
61. Bhatt, J.R., *et al.* Natural History of Renal Angiomyolipoma (AML): Most Patients with Large AMLs >4cm Can Be Offered Active Surveillance as an Initial Management Strategy. *Eur Urol*, 2016. 70: 85.  
<https://pubmed.ncbi.nlm.nih.gov/26873836/>
62. Fittschen, A., *et al.* Prevalence of sporadic renal angiomyolipoma: a retrospective analysis of 61,389 in- and out-patients. *Abdom Imaging*, 2014. 39: 1009.  
<https://pubmed.ncbi.nlm.nih.gov/24705668/>
63. Nese, N., *et al.* Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: A clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. *Am J Surg Pathol*, 2011. 35: 161.  
<https://pubmed.ncbi.nlm.nih.gov/21263237/>
64. Tsai, H.Y., *et al.* Clinicopathologic analysis of renal epithelioid angiomyolipoma: Consecutively excised 23 cases. *Kaohsiung J Med Sci*, 2019. 35: 33.  
<https://pubmed.ncbi.nlm.nih.gov/30844148/>
65. Fernández-Pello, S., *et al.* Management of Sporadic Renal Angiomyolipomas: A Systematic Review of Available Evidence to Guide Recommendations from the European Association of Urology Renal Cell Carcinoma Guidelines Panel. *Eur Urol Oncol*, 2020. 3: 57.  
<https://pubmed.ncbi.nlm.nih.gov/31171501/>
66. Nelson, C.P., *et al.* Contemporary diagnosis and management of renal angiomyolipoma. *J Urol*, 2002. 168: 1315.  
<https://pubmed.ncbi.nlm.nih.gov/12352384/>
67. Bissler, J.J., *et al.* Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangiomyomatosis: extension of a randomized controlled trial. *Nephrol Dial Transplant*, 2016. 31: 111.  
<https://pubmed.ncbi.nlm.nih.gov/26156073/>
68. Bissler, J.J., *et al.* Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. *PLoS One*, 2017. 12: e0180939.  
<https://pubmed.ncbi.nlm.nih.gov/28792952/>
69. Geynisman, D.M., *et al.* Sporadic Angiomyolipomas Growth Kinetics While on Everolimus: Results of a Phase II Trial. *J Urol*, 2020. 204: 531.  
<https://pubmed.ncbi.nlm.nih.gov/32250730/>

70. Abern, M.R., *et al.* Characteristics and outcomes of tumors arising from the distal nephron. *Urology*, 2012. 80: 140.  
<https://pubmed.ncbi.nlm.nih.gov/22626576/>
71. Husillos, A., *et al.* [Collecting duct renal cell carcinoma]. *Actas Urol Esp*, 2011. 35: 368.  
<https://pubmed.ncbi.nlm.nih.gov/21450372/>
72. Cimadamore, A., *et al.* Towards a new WHO classification of renal cell tumor: what the clinician needs to know-a narrative review. *Transl Androl Urol*, 2021. 10: 1506.  
<https://pubmed.ncbi.nlm.nih.gov/33850785/>
73. Schoots, I.G., *et al.* Bosniak Classification for Complex Renal Cysts Reevaluated: A Systematic Review. *J Urol*, 2017. 198: 12.  
<https://pubmed.ncbi.nlm.nih.gov/28286071/>
74. Tse, J.R., *et al.* Prevalence of Malignancy and Histopathological Association of Bosniak Classification, Version 2019 Class III and IV Cystic Renal Masses. *J Urol*, 2021. 205: 1031.  
<https://pubmed.ncbi.nlm.nih.gov/33085925/>
75. Defortescu, G., *et al.* Diagnostic performance of contrast-enhanced ultrasonography and magnetic resonance imaging for the assessment of complex renal cysts: A prospective study. *Int J Urol*, 2017. 24: 184.  
<https://pubmed.ncbi.nlm.nih.gov/28147450/>
76. Silverman, S.G., *et al.* Bosniak Classification of Cystic Renal Masses, Version 2019: An Update Proposal and Needs Assessment. *Radiology*, 2019. 292: 475.  
<https://pubmed.ncbi.nlm.nih.gov/31210616/>
77. Cantisani, V., *et al.* EFSUMB 2020 Proposal for a Contrast-Enhanced Ultrasound-Adapted Bosniak Cyst Categorization - Position Statement. *Ultraschall Med*, 2021. 42: 154.  
<https://pubmed.ncbi.nlm.nih.gov/33307594/>
78. Donin, N.M., *et al.* Clinicopathologic outcomes of cystic renal cell carcinoma. *Clin Genitourin Cancer*, 2015. 13: 67.  
<https://pubmed.ncbi.nlm.nih.gov/25088469/>
79. Park, J.J., *et al.* Postoperative Outcome of Cystic Renal Cell Carcinoma Defined on Preoperative Imaging: A Retrospective Study. *J Urol*, 2017. 197: 991.  
<https://pubmed.ncbi.nlm.nih.gov/27765694/>
80. Chandrasekar, T., *et al.* Natural History of Complex Renal Cysts: Clinical Evidence Supporting Active Surveillance. *J Urol*, 2018. 199: 633.  
<https://pubmed.ncbi.nlm.nih.gov/28941915/>
81. Nouhaud, F.X., *et al.* Contemporary assessment of the correlation between Bosniak classification and histological characteristics of surgically removed atypical renal cysts (UroCCR-12 study). *World J Urol*, 2018. 36: 1643.  
<https://pubmed.ncbi.nlm.nih.gov/29730837/>
82. Sobin L.H., G.M., Wittekind C. (eds). *TNM classification of malignant tumors, UICC International Union Against Cancer. Vol. 7th edn. 2009.*  
<https://www.ncbi.nlm.nih.gov/nlmcatalog/101511218>
83. Kim, S.P., *et al.* Independent validation of the 2010 American Joint Committee on Cancer TNM classification for renal cell carcinoma: results from a large, single institution cohort. *J Urol*, 2011. 185: 2035.  
<https://pubmed.ncbi.nlm.nih.gov/21496854/>
84. Novara, G., *et al.* Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? *Eur Urol*, 2010. 58: 588.  
<https://pubmed.ncbi.nlm.nih.gov/20674150/>
85. Waalkes, S., *et al.* Is there a need to further subclassify pT2 renal cell cancers as implemented by the revised 7th TNM version? *Eur Urol*, 2011. 59: 258.  
<https://pubmed.ncbi.nlm.nih.gov/21030143/>
86. Bertini, R., *et al.* Renal sinus fat invasion in pT3a clear cell renal cell carcinoma affects outcomes of patients without nodal involvement or distant metastases. *J Urol*, 2009. 181: 2027.  
<https://pubmed.ncbi.nlm.nih.gov/19286201/>
87. Poon, S.A., *et al.* Invasion of renal sinus fat is not an independent predictor of survival in pT3a renal cell carcinoma. *BJU Int*, 2009. 103: 1622.  
<https://pubmed.ncbi.nlm.nih.gov/19154464/>
88. Bedke, J., *et al.* Perinephric and renal sinus fat infiltration in pT3a renal cell carcinoma: possible prognostic differences. *BJU Int*, 2009. 103: 1349.  
<https://pubmed.ncbi.nlm.nih.gov/19076147/>



89. Izumi, K., *et al.* Contact with renal sinus is associated with poor prognosis in surgically treated pT1 clear cell renal cell carcinoma. *Int J Urol*, 2020. 27: 657.  
<https://pubmed.ncbi.nlm.nih.gov/32458519/>
90. Heidenreich, A., *et al.* Preoperative imaging in renal cell cancer. *World J Urol*, 2004. 22: 307.  
<https://pubmed.ncbi.nlm.nih.gov/15290202/>
91. Sheth, S., *et al.* Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. *Radiographics*, 2001. 21 Spec No: S237.  
<https://pubmed.ncbi.nlm.nih.gov/11598260/>
92. Capitanio, U., *et al.* A Renewal of the TNM Staging System for Patients with Renal Cancer To Comply with Current Decision-making: Proposal from the European Association of Urology Guidelines Panel. *Eur Urol*, 2022. 1: 3.  
<https://pubmed.ncbi.nlm.nih.gov/36253306/>
93. Amin, M.B., *et al.* The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*, 2017. 67: 93.  
<https://pubmed.ncbi.nlm.nih.gov/28094848/>
94. Klatte, T., *et al.* A Literature Review of Renal Surgical Anatomy and Surgical Strategies for Partial Nephrectomy. *Eur Urol*, 2015. 68: 980.  
<https://pubmed.ncbi.nlm.nih.gov/25911061/>
95. Spaliviero, M., *et al.* An Arterial Based Complexity (ABC) Scoring System to Assess the Morbidity Profile of Partial Nephrectomy. *Eur Urol*, 2016. 69: 72.  
<https://pubmed.ncbi.nlm.nih.gov/26298208/>
96. Hakky, T.S., *et al.* Zonal NePhRO scoring system: a superior renal tumor complexity classification model. *Clin Genitourin Cancer*, 2014. 12: e13.  
<https://pubmed.ncbi.nlm.nih.gov/24120084/>
97. Jayson, M., *et al.* Increased incidence of serendipitously discovered renal cell carcinoma. *Urology*, 1998. 51: 203.  
<https://pubmed.ncbi.nlm.nih.gov/9495698/>
98. Vasudev, N.S., *et al.* Challenges of early renal cancer detection: symptom patterns and incidental diagnosis rate in a multicentre prospective UK cohort of patients presenting with suspected renal cancer. *BMJ Open*, 2020. 10: e035938.  
<https://pubmed.ncbi.nlm.nih.gov/32398335/>
99. Patard, J.J., *et al.* Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur Urol*, 2003. 44: 226.  
<https://pubmed.ncbi.nlm.nih.gov/12875943/>
100. Lee, C.T., *et al.* Mode of presentation of renal cell carcinoma provides prognostic information. *Urol Oncol*, 2002. 7: 135.  
<https://pubmed.ncbi.nlm.nih.gov/12474528/>
101. Sacco, E., *et al.* Paraneoplastic syndromes in patients with urological malignancies. *Urol Int*, 2009. 83: 1.  
<https://pubmed.ncbi.nlm.nih.gov/19641351/>
102. Kim, H.L., *et al.* Paraneoplastic signs and symptoms of renal cell carcinoma: implications for prognosis. *J Urol*, 2003. 170: 1742.  
<https://pubmed.ncbi.nlm.nih.gov/14532767/>
103. Magera, J.S., Jr., *et al.* Association of abnormal preoperative laboratory values with survival after radical nephrectomy for clinically confined clear cell renal cell carcinoma. *Urology*, 2008. 71: 278.  
<https://pubmed.ncbi.nlm.nih.gov/18308103/>
104. Uzzo, R.G., *et al.* Nephron sparing surgery for renal tumors: indications, techniques and outcomes. *J Urol*, 2001. 166: 6.  
<https://pubmed.ncbi.nlm.nih.gov/11435813/>
105. Huang, W.C., *et al.* Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol*, 2006. 7: 735.  
<https://pubmed.ncbi.nlm.nih.gov/16945768/>
106. Israel, G.M., *et al.* How I do it: evaluating renal masses. *Radiology*, 2005. 236: 441.  
<https://pubmed.ncbi.nlm.nih.gov/16040900/>
107. Israel, G.M., *et al.* Pitfalls in renal mass evaluation and how to avoid them. *Radiographics*, 2008. 28: 1325.  
<https://pubmed.ncbi.nlm.nih.gov/18794310/>



108. Choudhary, S., *et al.* Renal oncocytoma: CT features cannot reliably distinguish oncocytoma from other renal neoplasms. *Clin Radiol*, 2009. 64: 517.  
<https://pubmed.ncbi.nlm.nih.gov/19348848/>
109. Rosenkrantz, A.B., *et al.* MRI features of renal oncocytoma and chromophobe renal cell carcinoma. *AJR Am J Roentgenol*, 2010. 195: W421.  
<https://pubmed.ncbi.nlm.nih.gov/21098174/>
110. Hindman, N., *et al.* Angiomyolipoma with minimal fat: can it be differentiated from clear cell renal cell carcinoma by using standard MR techniques? *Radiology*, 2012. 265: 468.  
<https://pubmed.ncbi.nlm.nih.gov/23012463/>
111. Pedrosa, I., *et al.* MR imaging of renal masses: correlation with findings at surgery and pathologic analysis. *Radiographics*, 2008. 28: 985.  
<https://pubmed.ncbi.nlm.nih.gov/18635625/>
112. Yamashita Y AA, S.K. The therapeutic value of lymph node dissection for renal cell carcinoma. *Nishinihon J Urol*, 1989: 777.  
<https://www.frontiersin.org/articles/10.3389/fonc.2021.790381/full>
113. Gong, I.H., *et al.* Relationship among total kidney volume, renal function and age. *J Urol*, 2012. 187: 344.  
<https://pubmed.ncbi.nlm.nih.gov/22099987/>
114. Ferda, J., *et al.* Assessment of the kidney tumor vascular supply by two-phase MDCT-angiography. *Eur J Radiol*, 2007. 62: 295.  
<https://pubmed.ncbi.nlm.nih.gov/17324548/>
115. Shao, P., *et al.* Precise segmental renal artery clamping under the guidance of dual-source computed tomography angiography during laparoscopic partial nephrectomy. *Eur Urol*, 2012. 62: 1001.  
<https://pubmed.ncbi.nlm.nih.gov/22695243/>
116. Vogel, C., *et al.* Imaging in Suspected Renal-Cell Carcinoma: Systematic Review. *Clin Genitourin Cancer*, 2019. 17: e345.  
<https://pubmed.ncbi.nlm.nih.gov/30528378/>
117. Fan, L., *et al.* Diagnostic efficacy of contrast-enhanced ultrasonography in solid renal parenchymal lesions with maximum diameters of 5 cm. *J Ultrasound Med*, 2008. 27: 875.  
<https://pubmed.ncbi.nlm.nih.gov/18499847/>
118. Correas, J.M., *et al.* [Guidelines for contrast enhanced ultrasound (CEUS)--update 2008]. *J Radiol*, 2009. 90: 123.  
<https://pubmed.ncbi.nlm.nih.gov/19212280/>
119. Mitterberger, M., *et al.* Contrast-enhanced ultrasound for diagnosis of prostate cancer and kidney lesions. *Eur J Radiol*, 2007. 64: 231.  
<https://pubmed.ncbi.nlm.nih.gov/17881175/>
120. Janus, C.L., *et al.* Comparison of MRI and CT for study of renal and perirenal masses. *Crit Rev Diagn Imaging*, 1991. 32: 69.  
<https://pubmed.ncbi.nlm.nih.gov/1863349/>
121. Mueller-Lisse, U.G., *et al.* Imaging of advanced renal cell carcinoma. *World J Urol*, 2010. 28: 253.  
<https://pubmed.ncbi.nlm.nih.gov/20458484/>
122. Kabala, J.E., *et al.* Magnetic resonance imaging in the staging of renal cell carcinoma. *Br J Radiol*, 1991. 64: 683.  
<https://pubmed.ncbi.nlm.nih.gov/1884119/>
123. Hallscheidt, P.J., *et al.* Preoperative staging of renal cell carcinoma with inferior vena cava thrombus using multidetector CT and MRI: prospective study with histopathological correlation. *J Comput Assist Tomogr*, 2005. 29: 64.  
<https://pubmed.ncbi.nlm.nih.gov/15665685/>
124. Putra, L.G., *et al.* Improved assessment of renal lesions in pregnancy with magnetic resonance imaging. *Urology*, 2009. 74: 535.  
<https://pubmed.ncbi.nlm.nih.gov/19604560/>
125. Giannarini, G., *et al.* Potential and limitations of diffusion-weighted magnetic resonance imaging in kidney, prostate, and bladder cancer including pelvic lymph node staging: a critical analysis of the literature. *Eur Urol*, 2012. 61: 326.  
<https://pubmed.ncbi.nlm.nih.gov/22000497/>
126. Johnson, B.A., *et al.* Diagnostic performance of prospectively assigned clear cell Likelihood scores (ccLS) in small renal masses at multiparametric magnetic resonance imaging. *Urol Oncol*, 2019. 37: 941.  
<https://pubmed.ncbi.nlm.nih.gov/31540830/>

