EAU Guidelines on

Renal Cell Carcinoma

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TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aims and scope

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

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

1.2 Panel composition

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

All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/renalcellcarcinoma/.

1.3 Acknowledgement

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

1.4 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices, presenting the main findings of the RCC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU RCC Guidelines [1, 2]. 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 2019 RCC Guidelines document presents a limited update of the 2018 publication.

1.5.2 Summary of changes

All chapters of the 2019 RCC Guidelines have been updated, based on the 2018 version of the Guidelines. References have been added throughout the document.

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

3.4 Recommendations for the management of other renal tumours

Recommendations	Strength rating
Treat Bosniak type III cysts the same as RCC or offer cautious surveillance.	Weak
Treat Bosniak type IV cysts the same as RCC.	Strong
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

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

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib or axitinib.	Strong

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic renal cell cancer

Summary of evidence	LE
Cytoreductive nephrectomy followed by sunitinib is non-inferior to sunitinib alone in patients with metastatic ccRCC.	1a
Sunitinib alone is non-inferior compared to immediate cytoreductive nephrectomy followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKIs.	1a

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

2. METHODS

2.1 Data identification

For the 2018 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the chapters as listed in Table 2.1.

A broad and comprehensive scoping search was performed, which was limited to studies representing high levels of evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between July 11th, 2017 and June 18th, 2018. Databases covered included Medline, EMBASE, and the Cochrane Library. After deduplication, a total of 996 unique records were identified, retrieved and screened for relevance.

A total of 39 new references have been included in the 2019 RCC Guidelines publication. A search strategy is published online: https://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [3, 4]. 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 [5];
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' [6]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Specific chapters were updated by way of SRs, commissioned and undertaken by the Panel in conjunction with the EAU Guidelines Office, based on topics or questions prioritised by the Guidelines Panel. These reviews were performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/aboutcochranesystematic-reviews.html.

Table 2.1: Description of update and summary of review methodology

Chapter	Brief description of review methodology
1. Introduction	Not applicable.
2. Methods	Not applicable.
3. Epidemiology, aetiology and pathology.	This chapter was updated by a narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a narrative review, based on a structured literature assessment.
5. Diagnostic evaluation	Section 5.2 (Diagnostic imaging) was revised based on a SR [7]. The remainder of the chapter was updated by a structured literature assessment.
6. Prognosis	This chapter was updated by a narrative review, based on a structured literature assessment.
7. Treatment (Disease management)	Sections 7.1.2 and 7.2.4 (Treatment of localised and locally advanced disease) were revised based on an updated SR. Section 7.4.6.2 (Non-clear-cell cancer) was updated by means of a SR [8] The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease: this section was updated by a SR.
8. Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a narrative review, based on a structured literature assessment. The findings of a prospective database set up by the RCC Panel have been included [9].

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

2.2 Review

All publications ensuring from SRs have been peer reviewed. This 2019 print of the RCC Guidelines has been peer-reviewed prior to publication.

2.3 Future goals

For their future updates, the RCC Guideline Panel aims to focus on patient-reported outcomes.

The use of clinical quality indicators is an area of interest for the RCC Panel. A number of key quality indicators for this patient group have been selected:

- thorax computed tomography (CT) for staging of pulmonary metastasis;
- proportion of patients with T1aN0M0 tumours undergoing nephron-sparing surgery as first treatment;
- the proportion of patients treated within six weeks after diagnosis;
- the proportion of patients with metastatic RCC (mRCC) offered systemic therapy;
- proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

The panel have set up a database to investigate current practice in follow-up of RCC patients in a number of European centres. Assessing patterns of recurrence and use of imaging techniques are primary outcomes for this project.