127. Steinberg, R.L., *et al.* Prospective performance of clear cell likelihood scores (ccLS) in renal masses evaluated with multiparametric magnetic resonance imaging. *Eur Radiol*, 2021. 31: 314.  
<https://pubmed.ncbi.nlm.nih.gov/32770377/>
128. Capogrosso, P., *et al.* Follow-up After Treatment for Renal Cell Carcinoma: The Evidence Beyond the Guidelines. *Eur Urol Focus*, 2016. 1: 272.  
<https://pubmed.ncbi.nlm.nih.gov/28723399/>
129. Furrer, M.A., *et al.* Comparison of the Diagnostic Performance of Contrast-enhanced Ultrasound with That of Contrast-enhanced Computed Tomography and Contrast-enhanced Magnetic Resonance Imaging in the Evaluation of Renal Masses: A Systematic Review and Meta-analysis. *Eur Urol Oncol*, 2020. 3: 464.  
<https://pubmed.ncbi.nlm.nih.gov/31570270/>
130. Park, J.W., *et al.* Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. *BJU Int*, 2009. 103: 615.  
<https://pubmed.ncbi.nlm.nih.gov/19007371/>
131. Bechtold, R.E., *et al.* Imaging approach to staging of renal cell carcinoma. *Urol Clin North Am*, 1997. 24: 507.  
<https://pubmed.ncbi.nlm.nih.gov/9275976/>
132. Miles, K.A., *et al.* CT staging of renal carcinoma: a prospective comparison of three dynamic computed tomography techniques. *Eur J Radiol*, 1991. 13: 37.  
<https://pubmed.ncbi.nlm.nih.gov/1889427/>
133. Lim, D.J., *et al.* Computerized tomography in the preoperative staging for pulmonary metastases in patients with renal cell carcinoma. *J Urol*, 1993. 150: 1112.  
<https://pubmed.ncbi.nlm.nih.gov/8371366/>
134. Larcher, A., *et al.* When to perform preoperative chest computed tomography for renal cancer staging. *BJU Int*, 2017. 120: 490.  
<https://pubmed.ncbi.nlm.nih.gov/27684653/>
135. Voss, J., *et al.* Chest computed tomography for staging renal tumours: validation and simplification of a risk prediction model from a large contemporary retrospective cohort. *BJU Int*, 2020. 125: 561.  
<https://pubmed.ncbi.nlm.nih.gov/31955483/>
136. Marshall, M.E., *et al.* Low incidence of asymptomatic brain metastases in patients with renal cell carcinoma. *Urology*, 1990. 36: 300.  
<https://pubmed.ncbi.nlm.nih.gov/2219605/>
137. Koga, S., *et al.* The diagnostic value of bone scan in patients with renal cell carcinoma. *J Urol*, 2001. 166: 2126.  
<https://pubmed.ncbi.nlm.nih.gov/11696720/>
138. Henriksson, C., *et al.* Skeletal metastases in 102 patients evaluated before surgery for renal cell carcinoma. *Scand J Urol Nephrol*, 1992. 26: 363.  
<https://pubmed.ncbi.nlm.nih.gov/1292074/>
139. Seaman, E., *et al.* Association of radionuclide bone scan and serum alkaline phosphatase in patients with metastatic renal cell carcinoma. *Urology*, 1996. 48: 692.  
<https://pubmed.ncbi.nlm.nih.gov/8911510/>
140. Beuselink, B., *et al.* Whole-body diffusion-weighted magnetic resonance imaging for the detection of bone metastases and their prognostic impact in metastatic renal cell carcinoma patients treated with angiogenesis inhibitors. *Acta Oncol*, 2020. 59: 818.  
<https://pubmed.ncbi.nlm.nih.gov/32297532/>
141. Kotecha, R.R., *et al.* Prognosis of Incidental Brain Metastases in Patients With Advanced Renal Cell Carcinoma. *J Natl Compr Canc Netw*, 2021. 19: 432.  
<https://pubmed.ncbi.nlm.nih.gov/33578374/>
142. Warren, K.S., *et al.* The Bosniak classification of renal cystic masses. *BJU Int*, 2005. 95: 939.  
<https://pubmed.ncbi.nlm.nih.gov/15839908/>
143. Bosniak, M.A. The use of the Bosniak classification system for renal cysts and cystic tumors. *J Urol*, 1997. 157: 1852.  
<https://pubmed.ncbi.nlm.nih.gov/9112545/>
144. Richard, P.O., *et al.* Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience. *Eur Urol*, 2015. 68: 1007.  
<https://pubmed.ncbi.nlm.nih.gov/25900781/>
145. Shannon, B.A., *et al.* The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. *J Urol*, 2008. 180: 1257.  
<https://pubmed.ncbi.nlm.nih.gov/18707712/>

146. Maturen, K.E., *et al.* Renal mass core biopsy: accuracy and impact on clinical management. *AJR Am J Roentgenol*, 2007. 188: 563.  
<https://pubmed.ncbi.nlm.nih.gov/17242269/>
147. Volpe, A., *et al.* Contemporary results of percutaneous biopsy of 100 small renal masses: a single center experience. *J Urol*, 2008. 180: 2333.  
<https://pubmed.ncbi.nlm.nih.gov/18930274/>
148. Veltri, A., *et al.* Diagnostic accuracy and clinical impact of imaging-guided needle biopsy of renal masses. Retrospective analysis on 150 cases. *Eur Radiol*, 2011. 21: 393.  
<https://pubmed.ncbi.nlm.nih.gov/20809129/>
149. Abel, E.J., *et al.* Percutaneous biopsy of primary tumor in metastatic renal cell carcinoma to predict high risk pathological features: comparison with nephrectomy assessment. *J Urol*, 2010. 184: 1877.  
<https://pubmed.ncbi.nlm.nih.gov/20850148/>
150. Richard, P.O., *et al.* Is Routine Renal Tumor Biopsy Associated with Lower Rates of Benign Histology following Nephrectomy for Small Renal Masses? *J Urol*, 2018. 200: 731.  
<https://pubmed.ncbi.nlm.nih.gov/29653161/>
151. Amaral, B.S., *et al.* Renal Tumor Biopsy: Rationale to Avoid Surgery in Small Renal Masses. *Curr Urol Rep*, 2021. 22: 46.  
<https://pubmed.ncbi.nlm.nih.gov/34487255/>
152. Marconi, L., *et al.* Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumour Biopsy. *Eur Urol*, 2016. 69: 660.  
<https://pubmed.ncbi.nlm.nih.gov/26323946/>
153. Leveridge, M.J., *et al.* Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. *Eur Urol*, 2011. 60: 578.  
<https://pubmed.ncbi.nlm.nih.gov/21704449/>
154. Breda, A., *et al.* Comparison of accuracy of 14-, 18- and 20-G needles in ex-vivo renal mass biopsy: a prospective, blinded study. *BJU Int*, 2010. 105: 940.  
<https://pubmed.ncbi.nlm.nih.gov/19888984/>
155. Cate, F., *et al.* Core Needle Biopsy and Fine Needle Aspiration Alone or in Combination: Diagnostic Accuracy and Impact on Management of Renal Masses. *J Urol*, 2017. 197: 1396.  
<https://pubmed.ncbi.nlm.nih.gov/28093293/>
156. Yang, C.S., *et al.* Percutaneous biopsy of the renal mass: FNA or core needle biopsy? *Cancer Cytopathol*, 2017. 125: 407.  
<https://pubmed.ncbi.nlm.nih.gov/28334518/>
157. Motzer, R.J., *et al.* Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2014. 32: 2765.  
<https://pubmed.ncbi.nlm.nih.gov/25049330/>
158. Wood, B.J., *et al.* Imaging guided biopsy of renal masses: indications, accuracy and impact on clinical management. *J Urol*, 1999. 161: 1470.  
<https://pubmed.ncbi.nlm.nih.gov/10210375/>
159. Somani, B.K., *et al.* Image-guided biopsy-diagnosed renal cell carcinoma: critical appraisal of technique and long-term follow-up. *Eur Urol*, 2007. 51: 1289.  
<https://pubmed.ncbi.nlm.nih.gov/17081679/>
160. Vasudevan, A., *et al.* Incidental renal tumours: the frequency of benign lesions and the role of preoperative core biopsy. *BJU Int*, 2006. 97: 946.  
<https://pubmed.ncbi.nlm.nih.gov/16643475/>
161. Neuzillet, Y., *et al.* Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 cm) renal masses. *J Urol*, 2004. 171: 1802.  
<https://pubmed.ncbi.nlm.nih.gov/15076280/>
162. Schmidbauer, J., *et al.* Diagnostic accuracy of computed tomography-guided percutaneous biopsy of renal masses. *Eur Urol*, 2008. 53: 1003.  
<https://pubmed.ncbi.nlm.nih.gov/18061339/>
163. Wunderlich, H., *et al.* The accuracy of 250 fine needle biopsies of renal tumors. *J Urol*, 2005. 174: 44.  
<https://pubmed.ncbi.nlm.nih.gov/15947574/>
164. Abel, E.J., *et al.* Multi-Quadrant Biopsy Technique Improves Diagnostic Ability in Large Heterogeneous Renal Masses. *J Urol*, 2015. 194: 886.  
<https://pubmed.ncbi.nlm.nih.gov/25837535/>
165. Macklin, P.S., *et al.* Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from a UK Tertiary Referral Centre. *Eur Urol*, 2019. 75: 861.  
<https://pubmed.ncbi.nlm.nih.gov/30591353/>

166. Cooper, S., *et al.* Diagnostic Yield and Complication Rate in Percutaneous Needle Biopsy of Renal Hilar Masses With Comparison With Renal Cortical Mass Biopsies in a Cohort of 195 Patients. *AJR Am J Roentgenol*, 2019. 212: 570.  
<https://pubmed.ncbi.nlm.nih.gov/30645159/>
167. Bratslavsky, G., *et al.* Genetic risk assessment for hereditary renal cell carcinoma: Clinical consensus statement. *Cancer*, 2021. 127: 3957.  
<https://pubmed.ncbi.nlm.nih.gov/34343338/>
168. Mucci, L.A., *et al.* Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA*, 2016. 315: 68.  
<https://pubmed.ncbi.nlm.nih.gov/26746459/>
169. Beckermann, K.E., *et al.* Renal Medullary Carcinoma: Establishing Standards in Practice. *J Oncol Pract*, 2017. 13: 414.  
<https://pubmed.ncbi.nlm.nih.gov/28697319/>
170. Kickuth, R., *et al.* Interventional management of hypervascular osseous metastasis: role of embolotherapy before orthopedic tumor resection and bone stabilization. *AJR Am J Roentgenol*, 2008. 191: W240.  
<https://pubmed.ncbi.nlm.nih.gov/19020210/>
171. Forauer, A.R., *et al.* Selective palliative transcatheter embolization of bony metastases from renal cell carcinoma. *Acta Oncol*, 2007. 46: 1012.  
<https://pubmed.ncbi.nlm.nih.gov/17851849/>
172. Appleman, L.J., *et al.* Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810). *J Clin Oncol*, 2019. 37: 4502.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15\\_suppl.4502](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4502)
173. Procopio, G., *et al.* Sorafenib Versus Observation Following Radical Metastasectomy for Clear-cell Renal Cell Carcinoma: Results from the Phase 2 Randomized Open-label RESORT Study. *Eur Urol Oncol*, 2019. 2: 699.  
<https://pubmed.ncbi.nlm.nih.gov/31542243/>
174. Amato, R.J. Chemotherapy for renal cell carcinoma. *Semin Oncol*, 2000. 27: 177.  
<https://pubmed.ncbi.nlm.nih.gov/10768596/>
175. Negrier, S., *et al.* Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer*, 2007. 110: 2468.  
<https://pubmed.ncbi.nlm.nih.gov/17932908/>
176. Motzer, R.J., *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*, 2007. 356: 115.  
<https://pubmed.ncbi.nlm.nih.gov/17215529/>
177. Carlo, M.I., *et al.* Familial Kidney Cancer: Implications of New Syndromes and Molecular Insights. *Eur Urol*, 2019. 76: 754.  
<https://pubmed.ncbi.nlm.nih.gov/31326218/>
178. Amin, M.B., *et al.*, *AJCC Cancer Staging Manual*. 8th ed. 2017.  
<https://link.springer.com/book/9783319406176>
179. Bierley, J.D., *et al.*, *UICC TNM classification of malignant tumours*. 2017, Chichester, UK.  
<https://www.uicc.org/resources/tnm-classification-malignant-tumours-8th-edition>
180. Sun, M., *et al.* Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. *Eur Urol*, 2011. 60: 644.  
<https://pubmed.ncbi.nlm.nih.gov/21741163/>
181. Zhang, L., *et al.* Tumor necrosis as a prognostic variable for the clinical outcome in patients with renal cell carcinoma: a systematic review and meta-analysis. *BMC Cancer*, 2018. 18: 870.  
<https://pubmed.ncbi.nlm.nih.gov/30176824/>
182. Fuhrman, S.A., *et al.* Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol*, 1982. 6: 655.  
<https://pubmed.ncbi.nlm.nih.gov/7180965/>
183. Delahunt, B., *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol*, 2013. 37: 1490.  
<https://pubmed.ncbi.nlm.nih.gov/24025520/>
184. Paner, G.P., *et al.* Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol*, 2018. 73: 560.  
<https://pubmed.ncbi.nlm.nih.gov/29325693/>

185. Dagher, J., *et al.* Clear cell renal cell carcinoma: validation of World Health Organization/International Society of Urological Pathology grading. *Histopathology*, 2017. 71: 918.  
<https://pubmed.ncbi.nlm.nih.gov/28718911/>
186. Leibovich, B.C., *et al.* Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. *J Urol*, 2010. 183: 1309.  
<https://pubmed.ncbi.nlm.nih.gov/20171681/>
187. Adibi, M., *et al.* Percentage of sarcomatoid component as a prognostic indicator for survival in renal cell carcinoma with sarcomatoid dedifferentiation. *Urol Oncol*, 2015. 33: 427.e17.  
<https://pubmed.ncbi.nlm.nih.gov/26004164/>
188. Kim, T., *et al.* Using percentage of sarcomatoid differentiation as a prognostic factor in renal cell carcinoma. *Clin Genitourin Cancer*, 2015. 13: 225.  
<https://pubmed.ncbi.nlm.nih.gov/25544725/>
189. Ohashi, R., *et al.* Multi-institutional re-evaluation of prognostic factors in chromophobe renal cell carcinoma: proposal of a novel two-tiered grading scheme. *Virchows Arch*, 2020. 476: 409.  
<https://pubmed.ncbi.nlm.nih.gov/31760491/>
190. Cheville, J.C., *et al.* Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol*, 2003. 27: 612.  
<https://pubmed.ncbi.nlm.nih.gov/12717246/>
191. Patard, J.J., *et al.* Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol*, 2005. 23: 2763.  
<https://pubmed.ncbi.nlm.nih.gov/15837991/>
192. Capitanio, U., *et al.* A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. *BJU Int*, 2009. 103: 1496.  
<https://pubmed.ncbi.nlm.nih.gov/19076149/>
193. Wagener, N., *et al.* Outcome of papillary versus clear cell renal cell carcinoma varies significantly in non-metastatic disease. *PLoS One*, 2017. 12: e0184173.  
<https://pubmed.ncbi.nlm.nih.gov/28934212/>
194. Linehan, W.M., *et al.* Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med*, 2016. 374: 135.  
<https://pubmed.ncbi.nlm.nih.gov/26536169/>
195. Wong, E.C.L., *et al.* Morphologic subtyping as a prognostic predictor for survival in papillary renal cell carcinoma: Type 1 vs. type 2. *Urol Oncol*, 2019. 37: 721.  
<https://pubmed.ncbi.nlm.nih.gov/31176614/>
196. Klatte, T., *et al.* The VENUSS prognostic model to predict disease recurrence following surgery for non-metastatic papillary renal cell carcinoma: Development and evaluation using the ASSURE prospective clinical trial cohort. *BMC Medicine*, 2019. 17: 182.  
<https://pubmed.ncbi.nlm.nih.gov/31578141/>
197. Deng, J., *et al.* A comparison of the prognosis of papillary and clear cell renal cell carcinoma: Evidence from a meta-analysis. *Medicine (Baltimore)*, 2019. 98: e16309.  
<https://pubmed.ncbi.nlm.nih.gov/31277173/>
198. Yang, C., *et al.* High WHO/ISUP Grade and Unfavorable Architecture, Rather Than Typing of Papillary Renal Cell Carcinoma, May Be Associated With Worse Prognosis. *Am J Surg Pathol*, 2020. 44: 582.  
<https://pubmed.ncbi.nlm.nih.gov/32101890/>
199. Klatte, T., *et al.* Renal cell carcinoma associated with transcription factor E3 expression and Xp11.2 translocation: incidence, characteristics, and prognosis. *Am J Clin Pathol*, 2012. 137: 761.  
<https://pubmed.ncbi.nlm.nih.gov/22523215/>
200. Linehan, W.M., *et al.* Genetic basis of cancer of the kidney: disease-specific approaches to therapy. *Clin Cancer Res*, 2004. 10: 6282S.  
<https://pubmed.ncbi.nlm.nih.gov/15448018/>
201. Yang, X.J., *et al.* A molecular classification of papillary renal cell carcinoma. *Cancer Res*, 2005. 65: 5628.  
<https://pubmed.ncbi.nlm.nih.gov/15994935/>
202. Furge, K.A., *et al.* Identification of deregulated oncogenic pathways in renal cell carcinoma: an integrated oncogenomic approach based on gene expression profiling. *Oncogene*, 2007. 26: 1346.  
<https://pubmed.ncbi.nlm.nih.gov/17322920/>
203. Boissier, R., *et al.* Long-term oncological outcomes of cystic renal cell carcinoma according to the Bosniak classification. *International Urology and Nephrology*, 2019. 51: 951.  
<https://pubmed.ncbi.nlm.nih.gov/30977021/>



204. Wahlgren, T., *et al.* Treatment and overall survival in renal cell carcinoma: a Swedish population-based study (2000-2008). *Br J Cancer*, 2013. 108: 1541.  
<https://pubmed.ncbi.nlm.nih.gov/23531701/>
205. Li, P., *et al.* Survival among patients with advanced renal cell carcinoma in the pretargeted versus targeted therapy eras. *Cancer Med*, 2016. 5: 169.  
<https://pubmed.ncbi.nlm.nih.gov/26645975/>
206. Golijanin, B., *et al.* The natural history of renal cell carcinoma with isolated lymph node metastases following surgical resection from 2006 to 2013. *Urol Oncol*, 2019. 37: 932.  
<https://pubmed.ncbi.nlm.nih.gov/31570248/>
207. Fukuda, S., *et al.* Impact of C-reactive protein flare-response on oncological outcomes in patients with metastatic renal cell carcinoma treated with nivolumab. *J Immunother Cancer*, 2021. 9.  
<https://pubmed.ncbi.nlm.nih.gov/33602695/>
208. Lee, Z., *et al.* Local Recurrence Following Resection of Intermediate-High Risk Nonmetastatic Renal Cell Carcinoma: An Anatomical Classification and Analysis of the ASSURE (ECOG-ACRIN E2805) Adjuvant Trial. *J Urol*, 2020. 203: 684.  
<https://pubmed.ncbi.nlm.nih.gov/31596672/>
209. Bensalah, K., *et al.* Prognostic value of thrombocytosis in renal cell carcinoma. *J Urol*, 2006. 175: 859.  
<https://pubmed.ncbi.nlm.nih.gov/16469566/>
210. Kim, H.L., *et al.* Cachexia-like symptoms predict a worse prognosis in localized t1 renal cell carcinoma. *J Urol*, 2004. 171: 1810.  
<https://pubmed.ncbi.nlm.nih.gov/15076282/>
211. Patard, J.J., *et al.* Multi-institutional validation of a symptom based classification for renal cell carcinoma. *J Urol*, 2004. 172: 858.  
<https://pubmed.ncbi.nlm.nih.gov/15310983/>
212. Cho, D.S., *et al.* Prognostic significance of modified Glasgow Prognostic Score in patients with non-metastatic clear cell renal cell carcinoma. *Scand J Urol*, 2016. 50: 186.  
<https://pubmed.ncbi.nlm.nih.gov/26878156/>
213. Patel, A., *et al.* Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor of Disease-free Survival in Postnephrectomy High-risk Locoregional Renal Cell Carcinoma: Analysis of the S-TRAC Trial. *Clin Cancer Res*, 2020. 26: 4863.  
<https://pubmed.ncbi.nlm.nih.gov/32546645/>
214. Shao, Y., *et al.* Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in renal cell carcinoma: a systematic review and meta-analysis. *BMC Urol*, 2020. 20: 90.  
<https://pubmed.ncbi.nlm.nih.gov/32631294/>
215. Albiges, L., *et al.* Body Mass Index and Metastatic Renal Cell Carcinoma: Clinical and Biological Correlations. *J Clin Oncol*, 2016. 34: 3655.  
<https://pubmed.ncbi.nlm.nih.gov/27601543/>
216. Donin, N.M., *et al.* Body Mass Index and Survival in a Prospective Randomized Trial of Localized High-Risk Renal Cell Carcinoma. *Cancer Epidemiol Biomarkers Prev*, 2016. 25: 1326.  
<https://pubmed.ncbi.nlm.nih.gov/27418270/>
217. Petrelli, F., *et al.* Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open*, 2021. 4: e213520.  
<https://pubmed.ncbi.nlm.nih.gov/33779745/>
218. Bagheri, M., *et al.* Renal cell carcinoma survival and body mass index: a dose-response meta-analysis reveals another potential paradox within a paradox. *Int J Obes (Lond)*, 2016. 40: 1817.  
<https://pubmed.ncbi.nlm.nih.gov/27686524/>
219. Dai, J., *et al.* The prognostic value of body fat components in metastasis renal cell carcinoma patients treated with TKIs. *Cancer Management and Research*, 2020. 12: 891.  
<https://pubmed.ncbi.nlm.nih.gov/32104071/>
220. Tsutsumi, T., *et al.* Distinct effect of body mass index by sex as a prognostic factor in localized renal cell carcinoma treated with nephrectomy ~ data from a multi-institutional study in Japan ~. *BMC Cancer*, 2021. 21: 201.  
<https://pubmed.ncbi.nlm.nih.gov/33639880/>
221. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Sunitinib Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma. NCT02231749. Access date January 2023.  
<https://clinicaltrials.gov/ct2/show/NCT02231749>
222. Fan, D., *et al.* Prognostic significance of PI3K/AKT/ mTOR signaling pathway members in clear cell renal cell carcinoma. *PeerJ*, 2020. 8: e9261.  
<https://pubmed.ncbi.nlm.nih.gov/32547875/>



223. Sim, S.H., *et al.* Prognostic utility of pre-operative circulating osteopontin, carbonic anhydrase IX and CRP in renal cell carcinoma. *Br J Cancer*, 2012. 107: 1131.  
<https://pubmed.ncbi.nlm.nih.gov/22918393/>
224. Sabatino, M., *et al.* Serum vascular endothelial growth factor and fibronectin predict clinical response to high-dose interleukin-2 therapy. *J Clin Oncol*, 2009. 27: 2645.  
<https://pubmed.ncbi.nlm.nih.gov/19364969/>
225. Li, G., *et al.* Serum carbonic anhydrase 9 level is associated with postoperative recurrence of conventional renal cell cancer. *J Urol*, 2008. 180: 510.  
<https://pubmed.ncbi.nlm.nih.gov/18550116/>
226. Choueiri, T.K., *et al.* A phase I study of cabozantinib (XL184) in patients with renal cell cancer. *Ann Oncol*, 2014. 25: 1603.  
<https://pubmed.ncbi.nlm.nih.gov/24827131/>
227. Raimondi, A., *et al.* Predictive Biomarkers of Response to Immunotherapy in Metastatic Renal Cell Cancer. *Front Oncol*, 2020. 10: 1644.  
<https://pubmed.ncbi.nlm.nih.gov/32903369/>
228. Ueda, K., *et al.* The Prognostic Value of Systemic Inflammatory Markers in Advanced Renal Cell Carcinoma Patients Treated With Molecular Targeted Therapies. *Anticancer Res*, 2020. 40: 1739.  
<https://pubmed.ncbi.nlm.nih.gov/32132082/>
229. Motzer, R.J., *et al.* Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma: biomarker analysis of the phase 3 JAVELIN Renal 101 trial. *Nat Med*, 2020. 26: 1733.  
<https://pubmed.ncbi.nlm.nih.gov/32895571/>
230. Rini, B.I., *et al.* Molecular correlates differentiate response to atezolizumab+ bevacizumab vs sunitinib: results from a phase III study (IMmotion151) in untreated metastatic renal cell carcinoma. *Ann Oncol*, 2018. 29: LBA31.  
[https://www.annalsofoncology.org/article/S0923-7534\(19\)50428-8/fulltext](https://www.annalsofoncology.org/article/S0923-7534(19)50428-8/fulltext)
231. Scelo, G., *et al.* KIM-1 as a Blood-Based Marker for Early Detection of Kidney Cancer: A Prospective Nested Case-Control Study. *Clin Cancer Res*, 2018. 24: 5594.  
<https://pubmed.ncbi.nlm.nih.gov/30037816/>
232. Zhang, K.J., *et al.* Diagnostic role of kidney injury molecule-1 in renal cell carcinoma. *Int Urol Nephrol*, 2019. 51: 1893.  
<https://pubmed.ncbi.nlm.nih.gov/31385177/>
233. Minardi, D., *et al.* Loss of nuclear BAP1 protein expression is a marker of poor prognosis in patients with clear cell renal cell carcinoma. *Urol Oncol*, 2016. 34: 338 e11.  
<https://pubmed.ncbi.nlm.nih.gov/27085487/>
234. Kapur, P., *et al.* Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol*, 2013. 14: 159.  
<https://pubmed.ncbi.nlm.nih.gov/23333114/>
235. Joseph, R.W., *et al.* Clear Cell Renal Cell Carcinoma Subtypes Identified by BAP1 and PBRM1 Expression. *J Urol*, 2016. 195: 180.  
<https://pubmed.ncbi.nlm.nih.gov/26300218/>
236. Klatte, T., *et al.* Cytogenetic profile predicts prognosis of patients with clear cell renal cell carcinoma. *J Clin Oncol*, 2009. 27: 746.  
<https://pubmed.ncbi.nlm.nih.gov/19124809/>
237. Turajlic, S., *et al.* Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. *Cell*, 2018. 173: 581.  
<https://pubmed.ncbi.nlm.nih.gov/29656895/>
238. Kroeger, N., *et al.* Deletions of chromosomes 3p and 14q molecularly subclassify clear cell renal cell carcinoma. *Cancer*, 2013. 119: 1547.  
<https://pubmed.ncbi.nlm.nih.gov/23335244/>
239. Rini, B., *et al.* A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol*, 2015. 16: 676.  
<https://pubmed.ncbi.nlm.nih.gov/25979595/>
240. Sorbellini, M., *et al.* A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol*, 2005. 173: 48.  
<https://pubmed.ncbi.nlm.nih.gov/15592023/>
241. Zisman, A., *et al.* Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*, 2001. 19: 1649.  
<https://pubmed.ncbi.nlm.nih.gov/11250993/>

242. Frank, I., *et al.* An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*, 2002. 168: 2395.  
<https://pubmed.ncbi.nlm.nih.gov/12441925/>
243. Leibovich, B.C., *et al.* Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*, 2003. 97: 1663.  
<https://pubmed.ncbi.nlm.nih.gov/12655523/>
244. Patard, J.J., *et al.* Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol*, 2004. 22: 3316.  
<https://pubmed.ncbi.nlm.nih.gov/15310775/>
245. Karakiewicz, P.I., *et al.* Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol*, 2007. 25: 1316.  
<https://pubmed.ncbi.nlm.nih.gov/17416852/>
246. Zigeuner, R., *et al.* External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. *Eur Urol*, 2010. 57: 102.  
<https://pubmed.ncbi.nlm.nih.gov/19062157/>
247. Rosiello, G., *et al.* Head-to-head comparison of all the prognostic models recommended by the European Association of Urology Guidelines to predict oncologic outcomes in patients with renal cell carcinoma. *Urol Oncol*, 2022. 40: 271.e19.  
<https://pubmed.ncbi.nlm.nih.gov/35140049/>
248. Okita, K., *et al.* Impact of Disagreement Between Two Risk Group Models on Prognosis in Patients With Metastatic Renal-Cell Carcinoma. *Clin Genitourin Cancer*, 2019. 17: e440.  
<https://pubmed.ncbi.nlm.nih.gov/30772204/>
249. Massari, F., *et al.* Addition of Primary Metastatic Site on Bone, Brain, and Liver to IMDC Criteria in Patients With Metastatic Renal Cell Carcinoma: A Validation Study. *Clin Genitourin Cancer*, 2021. 19: 32.  
<https://pubmed.ncbi.nlm.nih.gov/32694008/>
250. Kang, M., *et al.* Prognostic Impact of Bone Metastasis on Survival Outcomes in Patients with Metastatic Renal Cell Carcinoma Treated by First Line Tyrosine Kinase Inhibitors: A Propensity-Score Matching Analysis. *J Cancer*, 2020. 11: 7202.  
<https://pubmed.ncbi.nlm.nih.gov/33193883/>
251. Guida, A., *et al.* Identification of international metastatic renal cell carcinoma database consortium (IMDC) intermediate-risk subgroups in patients with metastatic clear-cell renal cell carcinoma. *Oncotarget*, 2020. 11: 4582.  
<https://pubmed.ncbi.nlm.nih.gov/33346231/>
252. Zisman, A., *et al.* Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. *J Clin Oncol*, 2002. 20: 4559.  
<https://pubmed.ncbi.nlm.nih.gov/12454113/>
253. Leibovich, B.C., *et al.* Predicting Oncologic Outcomes in Renal Cell Carcinoma After Surgery. *Eur Urol*, 2018. 73: 772.  
<https://pubmed.ncbi.nlm.nih.gov/29398265/>
254. Erdem, S., *et al.* External validation of the VENUSS prognostic model to predict recurrence after surgery in non-metastatic papillary renal cell carcinoma: A multi-institutional analysis. *Urol Oncol*, 2022. 40: 198.e9.  
<https://pubmed.ncbi.nlm.nih.gov/35172939/>
255. Buti, S., *et al.* Validation of a new prognostic model to easily predict outcome in renal cell carcinoma: the GRANT score applied to the ASSURE trial population. *Ann Oncol*, 2017. 28: 2747.  
<https://pubmed.ncbi.nlm.nih.gov/28945839/>
256. Motzer, R.J., *et al.* Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*, 2002. 20: 289.  
<https://pubmed.ncbi.nlm.nih.gov/11773181/>
257. Karnofsky, D., Abelmann, WH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. *Cancer* 1948. 1: 634.  
<https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/1097-0142%28194811%291%3A4%3C634%3A%3AAID-CNCR2820010410%3E3.0.CO%3B2-L>

258. Heng, D.Y., *et al.* External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*, 2013. 14: 141.  
<https://pubmed.ncbi.nlm.nih.gov/23312463/>
259. MacLennan, S., *et al.* Systematic review of perioperative and quality-of-life outcomes following surgical management of localised renal cancer. *Eur Urol*, 2012. 62: 1097.  
<https://pubmed.ncbi.nlm.nih.gov/22841673/>
260. Kunath, F., *et al.* Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. *Cochrane Database Syst Rev*, 2017. 5: CD012045.  
<https://pubmed.ncbi.nlm.nih.gov/28485814/>
261. Van Poppel, H., *et al.* A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol*, 2011. 59: 543.  
<https://pubmed.ncbi.nlm.nih.gov/21186077/>
262. Thompson, R.H., *et al.* Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol*, 2008. 179: 468.  
<https://pubmed.ncbi.nlm.nih.gov/18076931/>
263. Huang, W.C., *et al.* Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? *J Urol*, 2009. 181: 55.  
<https://pubmed.ncbi.nlm.nih.gov/19012918/>
264. Miller, D.C., *et al.* Renal and cardiovascular morbidity after partial or radical nephrectomy. *Cancer*, 2008. 112: 511.  
<https://pubmed.ncbi.nlm.nih.gov/18072263/>
265. Capitanio, U., *et al.* Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. *Eur Urol*, 2015. 67: 683.  
<https://pubmed.ncbi.nlm.nih.gov/25282367/>
266. Scosyrev, E., *et al.* Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *Eur Urol*, 2014. 65: 372.  
<https://pubmed.ncbi.nlm.nih.gov/23850254/>
267. Kates, M., *et al.* Increased risk of overall and cardiovascular mortality after radical nephrectomy for renal cell carcinoma 2 cm or less. *J Urol*, 2011. 186: 1247.  
<https://pubmed.ncbi.nlm.nih.gov/21849201/>
268. Thompson, R.H., *et al.* Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol*, 2015. 67: 252.  
<https://pubmed.ncbi.nlm.nih.gov/25108580/>
269. Sun, M., *et al.* Management of localized kidney cancer: calculating cancer-specific mortality and competing risks of death for surgery and nonsurgical management. *Eur Urol*, 2014. 65: 235.  
<https://pubmed.ncbi.nlm.nih.gov/23567066/>
270. Sun, M., *et al.* Comparison of partial vs radical nephrectomy with regard to other-cause mortality in T1 renal cell carcinoma among patients aged  $\geq 75$  years with multiple comorbidities. *BJU Int*, 2013. 111: 67.  
<https://pubmed.ncbi.nlm.nih.gov/22612472/>
271. Shuch, B., *et al.* Overall survival advantage with partial nephrectomy: a bias of observational data? *Cancer*, 2013. 119: 2981.  
<https://pubmed.ncbi.nlm.nih.gov/23674264/>
272. Lane, B.R., *et al.* Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate. *Eur Urol*, 2015. 68: 996.  
<https://pubmed.ncbi.nlm.nih.gov/26012710/>
273. Van Poppel, H., *et al.* A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol*, 2007. 51: 1606.  
<https://pubmed.ncbi.nlm.nih.gov/17140723/>
274. Poulakis, V., *et al.* Quality of life after surgery for localized renal cell carcinoma: comparison between radical nephrectomy and nephron-sparing surgery. *Urology*, 2003. 62: 814.  
<https://pubmed.ncbi.nlm.nih.gov/14624900/>
275. Mir, M.C., *et al.* Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1b and T2 Renal Tumors: A Systematic Review and Meta-analysis of Comparative Studies. *Eur Urol*, 2017. 71: 606.  
<https://pubmed.ncbi.nlm.nih.gov/27614693/>