The results of ongoing and new SRs will be included in the 2020 update of the RCC Guidelines:

- Ablative therapy vs. partial nephrectomy for T1-T2 renal cell cancer;
- What is the best treatment option for ≥ T2 tumours?;
- Systematic review and meta-analysis of systemic therapy of renal tumours (Cochrane Review);
- What are the indications for treatment of angiomyolipoma and what are the best options to perform this treatment?;
- Adjuvant targeted therapy for renal cell carcinoma at high risk for recurrence.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell cancer represents 2-3% of all cancers with the highest incidence in Western countries. Over the last two decades the incidence of RCC increased by about 2%, both worldwide and in Europe. The incidence varies globally, with the highest rates in developed countries such as North America and Europe and the lowest rates in Asia and Africa. In Western European countries this incidence stabilised over the past decade. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney-cancer-related deaths in the European Union [10, 11]. In Europe, overall mortality rates for RCC increased up to the early 1990s, before stabilising or declining thereafter [12]. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend. Data from the United States also show increased incidence [13].

There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity and hypertension [14]. Having a first-degree relative with RCC also increases the risk of RCC. A number of other factors associated with higher or lower RCC-risk include specific dietary habits, occupational exposure to specific carcinogens, acetaminophen and non-aspirin non-steroidal anti-inflammatory drugs, cruciferous vegetables, nephrolithiasis, and viral hepatitis [15], however, data from the literature are still inconclusive. Moderate alcohol consumption appears to have a protective effect for unknown reasons [16-19]. Effective prophylaxis includes avoidance of cigarette smoking and obesity [20, 21]. Physical inactivity, excessive alcohol consumption, unhealthy body weight and poor diet choices could account for more than 20% of cancer cases [10, 21].

Due to increased detection of tumours by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are usually smaller and of lower stage [22].

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

Summary of evidence	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

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

3.2 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [23]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). The RCC type classification has been confirmed by cytogenetic and genetic analyses [23] (LE: 2b). Collecting duct carcinoma and other rare renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type; evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and peri-renal fat, pT, or even pN categories.

The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [23].

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

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau *(VHL)* gene at chromosome 3p25 are frequently found, including additional tumour suppressor genes including *SETD2, BAP1*, and *PBRM1*; all genes are identified near the *VHL* gene within a region that is frequently deleted in ccRCC [24]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC [25, 26] even after stratification for stage and grade [27]. The five-year cancer-specific-survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated between 1987-1998), respectively [28]. For more details, see Section 6.3 - Histological factors.

3.2.2 ***Papillary renal cell cancer***

Papillary RCC is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [23]. Type I and II pRCC, which were shown to be clinically and biologically distinct; pRCC type I is associated with activating germline mutations of *MET* and pRCC type II is associated with activation of the NRF2-ARE pathway with at least three subtypes [29]. Macroscopically, pRCC is well circumscribed with a pseudocapsule, a yellow or brown colour, and a soft structure. Compared to ccRCC, pRCC has a significantly higher rate of organ-confined tumour (pT1-2N0M0) and a higher five-year CSS rate [30]. Papillary RCC type I is more common and generally considered to have a better prognosis than pRCC type II [23, 31]. Exophytic spherical growth, pseudo-necrotic changes and pseudocapsule are typical signs of pRCC type I. Tumours are fragile. On post-contrast CT, a hypodense central area of tumour surrounded by vital tumour tissue is seen, presented as a serpiginous contrast-enhancing margin on CT [32].

3.2.3 ***Chromophobe renal cell cancer***

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Chromophobe RCC cannot be graded (by the Fuhrman grading system), because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [23]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [23]. The prognosis is relatively good, with high five-year recurrence-free survival (RFS), and ten-year CSS [33]. The new WHO/ISUP Grading system merges former entity hybrid oncocytic chromophobe tumour with chRCC.

3.3 Other renal tumours

Other renal tumours constitute the remaining 10-15% of renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

3.3.1 ***Renal medullary carcinoma***

Renal medullary carcinoma (RMC) is a very rare tumour, comprising < 0.5% of all RCCs [34], it is predominantly diagnosed in young adults (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [35, 36] and most patients (~67%) will present with metastatic disease [35, 37]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter; often within a few weeks.

3.3.1.1 Treatment of renal medullary carcinoma

Despite treatment, median OS is 13 months in the most recent series [35]. Due to the infiltrative nature and medullary epicentre of RMC, radical nephrectomy (RN) is favoured over partial nephrectomy (PN) even in very early-stage disease. Retrospective data indicate that nephrectomy in localised disease results in superior OS (16.4 vs. 7.0 months) compared with systemic chemotherapy alone [35]. 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 [38, 39]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens, both tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors [35, 40, 41]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [40]. 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 methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has also shown efficacy against RMC [42] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine (CPG) [36]. Single-agent anti-PD-1 (monoclonal antibodies against programmed death-1) immune checkpoint therapy has produced responses in a few case reports, although, as yet, insufficient data are available to determine the response rate to this approach [38, 39]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

*3.3.2 **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 (end-stage renal disease). Renal cell cancers of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESRD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [43, 44]. The relatively indolent outcome of tumours in ESRD is due to the mode of diagnosis and a specific ACKD-related molecular pathway which has still to be determined [44]. Although the histological spectrum of ESRD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [43-45]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [46] with indolent clinical behaviour, likely due to early detection in patients with ESRD on periodic follow-up [23].

*3.3.3 **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 [47], according to the WHO 2016 classification [23].

*3.3.4 **Hereditary kidney tumours***

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (< 46 years old) of all RCC tumours [48]. Hereditary kidney tumours are found in the following entities: *VHL* syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial nonsyndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [46, 47, 49, 50].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [51, 52]. In most hereditary RCCs nephron-sparing approaches are recommended. The exception are HLRCC and SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of these lesions. For other hereditary syndromes such as VHL, surveillance is recommended until the largest solid tumour reaches 3 cm in diameter, to reduce interventions [53]. Active surveillance (AS) for VHL, BDH and HPRCC should, in individual patients, follow the growth kinetics, size and location of the tumours, rather than apply a standardised fixed follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes. Multi-disciplinary and co-ordinated care should be offered, where appropriate [54].

Although not hereditary, somatic fusion translocations of TFE3 and TFEB may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults with RCC [55].

*3.3.5 **Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [56]. Angiomyolipoma belongs to a family of so-called PEComas (perivascular epithelioid cell tumours), characterised by the proliferation of perivascular epithelioid cells. Some PEComas can behave aggressively and can even produce distant metastases. Classic AMLs are completely benign [23, 47, 57]. Ultrasound, CT, and magnetic resonance imaging (MRI) often lead to diagnosis of PEComas due to the presence of adipose tissue, however in fat poor AML, diagnostic imaging cannot reliably identify these lesions. Percutaneous biopsy is rarely useful. Pre-operatively, it may be difficult to differentiate between smooth muscle cell tumours and epithelial tumours. 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 [47, 57]. Epithelioid AMLs are potentially malignant with a highly variable proportion of cases with aggressive behaviour. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2016 [47, 57]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [58].

In some cases, larger AMLs can cause local pain. The main severe complication associated with renal AMLs is potentially life-threatening retroperitoneal bleeding or bleeding into the urinary collection system caused by spontaneous rupture of the tumour. This occurrence is triggered by the formation of irregular and aneurysmatic vessels within the angiogenic compartment of the lesions [59]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [59, 60]. Renal tumours that cannot be clearly identified as benign during the initial diagnostic work-up should be treated according to the recommendations given for the treatment of RCC in these Guidelines.

3.3.5.1 Treatment

Active surveillance is the most appropriate option for most AMLs [56, 58, 61] (LE: 3). The management of AMLs requires intervention in case of persistent pain or acute or repeated bleeding episodes. In addition, prophylactic resection of tumours ≥ 4-5 cm in diameter prevents spontaneous rupture and severe haemorrhage. The risk of bleeding due to rupture increases with the size of the AML. Nephron-sparing surgery is the treatment of choice. Transarterial selective catheter embolisation can be used in patients with larger tumours (≥ 4-5 cm) not suitable for surgery, and as an emergency approach in case of acute bleeding. In very large AMLs, upfront selective embolisation may induce tumour shrinkage prior to nephron-sparing surgery to better allow preservation of functioning renal parenchyma. Selective arterial embolisation is an efficient treatment for AML devascularisation, but only for volume reduction [62]; it has limited value in the long term [63, 64]. Radiofrequency ablation (RFA) can be an option in some patients [58, 59, 65]. 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 [66, 67].