276. Janssen, M.W.W., *et al.* Survival outcomes in patients with large ( $\geq 7$ cm) clear cell renal cell carcinomas treated with nephron-sparing surgery versus radical nephrectomy: Results of a multicenter cohort with long-term follow-up. *PLoS One*, 2018. 13: e0196427.  
<https://pubmed.ncbi.nlm.nih.gov/29723225/>
277. Patel, S.H., *et al.* Oncologic and Functional Outcomes of Radical and Partial Nephrectomy in pT3a Pathologically Upstaged Renal Cell Carcinoma: A Multi-institutional Analysis. *Clin Genitourin Cancer*, 2020. 18: e723.  
<https://pubmed.ncbi.nlm.nih.gov/32600941/>
278. Shah, P.H., *et al.* Partial Nephrectomy is Associated with Higher Risk of Relapse Compared with Radical Nephrectomy for Clinical Stage T1 Renal Cell Carcinoma Pathologically Up Staged to T3a. *J Urol*, 2017. 198: 289.  
<https://pubmed.ncbi.nlm.nih.gov/28274620/>
279. Liu, H., *et al.* A meta-analysis for comparison of partial nephrectomy vs. radical nephrectomy in patients with pT3a renal cell carcinoma. *Transl Androl Urol*, 2021. 10: 1170.  
<https://pubmed.ncbi.nlm.nih.gov/33850752/>
280. Lane, B.R., *et al.* Management of the adrenal gland during partial nephrectomy. *J Urol*, 2009. 181: 2430.  
<https://pubmed.ncbi.nlm.nih.gov/19371896/>
281. Bekema, H.J., *et al.* Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. *Eur Urol*, 2013. 64: 799.  
<https://pubmed.ncbi.nlm.nih.gov/23643550/>
282. Blom, J.H., *et al.* Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol*, 2009. 55: 28.  
<https://pubmed.ncbi.nlm.nih.gov/18848382/>
283. Capitano, U., *et al.* Lymph node dissection in renal cell carcinoma. *Eur Urol*, 2011. 60: 1212.  
<https://pubmed.ncbi.nlm.nih.gov/21940096/>
284. Gershman, B., *et al.* Radical Nephrectomy with or without Lymph Node Dissection for High Risk Nonmetastatic Renal Cell Carcinoma: A Multi-Institutional Analysis. *J Urol*, 2018. 199: 1143.  
<https://pubmed.ncbi.nlm.nih.gov/29225056/>
285. Kim S, T.H., Weight C, *et al.* The relationship of lymph node dissection with recurrence and survival for patients treated with nephrectomy for high-risk renal cell carcinoma. *J Urol*, 2012. 187: e233.  
<https://www.auajournals.org/doi/10.1016/j.juro.2012.02.649>
286. Dimashkieh, H.H., *et al.* Extranodal extension in regional lymph nodes is associated with outcome in patients with renal cell carcinoma. *J Urol*, 2006. 176: 1978.  
<https://pubmed.ncbi.nlm.nih.gov/17070225/>
287. Terrone, C., *et al.* Reassessing the current TNM lymph node staging for renal cell carcinoma. *Eur Urol*, 2006. 49: 324.  
<https://pubmed.ncbi.nlm.nih.gov/16386352/>
288. Whitson, J.M., *et al.* Lymphadenectomy improves survival of patients with renal cell carcinoma and nodal metastases. *J Urol*, 2011. 185: 1615.  
<https://pubmed.ncbi.nlm.nih.gov/21419453/>
289. Capitano, U., *et al.* Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). *BJU Int*, 2014. 114: 210.  
<https://pubmed.ncbi.nlm.nih.gov/24854206/>
290. Gershman, B., *et al.* Perioperative Morbidity of Lymph Node Dissection for Renal Cell Carcinoma: A Propensity Score-based Analysis. *Eur Urol*, 2018. 73: 469.  
<https://pubmed.ncbi.nlm.nih.gov/29132713/>
291. Herrlinger, A., *et al.* What are the benefits of extended dissection of the regional renal lymph nodes in the therapy of renal cell carcinoma. *J Urol*, 1991. 146: 1224.  
<https://pubmed.ncbi.nlm.nih.gov/1942267/>
292. Chapin, B.F., *et al.* The role of lymph node dissection in renal cell carcinoma. *Int J Clin Oncol*, 2011. 16: 186.  
<https://pubmed.ncbi.nlm.nih.gov/21523561/>
293. Kwon, T., *et al.* Reassessment of renal cell carcinoma lymph node staging: analysis of patterns of progression. *Urology*, 2011. 77: 373.  
<https://pubmed.ncbi.nlm.nih.gov/20817274/>

294. Bex, A., *et al.* Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. *World J Urol*, 2011. 29: 793.  
<https://pubmed.ncbi.nlm.nih.gov/21107845/>
295. Sherif, A.M., *et al.* Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. *BJU Int*, 2012. 109: 1134.  
<https://pubmed.ncbi.nlm.nih.gov/21883833/>
296. May, M., *et al.* Pre-operative renal arterial embolisation does not provide survival benefit in patients with radical nephrectomy for renal cell carcinoma. *Br J Radiol*, 2009. 82: 724.  
<https://pubmed.ncbi.nlm.nih.gov/19255117/>
297. Subramanian, V.S., *et al.* Utility of preoperative renal artery embolization for management of renal tumors with inferior vena caval thrombi. *Urology*, 2009. 74: 154.  
<https://pubmed.ncbi.nlm.nih.gov/19428069/>
298. Maxwell, N.J., *et al.* Renal artery embolisation in the palliative treatment of renal carcinoma. *Br J Radiol*, 2007. 80: 96.  
<https://pubmed.ncbi.nlm.nih.gov/17495058/>
299. Lamb, G.W., *et al.* Management of renal masses in patients medically unsuitable for nephrectomy--natural history, complications, and outcome. *Urology*, 2004. 64: 909.  
<https://pubmed.ncbi.nlm.nih.gov/15533476/>
300. Brewer, K., *et al.* Perioperative and renal function outcomes of minimally invasive partial nephrectomy for T1b and T2a kidney tumors. *J Endourol*, 2012. 26: 244.  
<https://pubmed.ncbi.nlm.nih.gov/22192099/>
301. Sprenkle, P.C., *et al.* Comparison of open and minimally invasive partial nephrectomy for renal tumors 4-7 centimeters. *Eur Urol*, 2012. 61: 593.  
<https://pubmed.ncbi.nlm.nih.gov/22154728/>
302. Peng B, *et al.* Retroperitoneal laparoscopic nephrectomy and open nephrectomy for radical treatment of renal cell carcinoma: A comparison of clinical outcomes. *Academic Journal of Second Military Medical University*, 2006. 12: 1167.  
<https://pesquisa.bvsalud.org/portal/resource/pt/wpr-841262>
303. Steinberg, A.P., *et al.* Laparoscopic radical nephrectomy for large (greater than 7 cm, T2) renal tumors. *J Urol*, 2004. 172: 2172.  
<https://pubmed.ncbi.nlm.nih.gov/15538225/>
304. Dursun, F., *et al.* Survival after minimally invasive vs. open radical nephrectomy for stage I and II renal cell carcinoma. *Int J Clin Oncol*, 2022. 27: 1068.  
<https://pubmed.ncbi.nlm.nih.gov/35319076/>
305. Gratzke, C., *et al.* Quality of life and perioperative outcomes after retroperitoneoscopic radical nephrectomy (RN), open RN and nephron-sparing surgery in patients with renal cell carcinoma. *BJU Int*, 2009. 104: 470.  
<https://pubmed.ncbi.nlm.nih.gov/19239445/>
306. Hemal, A.K., *et al.* Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. *J Urol*, 2007. 177: 862.  
<https://pubmed.ncbi.nlm.nih.gov/17296361/>
307. Laird, A., *et al.* Matched pair analysis of laparoscopic versus open radical nephrectomy for the treatment of T3 renal cell carcinoma. *World J Urol*, 2015. 33: 25.  
<https://pubmed.ncbi.nlm.nih.gov/24647880/>
308. Patel, P., *et al.* A Multicentered, Propensity Matched Analysis Comparing Laparoscopic and Open Surgery for pT3a Renal Cell Carcinoma. *J Endourol*, 2017. 31: 645.  
<https://pubmed.ncbi.nlm.nih.gov/28381117/>
309. Desai, M.M., *et al.* Prospective randomized comparison of transperitoneal versus retroperitoneal laparoscopic radical nephrectomy. *J Urol*, 2005. 173: 38.  
<https://pubmed.ncbi.nlm.nih.gov/15592021/>
310. Nambirajan, T., *et al.* Prospective, randomized controlled study: transperitoneal laparoscopic versus retroperitoneoscopic radical nephrectomy. *Urology*, 2004. 64: 919.  
<https://pubmed.ncbi.nlm.nih.gov/15533478/>
311. Nadler, R.B., *et al.* A prospective study of laparoscopic radical nephrectomy for T1 tumors--is transperitoneal, retroperitoneal or hand assisted the best approach? *J Urol*, 2006. 175: 1230.  
<https://pubmed.ncbi.nlm.nih.gov/16515966/>
312. Gabr, A.H., *et al.* Approach and specimen handling do not influence oncological perioperative and long-term outcomes after laparoscopic radical nephrectomy. *J Urol*, 2009. 182: 874.  
<https://pubmed.ncbi.nlm.nih.gov/19616234/>



313. Jeong, I.G., *et al.* Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy With Perioperative Outcomes and Health Care Costs, 2003 to 2015. *JAMA*, 2017. 318: 1561.  
<https://pubmed.ncbi.nlm.nih.gov/29067427/>
314. Li, J., *et al.* Comparison of Perioperative Outcomes of Robot-Assisted vs. Laparoscopic Radical Nephrectomy: A Systematic Review and Meta-Analysis. *Front Oncol*, 2020. 10: 551052.  
<https://pubmed.ncbi.nlm.nih.gov/33072578/>
315. Asimakopoulos, A.D., *et al.* Robotic radical nephrectomy for renal cell carcinoma: a systematic review. *BMC Urol*, 2014. 14: 75.  
<https://pubmed.ncbi.nlm.nih.gov/25234265/>
316. Soga, N., *et al.* Comparison of radical nephrectomy techniques in one center: minimal incision portless endoscopic surgery versus laparoscopic surgery. *Int J Urol*, 2008. 15: 1018.  
<https://pubmed.ncbi.nlm.nih.gov/19138194/>
317. Park Y, *et al.* Laparoendoscopic single-site radical nephrectomy for localized renal cell carcinoma: comparison with conventional laparoscopic surgery. *J Endourol* 2009. 23: A19.  
<https://pubmed.ncbi.nlm.nih.gov/20370595/>
318. Gill, I.S., *et al.* Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J Urol*, 2007. 178: 41.  
<https://pubmed.ncbi.nlm.nih.gov/17574056/>
319. Lane, B.R., *et al.* 7-year oncological outcomes after laparoscopic and open partial nephrectomy. *J Urol*, 2010. 183: 473.  
<https://pubmed.ncbi.nlm.nih.gov/20006866/>
320. Gong, E.M., *et al.* Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. *J Endourol*, 2008. 22: 953.  
<https://pubmed.ncbi.nlm.nih.gov/18363510/>
321. Marszalek, M., *et al.* Laparoscopic and open partial nephrectomy: a matched-pair comparison of 200 patients. *Eur Urol*, 2009. 55: 1171.  
<https://pubmed.ncbi.nlm.nih.gov/19232819/>
322. Kaneko, G., *et al.* The benefit of laparoscopic partial nephrectomy in high body mass index patients. *Jpn J Clin Oncol*, 2012. 42: 619.  
<https://pubmed.ncbi.nlm.nih.gov/22561514/>
323. Muramaki, M., *et al.* Prognostic Factors Influencing Postoperative Development of Chronic Kidney Disease in Patients with Small Renal Tumors who Underwent Partial Nephrectomy. *Curr Urol*, 2013. 6: 129.  
<https://pubmed.ncbi.nlm.nih.gov/24917730/>
324. Guglielmetti, G.B., *et al.* A Prospective, Randomized Trial Comparing the Outcomes of Open vs Laparoscopic Partial Nephrectomy. *J Urol*, 2022. 208: 259.  
<https://pubmed.ncbi.nlm.nih.gov/35404109/>
325. Tugcu, V., *et al.* Transperitoneal versus retroperitoneal laparoscopic partial nephrectomy: initial experience. *Arch Ital Urol Androl*, 2011. 83: 175.  
<https://pubmed.ncbi.nlm.nih.gov/22670314/>
326. Minervini, A., *et al.* Simple enucleation is equivalent to traditional partial nephrectomy for renal cell carcinoma: results of a nonrandomized, retrospective, comparative study. *J Urol*, 2011. 185: 1604.  
<https://pubmed.ncbi.nlm.nih.gov/21419454/>
327. Bazzi, W.M., *et al.* Comparison of laparoendoscopic single-site and multiport laparoscopic radical and partial nephrectomy: a prospective, nonrandomized study. *Urology*, 2012. 80: 1039.  
<https://pubmed.ncbi.nlm.nih.gov/22990064/>
328. Masson-Lecomte, A., *et al.* A prospective comparison of the pathologic and surgical outcomes obtained after elective treatment of renal cell carcinoma by open or robot-assisted partial nephrectomy. *Urol Oncol*, 2013. 31: 924.  
<https://pubmed.ncbi.nlm.nih.gov/21906969/>
329. Peyronnet, B., *et al.* Comparison of 1800 Robotic and Open Partial Nephrectomies for Renal Tumors. *Ann Surg Oncol*, 2016. 23: 4277.  
<https://pubmed.ncbi.nlm.nih.gov/27411552/>
330. Nisen, H., *et al.* Hand-assisted laparoscopic versus open partial nephrectomy in patients with T1 renal tumor: Comparative perioperative, functional and oncological outcome. *Scand J Urol*, 2015: 49: 446.  
<https://pubmed.ncbi.nlm.nih.gov/26317448/>
331. Chang, K.D., *et al.* Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: a multicentre comparative matched-pair analyses with a median of 5 years' follow-up. *BJU Int*, 2018. 122: 618.  
<https://pubmed.ncbi.nlm.nih.gov/29645344/>