*3.3.6 **Renal oncocytoma***

Oncocytoma is a benign tumour representing 3-7% of all solid renal tumours and its incidence increases to 18% when tumours < 4 cm are considered [23, 68]. The diagnostic accuracy of imaging modalities (CT, MRI) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [23, 68]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial or RN with subsequent histopathological verification. However, due to the inability of modern imaging techniques to differentiate benign from malignant renal masses, there is a renewed interest in renal mass biopsy (RMB) prior to surgical intervention. Accuracy of the biopsy and management of advanced/progressing oncocytomas need to be considered in this context since oncocytic renal neoplasms diagnosed by RMB at histological examination after surgery showed oncocytoma in only 64.6% of cases. The remainder of the tumours were mainly chRCC (18.7% including 6.3% hybrid oncocytic/chromophobe tumours which have now been grouped histologically with chRCC) [23], other RCC (12.5%), and other benign lesions (4.2%) [69]. The majority of oncocytomas slowly progress in size with an annual growth rate < 14 mm [70-72]. Preliminary data show that AS may be a safe way to manage oncocytoma in appropriately selected patients.

Table 3.1: Other renal cortical tumours, and recommendations for treatment (strength rating: weak) [23]

Entity	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery. Nivolumab and ipilimumab. Sunitinib, gemcitabine plus doxorubicin is also an option [73].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	Surgery, nephron-sparing surgery (NSS).
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The hazard ratio (HR) CSS in comparison with ccRCC is 4.49 [26].	High, very aggressive. Median survival 30 months [74].	Surgery. Response to targeted therapies is poor [75].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [74].	Surgery. Different chemotherapy regimes, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [76].	High	Surgery. Vascular endothelial growth factor (VEGF)-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS. VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS.
Acquired cystic disease-associated RCC		Low	Surgery.
Clear cell papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, new entity in the 2016 WHO classification, caused by a germline mutation of the fumarate hydratase gene [23].	High	Surgery. No data about treatment of metastatic disease.
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Variable	Surgery.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed epithelial and stromal tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS.
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [77, 78].	Benign	Observation (when histologically confirmed) [71, 72, 79]. NSS.

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

3.3.7 Cystic renal tumours

Cystic renal lesions are classified according to the Bosniak classification (see Section 5.2.5). Bosniak I and II cysts are benign lesions which do not require follow up [80]. Bosniak IV cysts are mostly malignant tumours with pseudocystic changes only. Bosniak IIF and III cysts remain challenging for clinicians. The differentiation of benign and malignant tumour in categories IIF/III is based on imaging, mostly CT, with an increasing role of MRI and contrast enhanced ultrasound (CEUS). Computed tomography shows poor sensitivity (36%) and specificity (76%; κ [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity (κ = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS (κ = 0.95) [81]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44-0.58) in Bosniak III and 0.89 (0.83-0.92) in Bosniak IV cysts, respectively. In a SR, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts, had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [80].

The most common histological type for Bosniak III cysts is ccRCC with pseudocytic changes and low malignant potential [82, 83]; multilocular cystic renal neoplasm of low malignant potential ([MCRNLMP], formerly mcRCC (see Section 3.2 and Table 3.1); pRCC type I (very low malignant potential); benign multilocular cyst; benign group of renal epithelial and stromal tumours (REST); and other rare entities. Surgery in Bosniak III cysts will result in overtreatment in 49% of the tumours which are lesions with a low malignant potential. In view of the excellent outcome of these patients in general, a surveillance approach may also be an alternative to surgical treatment [80, 84, 85].