332. Alimi, Q., *et al.* Comparison of Short-Term Functional, Oncological, and Perioperative Outcomes Between Laparoscopic and Robotic Partial Nephrectomy Beyond the Learning Curve. *J Laparoendosc Adv Surg Tech A*, 2018. 28: 1047.  
<https://pubmed.ncbi.nlm.nih.gov/29664692/>
333. Choi, J.E., *et al.* Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: a systematic review and meta-analysis. *Eur Urol*, 2015. 67: 891.  
<https://pubmed.ncbi.nlm.nih.gov/25572825/>
334. Hinata, N., *et al.* Robot-assisted partial nephrectomy versus standard laparoscopic partial nephrectomy for renal hilar tumor: A prospective multi-institutional study. *Int J Urol*, 2021. 28: 382.  
<https://pubmed.ncbi.nlm.nih.gov/33368639/>
335. Porpiglia, F., *et al.* Transperitoneal vs retroperitoneal minimally invasive partial nephrectomy: comparison of perioperative outcomes and functional follow-up in a large multi-institutional cohort (The RECORD 2 Project). *Surg Endosc*, 2021. 35: 4295.  
<https://pubmed.ncbi.nlm.nih.gov/32856156/>
336. Carbonara, U., *et al.* Retroperitoneal Robot-assisted Partial Nephrectomy: A Systematic Review and Pooled Analysis of Comparative Outcomes. *Eur Urol Open Sci*, 2022. 40: 27.  
<https://pubmed.ncbi.nlm.nih.gov/35515269/>
337. Minervini, A., *et al.* Impact of Resection Technique on Perioperative Outcomes and Surgical Margins after Partial Nephrectomy for Localized Renal Masses: A Prospective Multicenter Study. *J Urol*, 2020. 203: 496.  
<https://pubmed.ncbi.nlm.nih.gov/31609167/>
338. Arora, S., *et al.* What is the hospital volume threshold to optimize inpatient complication rate after partial nephrectomy? *Urol Oncol*, 2018. 36: 339.e17.  
<https://pubmed.ncbi.nlm.nih.gov/29773492/>
339. Xia, L., *et al.* Hospital volume and outcomes of robot-assisted partial nephrectomy. *BJU Int*, 2018. 121: 900.  
<https://pubmed.ncbi.nlm.nih.gov/29232025/>
340. Peyronnet, B., *et al.* Impact of hospital volume and surgeon volume on robot-assisted partial nephrectomy outcomes: a multicentre study. *BJU Int*, 2018. 121: 916.  
<https://pubmed.ncbi.nlm.nih.gov/29504226/>
341. Schiavina, R., *et al.* Predicting positive surgical margins in partial nephrectomy: A prospective multicentre observational study (the RECORd 2 project). *Eur J Surg Oncol*, 2020. 46: 1353.  
<https://pubmed.ncbi.nlm.nih.gov/32007380/>
342. Shanmugasundaram, S., *et al.* Preoperative embolization of renal cell carcinoma prior to partial nephrectomy: A systematic review and meta-analysis. *Clin Imaging*, 2021. 76: 205.  
<https://pubmed.ncbi.nlm.nih.gov/33964598/>
343. Tabayoyong, W., *et al.* Variation in Surgical Margin Status by Surgical Approach among Patients Undergoing Partial Nephrectomy for Small Renal Masses. *J Urol*, 2015. 194: 1548.  
<https://pubmed.ncbi.nlm.nih.gov/26094808/>
344. Porpiglia, F., *et al.* Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project). *Urology*, 2016. 89: 45.  
<https://pubmed.ncbi.nlm.nih.gov/26743388/>
345. Steinestel, J., *et al.* Positive surgical margins in nephron-sparing surgery: risk factors and therapeutic consequences. *World J Surg Oncol*, 2014. 12: 252.  
<https://pubmed.ncbi.nlm.nih.gov/25103683/>
346. Wood, E.L., *et al.* Local Tumor Bed Recurrence Following Partial Nephrectomy in Patients with Small Renal Masses. *J Urol*, 2018. 199: 393.  
<https://pubmed.ncbi.nlm.nih.gov/28941919/>
347. Bensalah, K., *et al.* Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol*, 2010. 57: 466.  
<https://pubmed.ncbi.nlm.nih.gov/19359089/>
348. Lopez-Costea, M.A., *et al.* Oncological outcomes and prognostic factors after nephron-sparing surgery in renal cell carcinoma. *Int Urol Nephrol*, 2016. 48: 681.  
<https://pubmed.ncbi.nlm.nih.gov/26861062/>
349. Shah, P.H., *et al.* Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High Risk Renal Tumors. *J Urol*, 2016. 196: 327.  
<https://pubmed.ncbi.nlm.nih.gov/26907508/>

350. Tellini, R., *et al.* Positive Surgical Margins Predict Progression-free Survival After Nephron-sparing Surgery for Renal Cell Carcinoma: Results From a Single Center Cohort of 459 Cases With a Minimum Follow-up of 5 Years. *Clin Genitourin Cancer*, 2019. 17: e26.  
<https://pubmed.ncbi.nlm.nih.gov/30266249/>
351. Ryan, S.T., *et al.* Impact of positive surgical margins on survival after partial nephrectomy in localized kidney cancer: analysis of the National Cancer Database. *Minerva Urol Nephrol*, 2021. 73: 233.  
<https://pubmed.ncbi.nlm.nih.gov/32748614/>
352. Sundaram, V., *et al.* Positive margin during partial nephrectomy: does cancer remain in the renal remnant? *Urology*, 2011. 77: 1400.  
<https://pubmed.ncbi.nlm.nih.gov/21411126/>
353. Kim, S.P., *et al.* Treatment of Patients with Positive Margins after Partial Nephrectomy. *J Urol*, 2016. 196: 301.  
<https://pubmed.ncbi.nlm.nih.gov/27188474/>
354. Antic, T., *et al.* Partial nephrectomy for renal tumors: lack of correlation between margin status and local recurrence. *Am J Clin Pathol*, 2015. 143: 645.  
<https://pubmed.ncbi.nlm.nih.gov/25873497/>
355. Lane, B.R., *et al.* Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer*, 2010. 116: 3119.  
<https://pubmed.ncbi.nlm.nih.gov/20564627/>
356. Hollingsworth, J.M., *et al.* Five-year survival after surgical treatment for kidney cancer: a population-based competing risk analysis. *Cancer*, 2007. 109: 1763.  
<https://pubmed.ncbi.nlm.nih.gov/17351954/>
357. Volpe, A., *et al.* The natural history of incidentally detected small renal masses. *Cancer*, 2004. 100: 738.  
<https://pubmed.ncbi.nlm.nih.gov/14770429/>
358. Zini, L., *et al.* A population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses. *BJU Int*, 2009. 103: 899.  
<https://pubmed.ncbi.nlm.nih.gov/19154499/>
359. Xing, M., *et al.* Comparative Effectiveness of Thermal Ablation, Surgical Resection, and Active Surveillance for T1a Renal Cell Carcinoma: A Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked Population Study. *Radiology*, 2018. 288: 81.  
<https://pubmed.ncbi.nlm.nih.gov/29737950/>
360. Sun, M., *et al.* Management of localized kidney cancer: calculating cancer-specific mortality and competing risks of death for surgery and nonsurgical management. *Eur Urol*, 2014. 65: 235.  
<https://pubmed.ncbi.nlm.nih.gov/23567066/>
361. Huang WC, *et al.* Surveillance for the management of small renal masses: outcomes in a population-based cohort. *J Urol*, 2013: e483.  
[https://ascopubs.org/doi/abs/10.1200/jco.2013.31.6\\_suppl.343](https://ascopubs.org/doi/abs/10.1200/jco.2013.31.6_suppl.343)
362. Hyams ES, *et al.* Partial nephrectomy vs. Non-surgical management for small renal masses: a population-based comparison of disease-specific and overall survival. *J Urol*, 2012. 187: E678.  
<https://www.auajournals.org/doi/full/10.1016/j.juro.2012.02.1552>
363. Jewett, M.A., *et al.* Active surveillance of small renal masses: progression patterns of early stage kidney cancer. *Eur Urol*, 2011. 60: 39.  
<https://pubmed.ncbi.nlm.nih.gov/21477920/>
364. Smaldone, M.C., *et al.* Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. *Cancer*, 2012. 118: 997.  
<https://pubmed.ncbi.nlm.nih.gov/21766302/>
365. Klatte, T., *et al.* Intermediate- and long-term oncological outcomes of active surveillance for localized renal masses: a systematic review and quantitative analysis. *BJU Int*, 2021. 128: 131.  
<https://pubmed.ncbi.nlm.nih.gov/34060192/>
366. Finelli, A., *et al.* Small Renal Mass Surveillance: Histology-specific Growth Rates in a Biopsy-characterized Cohort. *Eur Urol*, 2020. 78: 460.  
<https://pubmed.ncbi.nlm.nih.gov/32680677/>
367. Patel, N., *et al.* Active surveillance of small renal masses offers short-term oncological efficacy equivalent to radical and partial nephrectomy. *BJU Int*, 2012. 110: 1270.  
<https://pubmed.ncbi.nlm.nih.gov/22564495/>
368. Pierorazio, P.M., *et al.* Five-year analysis of a multi-institutional prospective clinical trial of delayed

- intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol*, 2015. 68: 408.  
<https://pubmed.ncbi.nlm.nih.gov/25698065/>
369. Uzosike, A.C., *et al.* Growth Kinetics of Small Renal Masses on Active Surveillance: Variability and Results from the DISSRM Registry. *J Urol*, 2018. 199: 641.  
<https://pubmed.ncbi.nlm.nih.gov/28951284/>
370. Abou Youssif, T., *et al.* Active surveillance for selected patients with renal masses: updated results with long-term follow-up. *Cancer*, 2007. 110: 1010.  
<https://pubmed.ncbi.nlm.nih.gov/17628489/>
371. Abouassaly, R., *et al.* Active surveillance of renal masses in elderly patients. *J Urol*, 2008. 180: 505.  
<https://pubmed.ncbi.nlm.nih.gov/18550113/>
372. Crispen, P.L., *et al.* Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. *Cancer*, 2009. 115: 2844.  
<https://pubmed.ncbi.nlm.nih.gov/19402168/>
373. Rosales, J.C., *et al.* Active surveillance for renal cortical neoplasms. *J Urol*, 2010. 183: 1698.  
<https://pubmed.ncbi.nlm.nih.gov/20299038/>
374. Pierorazio P, *et al.* Quality of life on active surveillance for small masses versus immediate intervention: interim analysis of the DISSRM (delayed intervention and surveillance for small renal masses) registry. *J Urol*, 2013. 189: e259.  
<https://www.auajournals.org/doi/full/10.1016/j.juro.2013.02.185>
375. Atwell, T.D., *et al.* Percutaneous ablation of renal masses measuring 3.0 cm and smaller: comparative local control and complications after radiofrequency ablation and cryoablation. *AJR Am J Roentgenol*, 2013. 200: 461.  
<https://pubmed.ncbi.nlm.nih.gov/23345372/>
376. Widdershoven, C.V., *et al.* Renal biopsies performed before versus during ablation of T1 renal tumors: implications for prevention of overtreatment and follow-up. *Abdom Radiol (NY)*, 2021. 46: 373.  
<https://pubmed.ncbi.nlm.nih.gov/32564209/>
377. Chan, V.W., *et al.* The changing trends of image-guided biopsy of small renal masses before intervention-an analysis of European multinational prospective EuRECA registry. *Eur Radiol*, 2022. 32: 4667.  
<https://pubmed.ncbi.nlm.nih.gov/35122492/>
378. Lay, A.H., *et al.* Oncologic Efficacy of Radio Frequency Ablation for Small Renal Masses: Clear Cell vs Papillary Subtype. *J Urol*, 2015. 194: 653.  
<https://pubmed.ncbi.nlm.nih.gov/25846416/>
379. McClure, T., *et al.* Efficacy of percutaneous radiofrequency ablation may vary with clear cell renal cell cancer histologic subtype. *Abdom Radiol (NY)*, 2018. 43: 1472.  
<https://pubmed.ncbi.nlm.nih.gov/28936542/>
380. Liu, N., *et al.* Percutaneous radiofrequency ablation for renal cell carcinoma vs. partial nephrectomy: Comparison of long-term oncologic outcomes in both clear cell and non-clear cell of the most common subtype. *Urol Oncol*, 2017. 35: 530.e1.  
<https://pubmed.ncbi.nlm.nih.gov/28408296/>
381. Breen, D.J., *et al.* Image-guided Cryoablation for Sporadic Renal Cell Carcinoma: Three- and 5-year Outcomes in 220 Patients with Biopsy-proven Renal Cell Carcinoma. *Radiology*, 2018. 289: 554.  
<https://pubmed.ncbi.nlm.nih.gov/30084744/>
382. Sisul, D.M., *et al.* RENAL nephrometry score is associated with complications after renal cryoablation: a multicenter analysis. *Urology*, 2013. 81: 775.  
<https://pubmed.ncbi.nlm.nih.gov/23434099/>
383. Kim, E.H., *et al.* Outcomes of laparoscopic and percutaneous cryoablation for renal masses. *J Urol*, 2013. 189: e492.  
<https://www.auajournals.org/doi/10.1016/j.juro.2013.02.2554>
384. Goyal, J., *et al.* Single-center comparative oncologic outcomes of surgical and percutaneous cryoablation for treatment of renal tumors. *J Endourol*, 2012. 26: 1413.  
<https://pubmed.ncbi.nlm.nih.gov/22642574/>
385. Jiang, K., *et al.* Laparoscopic cryoablation vs. percutaneous cryoablation for treatment of small renal masses: a systematic review and meta-analysis. *Oncotarget*, 2017. 8: 27635.  
<https://pubmed.ncbi.nlm.nih.gov/28199973/>
386. Zargar, H., *et al.* Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. *Eur Urol*, 2016. 69: 116.  
<https://pubmed.ncbi.nlm.nih.gov/25819723/>

387. Pickersgill, N.A., *et al.* Ten-Year Experience with Percutaneous Cryoablation of Renal Tumors: Tumor Size Predicts Disease Progression. *J Endourol*, 2020. 34: 1211.  
<https://pubmed.ncbi.nlm.nih.gov/32292059/>
388. Morkos, J., *et al.* Percutaneous Cryoablation for Stage 1 Renal Cell Carcinoma: Outcomes from a 10-year Prospective Study and Comparison with Matched Cohorts from the National Cancer Database. *Radiology*, 2020. 296: 452.  
<https://pubmed.ncbi.nlm.nih.gov/32515677/>
389. Hebbadj, S., *et al.* Safety Considerations and Local Tumor Control Following Percutaneous Image-Guided Cryoablation of T1b Renal Tumors. *Cardiovasc Intervent Radiol*, 2018. 41: 449.  
<https://pubmed.ncbi.nlm.nih.gov/29075877/>
390. Grange, R., *et al.* Computed tomography-guided percutaneous cryoablation of T1b renal tumors: safety, functional and oncological outcomes. *Int J Hyperthermia*, 2019. 36: 1065.  
<https://pubmed.ncbi.nlm.nih.gov/31648584/>
391. Pecoraro, A., *et al.* Cryoablation Predisposes to Higher Cancer Specific Mortality Relative to Partial Nephrectomy in Patients with Nonmetastatic pT1b Kidney Cancer. *J Urol*, 2019. 202: 1120.  
<https://pubmed.ncbi.nlm.nih.gov/31347950/>
392. Andrews, J.R., *et al.* Oncologic Outcomes Following Partial Nephrectomy and Percutaneous Ablation for cT1 Renal Masses. *Eur Urol*, 2019. 76: 244.  
<https://pubmed.ncbi.nlm.nih.gov/31060824/>
393. Sundelin, M.O., *et al.* Repeated Cryoablation as Treatment Modality after Failure of Primary Renal Cryoablation: A European Registry for Renal Cryoablation Multinational Analysis. *Journal of Endourology*, 2019. 33: 909.  
<https://pubmed.ncbi.nlm.nih.gov/31507206/>
394. Lian, H., *et al.* Single-center comparison of complications in laparoscopic and percutaneous radiofrequency ablation with ultrasound guidance for renal tumors. *Urology*, 2012. 80: 119.  
<https://pubmed.ncbi.nlm.nih.gov/22633890/>
395. Young, E.E., *et al.* Comparison of safety, renal function outcomes and efficacy of laparoscopic and percutaneous radio frequency ablation of renal masses. *J Urol*, 2012. 187: 1177.  
<https://pubmed.ncbi.nlm.nih.gov/22357170/>
396. Kim, S.D., *et al.* Radiofrequency ablation of renal tumors: four-year follow-up results in 47 patients. *Korean J Radiol*, 2012. 13: 625.  
<https://pubmed.ncbi.nlm.nih.gov/22977331/>
397. Trudeau, V., *et al.* Comparison of Postoperative Complications and Mortality Between Laparoscopic and Percutaneous Local Tumor Ablation for T1a Renal Cell Carcinoma: A Population-based Study. *Urology*, 2016. 89: 63.  
<https://pubmed.ncbi.nlm.nih.gov/26514977/>
398. Psutka, S.P., *et al.* Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. *Eur Urol*, 2013. 63: 486.  
<https://pubmed.ncbi.nlm.nih.gov/22959191/>
399. Johnson, B.A., *et al.* Ten-Year Outcomes of Renal Tumor Radio Frequency Ablation. *J Urol*, 2019. 201: 251.  
<https://pubmed.ncbi.nlm.nih.gov/30634350/>
400. Chang, X., *et al.* Radio frequency ablation versus partial nephrectomy for clinical T1b renal cell carcinoma: long-term clinical and oncologic outcomes. *J Urol*, 2015. 193: 430.  
<https://pubmed.ncbi.nlm.nih.gov/25106899/>
401. Abu-Ghanem, Y., *et al.* Limitations of Available Studies Prevent Reliable Comparison Between Tumour Ablation and Partial Nephrectomy for Patients with Localised Renal Masses: A Systematic Review from the European Association of Urology Renal Cell Cancer Guideline Panel. *Eur Urol Oncol*, 2020. 3: 433.  
<https://pubmed.ncbi.nlm.nih.gov/32245655/>
402. Guazzoni, G., *et al.* Oncologic results of laparoscopic renal cryoablation for clinical T1a tumors: 8 years of experience in a single institution. *Urology*, 2010. 76: 624.  
<https://pubmed.ncbi.nlm.nih.gov/20579705/>
403. Larcher, A., *et al.* Long-term oncologic outcomes of laparoscopic renal cryoablation as primary treatment for small renal masses. *Urol Oncol*, 2015. 33: 22.e1.  
<https://pubmed.ncbi.nlm.nih.gov/25301741/>
404. Haber, G.P., *et al.* Tumour in solitary kidney: laparoscopic partial nephrectomy vs laparoscopic cryoablation. *BJU Int*, 2012. 109: 118.  
<https://pubmed.ncbi.nlm.nih.gov/21895929/>