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

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

3.5 Recommendations for the management of other renal tumours

Recommendations	Strength rating
Treat Bosniak type III cysts the same as RCC or offer cautious surveillance.	Weak
Treat Bosniak type IV cysts the same as RCC.	Strong
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm wide is disputed); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate.	Weak
Offer systemic therapy to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak
Prior to management, perform pre-operative renal mass biopsies in patients with unclear kidney lesions.	Weak
Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak
Perform radical nephrectomy in patients with localised renal medullary carcinoma.	Weak
Base systemic therapy for renal medullary carcinoma on chemotherapy regiments containing cisplatinum such as cisplatin plus gemcitabine.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [86], but requires continuous re-assessment [23, 87]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single and multi-institution studies [88, 89]. 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 [90].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a.
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion, but, is nevertheless included in the same pT3a stage group [91-93] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [89].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [94, 95] (LE: 4).

Table 4.1: 2017 TNM classification system [86] **and TNM supplement 2012** [96]

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

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.

4.2 Anatomic classification systems

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the

description of renal tumours [97-99]. 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 always be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [89, 100] (LE: 3). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease [41, 101] (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [102] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [103] (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 [104], 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 [105, 106] (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 [100] (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 [107] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases [108-110] (LE: 3).

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

Computed tomography or MRI is used to characterise renal masses. Imaging must be performed before, and after, administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before, and after, contrast administration. A change of fifteen, or more, HUs demonstrates enhancement [111] (LE: 3). Computed

tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [77, 112-114] (LE: 3). Abdominal CT provides information on [115]:

- function and morphology of the contralateral kidney [116] (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 in case detailed information on the renal vascular supply is needed [117, 118].

If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [7] (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 [119-122] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [120, 123] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [124].

For the diagnosis of complex renal cysts (Bosniak IIF-III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%; κ = 0.11); MRI had 71% sensitivity and 91% specificity (κ = 0.64). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% (κ = 0.95) [81].

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 on a correlation between diagnostic radiation exposure and development of secondary cancers [125].

*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 [105, 106] (LE: 2a). Positron-emission tomography (PET) is not recommended [7, 126] (LE: 1b).

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

Chest CT is accurate for chest staging [94, 95, 127-129] (LE: 3). There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [127, 130, 131] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [130, 132, 133] (LE: 3).

*5.2.5 **Bosniak classification of renal cystic masses***

This classification system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [134, 135] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [134]

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

5.3 Renal tumour biopsy

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable medical and surgical treatment strategy in the setting of metastatic disease [136-141] (LE: 3).

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle aspiration (FNA). Biopsies can be performed with US or CT guidance, with a similar diagnostic yield [139, 142] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [136, 140, 143] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [136, 140] (LE: 3).

Core biopsies are preferred for the characterisation of solid renal masses while a combination with FNA can improve accuracy [144-146] (LE: 2a). An SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel. Fifty-seven articles with a total of 5,228 patients were included in the analysis. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [146]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [136, 139, 142] (LE: 2b).

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy. The above-mentioned meta-analysis showed that sensitivity and specificity of diagnostic core biopsies for the diagnosis of malignancy are 99.1% and 99.7%, respectively [146] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [137-143, 147] (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%) [136, 148-150].

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 [146].

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) [146] (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 [136, 139, 151, 152] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [153] (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 [154].

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended alone, unless areas with a solid pattern are present (Bosniak IV cysts) [136, 139, 146] (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [140, 147, 148, 155, 156] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [146]. Tumour seeding along the needle tract is anecdotal. Spontaneously resolving subcapsular/perinephric haematomas are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0-1.4%; 0.7% in the pooled analysis) and generally self-limiting [146].

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

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and mRCC.	2
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2
Contrast enhanced ultrasound (CEUS) has a high sensitivity and specificity for characterisation of renal masses.	2
Ultrasound, power-Doppler US and positron-emission tomography (PET) CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Use magnetic resonance imaging to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, mainly contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	Strong
Do not routinely use bone scan and/or positron-emission tomography CT for staging of RCC.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation for solid renal tumours.	Strong

6. PROGNOSTIC FACTORS

6.1 Classification

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

6.2 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [86] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system [157]. Fuhrman nuclear grade is the most widely accepted grading system [158]. Although affected by intra- and inter-observer discrepancies, Fuhrman nuclear grade is an independent prognostic factor [159]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [160, 161] (LE: 3). The new WHO/ISUP grading system [162] that will replace the Fuhrman grading, needs to be validated for prognostic systems and nomograms.