405. Turna, B., *et al.* Minimally invasive nephron sparing management for renal tumors in solitary kidneys. *J Urol*, 2009. 182: 2150.  
<https://pubmed.ncbi.nlm.nih.gov/19758655/>
406. Siva, S., *et al.* Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. *BJU Int*, 2017. 120: 623.  
<https://pubmed.ncbi.nlm.nih.gov/28188682/>
407. Correa, R.J.M., *et al.* The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. *Eur Urol Focus*, 2019. 5: 958.  
<https://pubmed.ncbi.nlm.nih.gov/31248849/>
408. Ali, M., *et al.* The Role of Stereotactic Ablative Body Radiotherapy in Renal Cell Carcinoma. *Eur Urol*, 2022. 82: 613.  
<https://pubmed.ncbi.nlm.nih.gov/35843777/>
409. Yu, J., *et al.* Percutaneous Microwave Ablation versus Laparoscopic Partial Nephrectomy for cT1a Renal Cell Carcinoma: A Propensity-matched Cohort Study of 1955 Patients. *Radiology*, 2020. 294: 698.  
<https://pubmed.ncbi.nlm.nih.gov/31961239/>
410. Shapiro, D.D., *et al.* Comparing Outcomes for Patients with Clinical T1b Renal Cell Carcinoma Treated With Either Percutaneous Microwave Ablation or Surgery. *Urology*, 2020. 135: 88.  
<https://pubmed.ncbi.nlm.nih.gov/31585198/>
411. Zhou, W., *et al.* Radiofrequency Ablation, Cryoablation, and Microwave Ablation for T1a Renal Cell Carcinoma: A Comparative Evaluation of Therapeutic and Renal Function Outcomes. *Journal of Vascular and Interventional Radiology*, 2019. 30: 1035.  
<https://pubmed.ncbi.nlm.nih.gov/30956075/>
412. Bhandi, B., *et al.* The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. *BJU Int*, 2018. 121: 684.  
<https://pubmed.ncbi.nlm.nih.gov/29319926/>
413. Luo, X., *et al.* Influence of lymph node dissection in patients undergoing radical nephrectomy for non-metastatic renal cell carcinoma: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*, 2019. 23: 6079.  
<https://pubmed.ncbi.nlm.nih.gov/31364109/>
414. Capitanio, U., *et al.* When to perform lymph node dissection in patients with renal cell carcinoma: a novel approach to the preoperative assessment of risk of lymph node invasion at surgery and of lymph node progression during follow-up. *BJU Int*, 2013. 112: E59.  
<https://pubmed.ncbi.nlm.nih.gov/23795799/>
415. Tsui, K.H., *et al.* Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. *J Urol*, 2000. 163: 1090.  
<https://pubmed.ncbi.nlm.nih.gov/10737472/>
416. Wagner, B., *et al.* Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. *Eur Urol*, 2009. 55: 452.  
<https://pubmed.ncbi.nlm.nih.gov/18692951/>
417. Klatte, T., *et al.* Prognostic factors for renal cell carcinoma with tumor thrombus extension. *J Urol*, 2007. 178: 1189.  
<https://pubmed.ncbi.nlm.nih.gov/17698087/>
418. Lardas, M., *et al.* Systematic Review of Surgical Management of Nonmetastatic Renal Cell Carcinoma with Vena Caval Thrombus. *Eur Urol*, 2016. 70: 265.  
<https://pubmed.ncbi.nlm.nih.gov/26707869/>
419. Garg, H., *et al.* A Decade of Robotic-Assisted Radical Nephrectomy with Inferior Vena Cava Thrombectomy: A Systematic Review and Meta-Analysis of Perioperative Outcomes. *J Urol*, 2022. 208: 542.  
<https://pubmed.ncbi.nlm.nih.gov/35762219/>
420. Stewart, G.D., *et al.* A Phase II study of neoadjuvant axitinib for reducing the extent of venous tumour thrombus in clear cell renal cell cancer with venous invasion (NAXIVA). *Br J Cancer*, 2022. 127: 1051.  
<https://pubmed.ncbi.nlm.nih.gov/35739300/>
421. Ljungberg, B., *et al.* European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. *Eur Urol*, 2022. 82: 399.  
<https://pubmed.ncbi.nlm.nih.gov/35346519/>
422. Hallscheidt, P., *et al.* [Preoperative and palliative embolization of renal cell carcinomas: follow-up of 49 patients]. *Rofo*, 2006. 178: 391.  
<https://pubmed.ncbi.nlm.nih.gov/16612730/>



423. Wright, B., *et al.* Trans-arterial embolization of renal cell carcinoma: a systematic review and meta-analysis. *Abdom Radiol (NY)*, 2022. 47: 2238.  
<https://pubmed.ncbi.nlm.nih.gov/35380246/>
424. Rodríguez-Fernández, I.A., *et al.* Adjuvant Radiation Therapy After Radical Nephrectomy in Patients with Localized Renal Cell Carcinoma: A Systematic Review and Meta-analysis. *Eur Urol Oncol*, 2019. 2: 448.  
<https://pubmed.ncbi.nlm.nih.gov/31277782/>
425. Galligioni, E., *et al.* Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. *Cancer*, 1996. 77: 2560.  
<https://pubmed.ncbi.nlm.nih.gov/8640706/>
426. Figlin, R.A., *et al.* Multicenter, randomized, phase III trial of CD8(+) tumor-infiltrating lymphocytes in combination with recombinant interleukin-2 in metastatic renal cell carcinoma. *J Clin Oncol*, 1999. 17: 2521.  
<https://pubmed.ncbi.nlm.nih.gov/10561318/>
427. Clark, J.I., *et al.* Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol*, 2003. 21: 3133.  
<https://pubmed.ncbi.nlm.nih.gov/12810695/>
428. Atzpodiën, J., *et al.* Adjuvant treatment with interleukin-2- and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). *Br J Cancer*, 2005. 92: 843.  
<https://pubmed.ncbi.nlm.nih.gov/15756254/>
429. Jocham, D., *et al.* Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. *Lancet*, 2004. 363: 594.  
<https://pubmed.ncbi.nlm.nih.gov/14987883/>
430. Chamie, K., *et al.* Adjuvant Weekly Girentuximab Following Nephrectomy for High-Risk Renal Cell Carcinoma: The ARISER Randomized Clinical Trial. *JAMA Oncol*, 2017. 3: 913.  
<https://pubmed.ncbi.nlm.nih.gov/27787547/>
431. Haas, N.B., *et al.* Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. *JAMA Oncol*, 2017. 3: 1249.  
<https://pubmed.ncbi.nlm.nih.gov/28278333/>
432. Haas, N.B., *et al.* Initial results from ASSURE (E2805): Adjuvant sorafenib or sunitinib for unfavorable renal carcinoma, an ECOG-ACRIN-led, NCTN phase III trial. *ASCO Meeting Abstracts*, 2015. 33: 403.  
[https://ascopubs.org/doi/abs/10.1200/jco.2015.33.7\\_suppl.403](https://ascopubs.org/doi/abs/10.1200/jco.2015.33.7_suppl.403)
433. Motzer, R.J., *et al.* Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. *J Clin Oncol*, 2017. 35: 3916.  
<https://pubmed.ncbi.nlm.nih.gov/28902533/>
434. Motzer, R.J., *et al.* Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma: Final Overall Survival Analysis of the Phase 3 PROTECT Trial. *Eur Urol*, 2021. 79: 334.  
<https://pubmed.ncbi.nlm.nih.gov/33461782/>
435. Harshman, L.C., *et al.* Meta-analysis of disease free survival (DFS) as a surrogate for overall survival (OS) in localized renal cell carcinoma (RCC). *J Clin Oncol*, 2017. 35: 459.  
<https://pubmed.ncbi.nlm.nih.gov/29266178/>
436. Lenis, A.T., *et al.* Adjuvant Therapy for High Risk Localized Kidney Cancer: Emerging Evidence and Future Clinical Trials. *J Urol*, 2018. 199: 43.  
<https://pubmed.ncbi.nlm.nih.gov/28479237/>
437. Gross-Goupil, M., *et al.* Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann Oncol*, 2018. 29: 2371.  
<https://pubmed.ncbi.nlm.nih.gov/30346481/>
438. Motzer, R.J., *et al.* Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. *Eur Urol*, 2018. 73: 62.  
<https://pubmed.ncbi.nlm.nih.gov/28967554/>
439. Ryan, C.W., *et al.* EVEREST: Everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249). *J Clin Oncol*, 2022. 40: LBA4500.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17\\_suppl.LBA4500](https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA4500)



440. Powles, T., *et al.* Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*, 2022. 23: 1133.  
<https://pubmed.ncbi.nlm.nih.gov/36055304/>
441. Choueiri, T.K., *et al.* Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. *N Engl J Med*, 2021. 385: 683.  
<https://pubmed.ncbi.nlm.nih.gov/34407342/>
442. Pal, S.K., *et al.* Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*, 2022. 400: 1103.  
<https://pubmed.ncbi.nlm.nih.gov/36099926/>
443. Motzer, R.J., *et al.* Adjuvant nivolumab plus ipilimumab (NIVO+IPI) vs placebo (PBO) for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy: Results from the randomized, phase III CheckMate 914 trial. *Ann Oncol*, 2022. 33 Suppl 7: S808.  
<https://kidney.uroonco.uroweb.org/publication/adjuvant-nivolumab-plus-ipilimumab-nivoipi-vs-placebo-pbo-for-localized-renal-cell-carcinoma-rcc-at-high-risk-of-relapse-after-nephrectomy-results-from-the-randomized-phase-iii-checkmate-914/>
444. Allaf, M., *et al.* Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol*, 2022. 33 Suppl 7: S808.  
<https://oncologypro.esmo.org/meeting-resources/esmo-congress/phase-iii-randomized-study-comparing-perioperative-nivolumab-nivo-versus-observation-in-patients-pts-with-renal-cell-carcinoma-rcc-undergoing>
445. Bedke, J., *et al.* 2021 Updated European Association of Urology Guidelines on the Use of Adjuvant Pembrolizumab for Renal Cell Carcinoma. *Eur Urol*, 2022. 81: 134.  
<https://pubmed.ncbi.nlm.nih.gov/34920897/>
446. Bedke, J., *et al.* The 2022 Updated European Association of Urology Guidelines on the Use of Adjuvant Immune Checkpoint Inhibitor Therapy for Renal Cell Carcinoma. *Eur Urol*, 2023. 83: 10.  
<https://pubmed.ncbi.nlm.nih.gov/36511268/>
447. Flanigan, R.C., *et al.* Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*, 2004. 171: 1071.  
<https://pubmed.ncbi.nlm.nih.gov/14767273/>
448. Mejean, A., *et al.* Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. *N Engl J Med*, 2018. 379: 417.  
<https://pubmed.ncbi.nlm.nih.gov/29860937/>
449. Bex, A., *et al.* Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. *JAMA Oncol*, 2019. 5: 164.  
<https://pubmed.ncbi.nlm.nih.gov/30543350/>
450. Bhindi, B., *et al.* Systematic Review of the Role of Cytoreductive Nephrectomy in the Targeted Therapy Era and Beyond: An Individualized Approach to Metastatic Renal Cell Carcinoma. *Eur Urol*, 2019. 75: 111.  
<https://pubmed.ncbi.nlm.nih.gov/30467042/>
451. Powles, T., *et al.* The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer. *Eur Urol*, 2011. 60: 448.  
<https://pubmed.ncbi.nlm.nih.gov/21612860/>
452. Heng, D.Y., *et al.* Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol*, 2014. 66: 704.  
<https://pubmed.ncbi.nlm.nih.gov/24931622/>
453. de Bruijn, R., *et al.* Deferred Cytoreductive Nephrectomy Following Presurgical Vascular Endothelial Growth Factor Receptor-targeted Therapy in Patients with Primary Metastatic Clear Cell Renal Cell Carcinoma: A Pooled Analysis of Prospective Trial Data. *Eur Urol Oncol*, 2020. 3: 168.  
<https://pubmed.ncbi.nlm.nih.gov/31956080/>
454. Ljungberg, B., *et al.* Survival advantage of upfront cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma compared with systemic and palliative treatments in a real-world setting. *Scand J Urol*, 2020. 54: 487.  
<https://pubmed.ncbi.nlm.nih.gov/32897123/>

455. Motzer, R.J., *et al.* Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2018. 378: 1277.  
<https://pubmed.ncbi.nlm.nih.gov/29562145/>
456. Choueiri, T.K., *et al.* 696O\_PR - Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: First results from the randomized phase III CheckMate 9ER trial. *Ann Oncol* 2020. 31: S1159.  
[https://www.annalsofncology.org/article/S0923-7534\(20\)42339-7/fulltext](https://www.annalsofncology.org/article/S0923-7534(20)42339-7/fulltext)
457. Motzer, R.J., *et al.* Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2019. 380: 1103.  
<https://pubmed.ncbi.nlm.nih.gov/30779531/>
458. Soulières, D., *et al.* Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma (RCC): Subgroup Analysis From KEYNOTE-426 by Prior Nephrectomy 19th annual meeting of the International Kidney Cancer Symposium, 2020. A Virtual Experience. Access date January 2023.  
<https://www.urotoday.com/conference-highlights/asco-2021/asco-2021-kidney-cancer/130133>
459. Motzer, R.J., *et al.* Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study). *J Clin Oncol*, 2021. 39: 269.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.6\\_suppl.269](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.6_suppl.269)
460. Dabestani, S., *et al.* Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol*, 2014. 15: e549.  
<https://pubmed.ncbi.nlm.nih.gov/25439697/>
461. Dabestani, S., *et al.* EAU Renal Cell Carcinoma Guideline Panel. Systematic review methodology for the EAU RCC Guideline 2013.
462. Brinkmann, O.A., *et al.* The Role of Residual Tumor Resection in Patients with Metastatic Renal Cell Carcinoma and Partial Remission following Immunochemotherapy. *Eur Urol Suppl*, 2007. 6: 641.  
<https://www.sciencedirect.com/science/article/abs/pii/S1569905607000978>
463. Alt, A.L., *et al.* Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer*, 2011. 117: 2873.  
<https://pubmed.ncbi.nlm.nih.gov/21692048/>
464. Kwak, C., *et al.* Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. *Urol Int*, 2007. 79: 145.  
<https://pubmed.ncbi.nlm.nih.gov/17851285/>
465. Petralia, G., *et al.* 450 Complete metastasectomy is an independent predictor of cancer-specific survival in patients with clinically metastatic renal cell carcinoma. *Eur Urol Suppl*, 2010. 9: 162.  
[https://www.eusupplements.europeanurology.com/article/S1569-9056\(10\)60446-0/abstract](https://www.eusupplements.europeanurology.com/article/S1569-9056(10)60446-0/abstract)
466. Russo, P., *et al.* Cytoreductive nephrectomy and nephrectomy/complete metastasectomy for metastatic renal cancer. *Scientific World J*, 2007. 7: 768.  
<https://pubmed.ncbi.nlm.nih.gov/17619759/>
467. Staehler, M.D., *et al.* Metastasectomy significantly prolongs survival in patients with metastatic renal cell cancer. *J. Urol*, 2009. 181: 498.  
[https://www.auajournals.org/article/S0022-5347\(09\)61409-9/pdf](https://www.auajournals.org/article/S0022-5347(09)61409-9/pdf)
468. Eggener, S.E., *et al.* Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. *J Urol*, 2008. 180: 873.  
<https://pubmed.ncbi.nlm.nih.gov/18635225/>
469. Lee, S.E., *et al.* Metastatectomy prior to immunochemotherapy for metastatic renal cell carcinoma. *Urol Int*, 2006. 76: 256.  
<https://pubmed.ncbi.nlm.nih.gov/16601390/>
470. Fuchs, B., *et al.* Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. *Clin Orthop Relat Res*, 2005: 187.  
<https://pubmed.ncbi.nlm.nih.gov/15685074/>
471. Hunter, G.K., *et al.* The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. *Pract Radiat Oncol*, 2012. 2: e95.  
<https://pubmed.ncbi.nlm.nih.gov/24674192/>
472. Zelefsky, M.J., *et al.* Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*, 2012. 82: 1744.  
<https://pubmed.ncbi.nlm.nih.gov/21596489/>

473. Fokas, E., *et al.* Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. *Strahlenther Onkol*, 2010. 186: 210.  
<https://pubmed.ncbi.nlm.nih.gov/20165820/>
474. Ikushima, H., *et al.* Fractionated stereotactic radiotherapy of brain metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*, 2000. 48: 1389.  
<https://pubmed.ncbi.nlm.nih.gov/11121638/>
475. Staehler, M.D., *et al.* Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. *World J Urol*, 2010. 28: 543.  
<https://pubmed.ncbi.nlm.nih.gov/20440505/>
476. Amiraliev, A. Treatment strategy in patients with pulmonary metastases of renal cell cancer. *Int Cardiovasc Thor Surg*, 2012. S20.  
<https://www.researchgate.net/publication/284295837>
477. Zerbi, A., *et al.* Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? *Ann Surg Oncol*, 2008. 15: 1161.  
<https://pubmed.ncbi.nlm.nih.gov/18196343/>
478. Chanez, B., *et al.* Endoscopic Ultrasound-Guided Radiofrequency Ablation as an Future Alternative to Pancreatectomy for Pancreatic Metastases from Renal Cell Carcinoma: A Prospective Study. *Cancers (Basel)*, 2021. 13: 5267.  
<https://pubmed.ncbi.nlm.nih.gov/34771431/>
479. Kroeze, S.G.C., *et al.* Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma. *BJU Int*, 2021. 127: 703.  
<https://pubmed.ncbi.nlm.nih.gov/33113260/>
480. Franzese, C., *et al.* The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group. *Clin Exp Metastasis*, 2021. 38: 527.  
<https://pubmed.ncbi.nlm.nih.gov/34748125/>
481. Cheung, P., *et al.* Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study. *Eur Urol*, 2021. 80: 693.  
<https://pubmed.ncbi.nlm.nih.gov/34399998/>
482. Heng, D.Y., *et al.* Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*, 2009. 27: 5794.  
<https://pubmed.ncbi.nlm.nih.gov/19826129/>
483. Bedke, J., *et al.* The 2021 Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibitor-based Combination Therapies for Treatment-naive Metastatic Clear-cell Renal Cell Carcinoma Are Standard of Care. *Eur Urol*, 2021. 80: 393.  
<https://pubmed.ncbi.nlm.nih.gov/34074559/>
484. Harrison, M.R., *et al.* Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). *Cancer*, 2021. 127: 2204.  
<https://pubmed.ncbi.nlm.nih.gov/33765337/>
485. Rini, B.I., *et al.* Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol*, 2016. 17: 1317.  
<https://pubmed.ncbi.nlm.nih.gov/27498080/>
486. Patel, P.H., *et al.* Targeting von Hippel-Lindau pathway in renal cell carcinoma. *Clin Cancer Res*, 2006. 12: 7215.  
<https://pubmed.ncbi.nlm.nih.gov/17189392/>
487. Yang, J.C., *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*, 2003. 349: 427.  
<https://pubmed.ncbi.nlm.nih.gov/12890841/>
488. Patard, J.J., *et al.* Understanding the importance of smart drugs in renal cell carcinoma. *Eur Urol*, 2006. 49: 633.  
<https://pubmed.ncbi.nlm.nih.gov/16481093/>
489. Motzer, R.J., *et al.* Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2009. 27: 3584.  
<https://pubmed.ncbi.nlm.nih.gov/19487381/>
490. Motzer, R.J., *et al.* Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *J Clin Oncol*, 2012. 30: 1371.  
<https://pubmed.ncbi.nlm.nih.gov/22430274/>

491. Bracarda, S., *et al.* Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol*, 2016. 27: 366.  
<https://pubmed.ncbi.nlm.nih.gov/26685011/>
492. Jonasch, E., *et al.* A randomized phase 2 study of MK-2206 versus everolimus in refractory renal cell carcinoma. *Ann Oncol*, 2017. 28: 804.  
<https://pubmed.ncbi.nlm.nih.gov/28049139/>
493. Sternberg, C.N., *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*, 2010. 28: 1061.  
<https://pubmed.ncbi.nlm.nih.gov/20100962/>
494. Motzer, R.J., *et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*, 2013. 369: 722.  
<https://pubmed.ncbi.nlm.nih.gov/23964934/>
495. Escudier, B., *et al.* Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *J Clin Oncol*, 2014. 32: 1412.  
<https://pubmed.ncbi.nlm.nih.gov/24687826/>
496. Rini, B.I., *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*, 2011. 378: 1931.  
<https://pubmed.ncbi.nlm.nih.gov/22056247/>
497. Motzer, R.J., *et al.* Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*, 2013. 14: 552.  
<https://pubmed.ncbi.nlm.nih.gov/23598172/>
498. Hutson, T.E., *et al.* Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*, 2013. 14: 1287.  
<https://pubmed.ncbi.nlm.nih.gov/24206640/>
499. Choueiri, T.K., *et al.* Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2015. 373: 1814.  
<https://pubmed.ncbi.nlm.nih.gov/26406150/>
500. Choueiri, T.K., *et al.* Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*, 2016. 17: 917.  
<https://pubmed.ncbi.nlm.nih.gov/27279544/>
501. Choueiri, T.K., *et al.* Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *J Clin Oncol*, 2017. 35: 591.  
<https://pubmed.ncbi.nlm.nih.gov/28199818/>
502. Choueiri, T.K., *et al.* Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. *Eur J Cancer*, 2018. 94: 115.  
<https://pubmed.ncbi.nlm.nih.gov/29550566/>
503. Motzer, R.J., *et al.* Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*, 2015. 16: 1473.  
<https://pubmed.ncbi.nlm.nih.gov/26482279/>
504. Motzer, R.J., *et al.* Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol*, 2013. 31: 3791.  
<https://pubmed.ncbi.nlm.nih.gov/24019545/>
505. Molina, A.M., *et al.* Efficacy of tivozanib treatment after sorafenib in patients with advanced renal cell carcinoma: crossover of a phase 3 study. *Eur J Cancer*, 2018. 94: 87.  
<https://pubmed.ncbi.nlm.nih.gov/29547835/>
506. Escudier B., *et al.* Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol*, 2010. 28: 2144.  
<https://pubmed.ncbi.nlm.nih.gov/20368553/>
507. Rini, B.I., *et al.* Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*, 2008. 26: 5422.  
<https://pubmed.ncbi.nlm.nih.gov/18936475/>
508. Rini, B.I., *et al.* Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol*, 2010. 28: 2137.  
<https://pubmed.ncbi.nlm.nih.gov/20368558/>

509. Rini, B.I., *et al.* Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet*, 2019. 393: 2404.  
<https://pubmed.ncbi.nlm.nih.gov/31079938/>
510. Larkin, J.M., *et al.* Kinase inhibitors in the treatment of renal cell carcinoma. *Crit Rev Oncol Hematol*, 2006. 60: 216.  
<https://pubmed.ncbi.nlm.nih.gov/16860997/>
511. Motzer, R.J., *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*, 2008. 372: 449.  
<https://pubmed.ncbi.nlm.nih.gov/18653228/>
512. Ribas, A. Tumor immunotherapy directed at PD-1. *N Engl J Med*, 2012. 366: 2517.  
<https://pubmed.ncbi.nlm.nih.gov/22658126/>
513. Motzer, R.J., *et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2015. 373: 1803.  
<https://pubmed.ncbi.nlm.nih.gov/26406148/>
514. Motzer, R.J., *et al.* Nivolumab versus everolimus in patients with advanced renal cell carcinoma: Updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. *Cancer*, 2020.  
<https://pubmed.ncbi.nlm.nih.gov/32673417/>
515. McDermott, D.F., *et al.* Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*, 2018. 24: 749.  
<https://pubmed.ncbi.nlm.nih.gov/29867230/>
516. McDermott, D.F., *et al.* Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (ccRCC): Results from cohort A of KEYNOTE-427. *J Clin Oncol*, 2018. 36.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15\\_suppl.4500](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4500)
517. Atkins, M.B., *et al.* Phase II Study of Nivolumab and Salvage Nivolumab/Ipilimumab in Treatment-Naive Patients With Advanced Clear Cell Renal Cell Carcinoma (HCRN GU16-260-Cohort A). *J Clin Oncol*, 2022. 40: 2913.  
<https://pubmed.ncbi.nlm.nih.gov/35442713/>
518. Choueiri, T.K., *et al.* FRACTION-RCC: nivolumab plus ipilimumab for advanced renal cell carcinoma after progression on immuno-oncology therapy. *J Immunother Cancer*, 2022. 10.  
<https://pubmed.ncbi.nlm.nih.gov/36328377/>
519. Ljungberg, B., *et al.* European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur Urol*, 2019. 75: 799.  
<https://pubmed.ncbi.nlm.nih.gov/30803729/>
520. Motzer, R.J., *et al.* 661P Conditional survival and 5-year follow-up in CheckMate 214: First-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *Ann Oncol*, 2021. 32: S685.  
[https://www.annalsofoncology.org/article/S0923-7534\(21\)02271-7/fulltext](https://www.annalsofoncology.org/article/S0923-7534(21)02271-7/fulltext)
521. Choueiri, T., *et al.* LBA8 - Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). *Ann Oncol*, 2022. 33 Suppl. 7.  
<https://oncologypro.esmo.org/meeting-resources/esmo-congress/phase-iii-study-of-cabozantinib-c-in-combination-with-nivolumab-n-and-ipilimumab-i-in-previously-untreated-advanced-renal-cell-carcinoma-arc>
522. Motzer R.J., *et al.* Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer*. 2022. 128: 2085.  
<https://pubmed.ncbi.nlm.nih.gov/35383908/>
523. Rini, B.I., *et al.* Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2019. 380: 1116.  
<https://pubmed.ncbi.nlm.nih.gov/30779529/>
524. Rini, B.I., *et al.* Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426. *J Clin Oncol*, 2021. 39: 4500.  
<https://www.urotoday.com/conference-highlights/asco-2021/asco-2021-kidney-cancer/130182>
525. Choueiri, T.K., *et al.* Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2021. 384: 829.  
<https://pubmed.ncbi.nlm.nih.gov/33657295/>



526. Motzer, R.J., *et al.* Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*, 2022. 23: 888.  
<https://pubmed.ncbi.nlm.nih.gov/35688173/>
527. Motzer, R., *et al.* Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*, 2021.  
<https://pubmed.ncbi.nlm.nih.gov/33616314/>
528. Choueiri, T.K., *et al.* Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*, 2020. 31: 1030.  
<https://pubmed.ncbi.nlm.nih.gov/32339648/>
529. Motzer, R.J., *et al.* Final Overall Survival and Molecular Analysis in IMmotion151, a Phase 3 Trial Comparing Atezolizumab Plus Bevacizumab vs Sunitinib in Patients With Previously Untreated Metastatic Renal Cell Carcinoma. *JAMA Oncol*, 2022. 8: 275.  
<https://pubmed.ncbi.nlm.nih.gov/34940781/>
530. Powles, T., *et al.* Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol*, 2020. 21: 1563.  
<https://pubmed.ncbi.nlm.nih.gov/33284113/>
531. Choueiri T, *et al.*, A phase 3 trial of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma: overall survival follow-up analysis (the CLEAR study), in *Kidney Cancer Research Summit*. 2021: Philadelphia, USA.
532. Tannir, N.M., *et al.* Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). *J Clin Oncol*, 2019. 37: 547.  
[https://ascopubs.org/doi/10.1200/JCO.2019.37.7\\_suppl.547](https://ascopubs.org/doi/10.1200/JCO.2019.37.7_suppl.547)
533. Motzer R.J., *et al.* Nivolumab + Ipilimumab (N+I) vs Sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (aRCC): results from CheckMate 214, including overall survival by subgroups *J Immunother Cancer*, 2017. 5: 3.  
<https://link.springer.com/article/10.1186/s40425-017-0297-3>
534. Auvray, M., *et al.* Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma. *Eur J Cancer*, 2019. 108: 33.  
<https://pubmed.ncbi.nlm.nih.gov/30616146/>
535. Ornstein, M.C., *et al.* Prospective phase II multi-center study of individualized axitinib (Axi) titration for metastatic renal cell carcinoma (mRCC) after treatment with PD-1 / PD-L1 inhibitors. *J Clin Oncol*, 2018. 36.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15\\_suppl.4517](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4517)
536. Pal, S.K., *et al.* Assessing the Safety and Efficacy of Two Starting Doses of Lenvatinib Plus Everolimus in Patients with Renal Cell Carcinoma: A Randomized Phase 2 Trial. *Eur Urol*, 2022. 82: 283.  
<https://pubmed.ncbi.nlm.nih.gov/35210132/>
537. Lee, C.H., *et al.* Lenvatinib plus pembrolizumab in patients with either treatment-naïve or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study. *Lancet Oncol*, 2021. 22: 946.  
<https://pubmed.ncbi.nlm.nih.gov/34143969/>
538. Coppin, C., *et al.* Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. *BJU Int*, 2011. 108: 1556.  
<https://pubmed.ncbi.nlm.nih.gov/21952069/>
539. Rini, B.I., *et al.* Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol*, 2020. 21: 95.  
<https://pubmed.ncbi.nlm.nih.gov/31810797/>
540. Rini, B.I., *et al.* Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. *J Clin Oncol*, 2019. 37: 4500.  
[https://ascopubs.org/doi/10.1200/JCO.2019.37.15\\_suppl.4500](https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.4500)
541. Choueiri, T.K., *et al.* Efficacy and biomarker analysis of patients (pts) with advanced renal cell carcinoma (aRCC) with sarcomatoid histology (sRCC): Subgroup analysis from the phase III JAVELIN renal 101 trial of first-line avelumab plus axitinib (A + Ax) vs sunitinib (S). *Ann Oncol*, 2019. 30: v361.  
[https://www.annalsofncology.org/article/S0923-7534\(19\)59126-8/fulltext](https://www.annalsofncology.org/article/S0923-7534(19)59126-8/fulltext)