In a univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [163, 164]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [25, 164] (LE: 3). In a cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were shown, whereas pRCC type I displayed a significantly reduced risk of death compared with ccRCC and pRCC type II [165].

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

Table 6.1: Basic characteristics of three main types of RCC [25, 26, 166]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [167]	CSS (HR)
clear-cell RCC	80-90%	28%	28.5%	Referent
papillary RCC	6-15%	17.6%	28.8%	0.64 - 0.85
chromophobe RCC	2-5%	16.9%	32.7%*	0.24 - 0.56

** The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC.*
CSS = cancer-specific survival; HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The five-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of TKIs [168, 169]. Sarcomatoid changes can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: Cancer-specific survival by stage and histopathological grade in RCCs [26]

Grade	HR (95% CI)
T1N0M0	Referent
T2N0M0	2.71 (2.17-3.39)
T3N0M0	5.20 (4.36-6.21)
T4N0M0	16.88 (12.40-22.98)
N+M0	16.33 (12.89-20.73)
M+	33.23 (28.18-39.18)
Grade 1	Referent
Grade 2	1.16 (0.94-1.42)
Grade 3	1.97 (1.60-2.43)
Grade 4	2.82 (2.08-3.31)

CI = confidential interval. HR = hazard ratio.

Long-term survival in RCC patients treated by RN or PN between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [166] (Table 6.3).

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

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

Two subgroups of pRCC with different outcomes have been identified [170]. Type I have a favourable prognosis. Type II are mostly high-grade tumours with a propensity for metastases (LE: 3). For more details, see Section 3.2 - Histological diagnosis. Renal cell cancer with Xp 11.2 translocation has a poor prognosis [171]. Its incidence is low, but it should be systematically addressed in young patients. Renal cell cancer type classification has been confirmed by cytogenetic and genetic analyses [167, 172, 173] (LE: 2b).

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil-lymphocyte ratio, C-reactive protein (CRP) and albumin [103, 174-178] (LE: 3).

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [179], PTEN (phosphatase and tensin homolog) cell cycle, E-cadherin, osteopontin [180] CD44 (cell adhesion) [181, 182], CXCR4 [183], and other cell cycle and proliferative markers [63, 184] are being investigated (LE: 3). None of these markers have clearly improved the predictive accuracy of current prognostic systems and, so far, none have been externally validated. Their routine use in clinical practice is, at present, not recommended.

Several retrospective studies and large molecular screening programmes have identified mutated genes in ccRCC with distinct clinical outcomes. The expression of the *BAP1* and *PBRM1* genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [185-187]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [186]. Validated data from surgical series can predict relapse using a sixteen gene signature. This signature is likely to be adopted in clinical trials and may be helpful in the clinical setting in due time [188].

The recognition of the potential relevance of immunotherapy as an approach to RCC management is growing. Prognostic information of cytokines and blockade of immune-inhibitory molecules such as PD-L1 have shown promising therapeutic results. Emerging evidence of chromosomal alterations, through Genome-Wide Association Studies (GWAS), miRNA, SNPs and gene methylations all contribute to improving diagnostic and prognostic information. A number of studies have confirmed prognostic information based on gain of chromosomal regions 7q, 8q and 20q, and chromosomal losses of regions 9p, 9q and 14q, which are associated with poor survival. CpG-methylation-based assays also independently predict survival in ccRCC [189, 190]. An international collaboration is currently investigating GWAS loci for prognostic information.

6.6 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [191-197]. These may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An advantage of nomograms is their ability to measure predictive accuracy, allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its predictive accuracy is superior to conventional post-operative prognostic schemes [198]. Recently, new pre-operative nomograms with excellent predictive accuracy have been designed [199, 200].