542. Choueiri, T.K., *et al.* Efficacy and correlative analyses of avelumab plus axitinib versus sunitinib in sarcomatoid renal cell carcinoma: post hoc analysis of a randomized clinical trial. *ESMO Open*, 2021. 6: 100101.  
<https://pubmed.ncbi.nlm.nih.gov/33901870/>
543. Rini, B.I., *et al.* Atezolizumab plus Bevacizumab Versus Sunitinib for Patients with Untreated Metastatic Renal Cell Carcinoma and Sarcomatoid Features: A Prespecified Subgroup Analysis of the IMmotion151 Clinical Trial. *Eur Urol*, 2021. 79: 659.  
<https://pubmed.ncbi.nlm.nih.gov/32654802/>
544. McDermott, D.F., *et al.* CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. *J Clin Oncol*, 2019. 37: 4513.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15\\_suppl.4513](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4513)
545. Motzer, R.J., *et al.* Nivolumab + cabozantinib (NIVO+CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): Outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. *J Clin Oncol*, 2021. 39: 308.  
[https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.6\\_suppl.308](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.6_suppl.308)
546. Choueiri, T., *et al.* 660P Phase III CLEAR trial in advanced renal cell carcinoma (aRCC): Outcomes in subgroups and toxicity update. *Ann Oncol*, 2021. 32: S683.  
<https://oncologypro.esmo.org/meeting-resources/esmo-congress/phase-iii-clear-trial-in-advanced-renal-cell-carcinoma-arcc-outcomes-in-subgroups-and-toxicity-update>
547. Hudes, G., *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*, 2007. 356: 2271.  
<https://pubmed.ncbi.nlm.nih.gov/17538086/>
548. Gore, M.E., *et al.* Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol*, 2009. 10: 757.  
<https://pubmed.ncbi.nlm.nih.gov/19615940/>
549. Sánchez P, *et al.* Non-clear cell advanced kidney cancer: is there a gold standard? *Anticancer Drugs* 2011. 22 S9.  
<https://pubmed.ncbi.nlm.nih.gov/21173605/>
550. Koh, Y., *et al.* Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. *Ann Oncol*, 2013. 24: 1026.  
<https://pubmed.ncbi.nlm.nih.gov/23180114/>
551. Fernández-Pello, S., *et al.* A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma. *Eur Urol*, 2017. 71: 426.  
<https://pubmed.ncbi.nlm.nih.gov/27939075/>
552. Tannir, N.M., *et al.* A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol*, 2012. 62: 1013.  
<https://pubmed.ncbi.nlm.nih.gov/22771265/>
553. Ravaud A, *et al.* First-line sunitinib in type I and II papillary renal cell carcinoma (PRCC): SUPAP, a phase II study of the French Genito-Urinary Group (GETUG) and the Group of Early Phase trials (GEP) *J Clin Oncol*, 2009. Vol 27, No 15S: 5146.  
[https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15\\_suppl.5146](https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15_suppl.5146)
554. Escudier, B., *et al.* Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer*, 2016. 69: 226.  
<https://pubmed.ncbi.nlm.nih.gov/27680407/>
555. Pal, S.K., *et al.* A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet*, 2021. 397: 695.  
<https://pubmed.ncbi.nlm.nih.gov/33592176/>
556. Choueiri, T.K., *et al.* Efficacy of Savolitinib vs Sunitinib in Patients With MET-Driven Papillary Renal Cell Carcinoma: The SAVOIR Phase 3 Randomized Clinical Trial. *JAMA Oncol*, 2020. 6: 1247.  
<https://pubmed.ncbi.nlm.nih.gov/32469384/>
557. Albiges, L., *et al.* 1448O Phase II KEYNOTE-B61 study of pembrolizumab (Pembro) + lenvatinib (Lenva) as first-line treatment for non-clear cell renal cell carcinoma (nccRCC). *Ann Oncol*, 2022. 33: S1204.  
<https://oncologypro.esmo.org/meeting-resources/esmo-congress/phase-ii-keynote-b61-study-of-pembrolizumab-pembro-lenvatinib-lenva-as-first-line-treatment-for-non-clear-cell-renal-cell-carcinoma-nccrcc>

558. Lee, C.H., *et al.* Phase II Trial of Cabozantinib Plus Nivolumab in Patients With Non-Clear-Cell Renal Cell Carcinoma and Genomic Correlates. *J Clin Oncol*, 2022. 40: 2333.  
<https://pubmed.ncbi.nlm.nih.gov/35298296/>
559. McDermott, D.F., *et al.* Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Non-Clear Cell Renal Cell Carcinoma. *J Clin Oncol*, 2021. 39: 1029.  
<https://pubmed.ncbi.nlm.nih.gov/33529058/>
560. Msaouel, P., *et al.* Updated Recommendations on the Diagnosis, Management, and Clinical Trial Eligibility Criteria for Patients With Renal Medullary Carcinoma. *Clin Genitourin Cancer*, 2019. 17: 1.  
<https://pubmed.ncbi.nlm.nih.gov/30287223/>
561. Beckermann, K.E., *et al.* Clinical and immunologic correlates of response to PD-1 blockade in a patient with metastatic renal medullary carcinoma. *J Immunother Cancer*, 2017. 5: 1.  
<https://pubmed.ncbi.nlm.nih.gov/28105368/>
562. Sodji, Q., *et al.* Predictive role of PD-L1 expression in the response of renal Medullary carcinoma to PD-1 inhibition. *J Immunother Cancer*, 2017. 5: 62.  
<https://pubmed.ncbi.nlm.nih.gov/28807004/>
563. Rathmell, W.K., *et al.* High-dose-intensity MVAC for Advanced Renal Medullary Carcinoma: Report of Three Cases and Literature Review. *Urology*, 2008. 72: 659.  
<https://pubmed.ncbi.nlm.nih.gov/18649931/>
564. Jonasch, E., *et al.* Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. *N Engl J Med*, 2021. 385: 2036.  
<https://pubmed.ncbi.nlm.nih.gov/34818478/>
565. Jonasch, E., *et al.* Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. *Lancet Oncol*, 2018. 19: 1351.  
<https://pubmed.ncbi.nlm.nih.gov/30236511/>
566. Srinivasan, R., *et al.* LBA69 - Belzutifan, a HIF-2 $\alpha$  Inhibitor, for von Hippel-Lindau (VHL) disease-associated neoplasms: 36 months of follow-up of the phase II LITESPARK-004 study. *Ann Oncol*, 2022. 33: S808.  
<https://oncologypro.esmo.org/meeting-resources/esmo-congress/belzutifan-a-hif-2a-inhibitor-for-von-hippel-lindau-vhl-disease-associated-neoplasms-36-months-of-follow-up-of-the-phase-ii-litespark-004-study>
567. Antonelli, A., *et al.* Features of Ipsilateral Renal Recurrences After Partial Nephrectomy: A Proposal of a Pathogenetic Classification. *Clin Genitourin Cancer*, 2017. 15: 540.  
<https://pubmed.ncbi.nlm.nih.gov/28533051/>
568. Bertolo, R., *et al.* Low Rate of Cancer Events After Partial Nephrectomy for Renal Cell Carcinoma: Clinicopathologic Analysis of 1994 Cases with Emphasis on Definition of "Recurrence". *Clin Genitourin Cancer*, 2019. 17: 209.  
<https://pubmed.ncbi.nlm.nih.gov/31000486/>
569. Kreshover, J.E., *et al.* Renal cell recurrence for T1 tumors after laparoscopic partial nephrectomy. *J Endourol*, 2013. 27: 1468.  
<https://pubmed.ncbi.nlm.nih.gov/24074156/>
570. Wah, T.M., *et al.* Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. *BJU Int*, 2014. 113: 416.  
<https://pubmed.ncbi.nlm.nih.gov/24053769/>
571. Herout, R., *et al.* Surgical resection of locally recurrent renal cell carcinoma after nephrectomy: Oncological outcome and predictors of survival. *Urol Oncol*, 2018. 36: 11 e1.  
<https://pubmed.ncbi.nlm.nih.gov/28927783/>
572. Thomas, A.Z., *et al.* Surgical Management of Local Retroperitoneal Recurrence of Renal Cell Carcinoma after Radical Nephrectomy. *J Urol*, 2015. 194: 316.  
<https://pubmed.ncbi.nlm.nih.gov/25758610/>
573. Marchioni, M., *et al.* Management of local recurrence after radical nephrectomy: surgical removal with or without systemic treatment is still the gold standard. Results from a multicenter international cohort. *Int Urol Nephrol*, 2021. 53: 2273.  
<https://pubmed.ncbi.nlm.nih.gov/34417970/>
574. Itano, N.B., *et al.* Outcome of isolated renal cell carcinoma fossa recurrence after nephrectomy. *J Urol*, 2000. 164: 322.  
<https://pubmed.ncbi.nlm.nih.gov/10893575/>
575. Margulis, V., *et al.* Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol*, 2009. 181: 2044.  
<https://pubmed.ncbi.nlm.nih.gov/19286220/>

576. Russell, C.M., *et al.* Multi-institutional Survival Analysis of Incidental Pathologic T3a Upstaging in Clinical T1 Renal Cell Carcinoma Following Partial Nephrectomy. *Urology*, 2018. 117: 95.  
<https://pubmed.ncbi.nlm.nih.gov/29678662/>
577. Srivastava, A., *et al.* Incidence of T3a up-staging and survival after partial nephrectomy: Size-stratified rates and implications for prognosis. *Urol Oncol*, 2018. 36: 12.e7.  
<https://pubmed.ncbi.nlm.nih.gov/28970053/>
578. Sandhu, S.S., *et al.* Surgical excision of isolated renal-bed recurrence after radical nephrectomy for renal cell carcinoma. *BJU Int*, 2005. 95: 522.  
<https://pubmed.ncbi.nlm.nih.gov/15705072/>
579. Master, V.A., *et al.* Management of isolated renal fossa recurrence following radical nephrectomy. *J Urol*, 2005. 174: 473.  
<https://pubmed.ncbi.nlm.nih.gov/16006867/>
580. Psutka, S.P., *et al.* Renal fossa recurrence after nephrectomy for renal cell carcinoma: prognostic features and oncological outcomes. *BJU Int*, 2017. 119: 116.  
<https://pubmed.ncbi.nlm.nih.gov/27489013/>
581. Martini, A., *et al.* Salvage Robot-assisted Renal Surgery for Local Recurrence After Surgical Resection or Renal Mass Ablation: Classification, Techniques, and Clinical Outcomes. *Eur Urol*, 2021. 80: 730.  
<https://pubmed.ncbi.nlm.nih.gov/34088520/>
582. Ierardi, A.M., *et al.* Percutaneous microwave ablation therapy of renal cancer local relapse after radical nephrectomy: a feasibility and efficacy study. *Medical Oncology*, 2020. 37: 27.  
<https://pubmed.ncbi.nlm.nih.gov/32166412/>
583. Ushijima, Y., *et al.* Cryoablation for Secondary Renal Cell Carcinoma After Surgical Nephrectomy. *Cardiovasc Intervent Radiol*, 2021. 44: 414.  
<https://pubmed.ncbi.nlm.nih.gov/33205290/>
584. Johnson, A., *et al.* Feasibility and outcomes of repeat partial nephrectomy. *J Urol*, 2008. 180: 89.  
<https://pubmed.ncbi.nlm.nih.gov/18485404/>
585. Mouracade, P., *et al.* Imaging strategy and outcome following partial nephrectomy. *Urol Oncol*, 2017. 35: 660.e1.  
<https://pubmed.ncbi.nlm.nih.gov/28863862/>
586. Dabestani, S., *et al.* Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized R.C.C.: results from a European multicenter database (R.E.C.U.R.). *Scand J Urol*, 2019. 53: 14.  
<https://pubmed.ncbi.nlm.nih.gov/30907214/>
587. Rieken, M., *et al.* Predictors of Cancer-specific Survival After Disease Recurrence in Patients With Renal Cell Carcinoma: The Effect of Time to Recurrence. *Clin Genitourin Cancer*, 2018. 16: e903.  
<https://pubmed.ncbi.nlm.nih.gov/29653814/>
588. Capitanio, U., *et al.* Hypertension and Cardiovascular Morbidity Following Surgery for Kidney Cancer. *Eur Urol Oncol*, 2020. 3: 209.  
<https://pubmed.ncbi.nlm.nih.gov/31411993/>
589. Lam, J.S., *et al.* Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy. *J Urol*, 2005. 173: 1853.  
<https://pubmed.ncbi.nlm.nih.gov/15879764/>
590. Scoll, B.J., *et al.* Age, tumor size and relative survival of patients with localized renal cell carcinoma: a surveillance, epidemiology and end results analysis. *J Urol*, 2009. 181: 506.  
<https://pubmed.ncbi.nlm.nih.gov/19084868/>
591. Beisland, C., *et al.* A prospective risk-stratified follow-up programme for radically treated renal cell carcinoma patients: evaluation after eight years of clinical use. *World J Urol*, 2016. 34: 1087.  
<https://pubmed.ncbi.nlm.nih.gov/26922650/>
592. Stewart-Merrill, S.B., *et al.* Oncologic Surveillance After Surgical Resection for Renal Cell Carcinoma: A Novel Risk-Based Approach. *J Clin Oncol*, 2015. 33: 4151.  
<https://pubmed.ncbi.nlm.nih.gov/26351352/>
593. Dabestani, S., *et al.* Long-term Outcomes of Follow-up for Initially Localised Clear Cell Renal Cell Carcinoma: RECUR Database Analysis. *Eur Urol Focus*, 2019. 5: 857.  
<https://pubmed.ncbi.nlm.nih.gov/29525381/>
594. Rini, B.I., *et al.* Validation of the 16-Gene Recurrence Score in Patients with Locoregional, High-Risk Renal Cell Carcinoma from a Phase III Trial of Adjuvant Sunitinib. *Clin Cancer Res*, 2018. 24: 4407.  
<https://pubmed.ncbi.nlm.nih.gov/29773662/>

595. Bruno, J.J., 2nd, *et al.* Renal cell carcinoma local recurrences: impact of surgical treatment and concomitant metastasis on survival. *BJU Int*, 2006. 97: 933.  
<https://pubmed.ncbi.nlm.nih.gov/16643473/>
596. Bani-Hani, A.H., *et al.* Associations with contralateral recurrence following nephrectomy for renal cell carcinoma using a cohort of 2,352 patients. *J Urol*, 2005. 173: 391.  
<https://pubmed.ncbi.nlm.nih.gov/15643178/>
597. Schaner, E.G., *et al.* Comparison of computed and conventional whole lung tomography in detecting pulmonary nodules: a prospective radiologic-pathologic study. *Am J Roentgenol*, 1978. 131: 51.  
<https://pubmed.ncbi.nlm.nih.gov/97985/>
598. Patel, T. Lung Metastases Imaging. 2017.  
<https://emedicine.medscape.com/article/358090-overview>
599. Chang, A.E., *et al.* Evaluation of computed tomography in the detection of pulmonary metastases: a prospective study. *Cancer*, 1979. 43: 913.  
<https://pubmed.ncbi.nlm.nih.gov/284842/>
600. Doornweerd, B.H., *et al.* Chest X-ray in the follow-up of renal cell carcinoma. *World J Urol*, 2014. 32: 1015.  
<https://pubmed.ncbi.nlm.nih.gov/24096433/>
601. Sountoulides, P., *et al.* Atypical presentations and rare metastatic sites of renal cell carcinoma: a review of case reports. *J Med Case Rep*, 2011. 5: 429.  
<https://pubmed.ncbi.nlm.nih.gov/21888643/>
602. Kattan, M.W., *et al.* A postoperative prognostic nomogram for renal cell carcinoma. *J Urol*, 2001. 166: 63.  
<https://pubmed.ncbi.nlm.nih.gov/11435824/>
603. Lam, J.S., *et al.* Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. *J Urol*, 2005. 174: 466.  
<https://pubmed.ncbi.nlm.nih.gov/16006866/>
604. Cindolo, L., *et al.* Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy: a multicenter European study. *Cancer*, 2005. 104: 1362.  
<https://pubmed.ncbi.nlm.nih.gov/16116599/>
605. Skolarikos, A., *et al.* A review on follow-up strategies for renal cell carcinoma after nephrectomy. *Eur Urol*, 2007. 51: 1490.  
<https://pubmed.ncbi.nlm.nih.gov/17229521/>
606. Chin, A.I., *et al.* Surveillance strategies for renal cell carcinoma patients following nephrectomy. *Rev Urol*, 2006. 8: 1.  
<https://pubmed.ncbi.nlm.nih.gov/16985554/>
607. Karakiewicz, P.I., *et al.* A preoperative prognostic model for patients treated with nephrectomy for renal cell carcinoma. *Eur Urol*, 2009. 55: 287.  
<https://pubmed.ncbi.nlm.nih.gov/18715700/>
608. Cho, H., *et al.* Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. *Ann Intern Med*, 2013. 159: 667.  
<https://pubmed.ncbi.nlm.nih.gov/24247672/>

## 10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <https://uroweb.org/guideline/renalcell-carcinoma/?type=panel/>.

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