Table 6.4 summarises the current most relevant prognostic systems.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour nuclear grade, and RCC subtype provide important prognostic information [201].	2

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

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

Prognostic Models	Variables													
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS	x	x			x								
	SSIGN	x				x	x	x						
	Post-operative Karakiewicz's nomogram	x			x	x		x						
Metastatic RCC	MSKCC prognostic system			x					x	x	x	x		
	IMDC			x	x						x	x	x	x
	Heng score			x					x		x	x	x	x

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

7. DISEASE MANAGEMENT

7.1 Treatment of localised renal cell cancer

*7.1.1 **Introduction***

Sections 7.1.2 and 7.2.4.2 are underpinned by a SR which includes all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [202]. 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 vs. radical nephrectomy

Multiple retrospective series as well as one prospective RCT including patients with organ-confined RCC of limited size (pT1), have demonstrated a comparable CSS for PN vs. RN [203-207]. However, trials that directly compared both approaches in terms of their oncological safety are rarely available. Therefore, the data presented is based on a comparison of data available from retrospective series that have included patient cohorts of varied and limited size. In addition, PN demonstrated better preserved kidney function, thereby potentially lowering the risk of development of cardiovascular disorders [202, 208-210].

When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiac-specific mortality [209, 211] as well as improved OS for PN as compared to RN. However, in some series this held true only for a younger patient population and/or patients without significant comorbidity at the time of the surgical intervention [212, 213].

A Cochrane SR found that PN for clinically localised RCC was associated with a reduced time-to-death of any cause compared to RN, whereas serious adverse event rates, CSS and time-to-recurrence were similar between the two groups [214].

An analysis of the Medicare database [215] could not demonstrate an OS benefit for patients ≥ 75 years of age when RN or PN were compared with non-surgical management. Another series that addressed this question and also included Medicare patients suggested an OS benefit in an older RCC patient population (75-80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.* compared patients subjected to PN for RCC with a non-cancer healthy control group via a retrospective database analysis, showing an OS benefit for the cancer cohort [216]. These conflicting results may be an indication that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries.

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

It has been suggested that the more pronounced deterioration of renal function after RN negatively affects patients´ OS [208, 217]. Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment, generally present with a stable long-term renal function [218]. In contrast, adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical chronic kidney disease (CKD) [219]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD which requires haemodialysis.

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN, irrespective of the surgical approach used (open vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general patients' health status deteriorated following both approaches [203, 204, 206, 220-224].

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, there was no difference in the length of hospital stay [204, 205, 223], the number of red blood cell (RBC) units applied [204, 223, 224], or the mean intra-operative blood loss [204, 223]. Complication rates were inconsistently reported and one intervention was not favoured over another [225]. One study indicated a longer operation time for open PN [225], but this was not confirmed by others [202].

In view of the above, and since oncological safety (CSS and RFS) of PN has been proven to be similar for RN, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term potentially limits the incidence of cardiovascular disorders. Whether decreased mortality from any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment

option as it avoids further deterioration of kidney function, the latter being associated with a higher risk of development of ESRD and the need for haemodialysis.

A study compared the survival outcomes in patients with larger (≥ 7 cm) ccRCC treated with PN vs. RN with long-term follow-up (median 102 months). Compared to the RN group, the PN group had a significantly longer median OS (p = 0.014) and median CSS (p = 0.04) [226]. An SR and meta-analysis of comparative studies of PN vs. RN for cT1b and T2 RCCs observed that the PN group had a lower likelihood of tumour recurrence (OR 0.6, p < 0.001), cancer-specific mortality (OR 0.58, p = 0.001), and all-cause mortality (OR 0.67, p = 0.005) compared to the RN group. For T2 tumours the estimated blood loss was higher for PN (p < 0.001), as was the likelihood of complications (RR 2.0, p < 0.001). Both the recurrence rate (RR 0.61, p = 0.004) and cancer-specific mortality (RR 0.65, p = 0.03) were lower for PN [227].

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

- insufficient volume of remaining parenchyma to maintain proper organ function;
- renal vein thrombosis.

In these situations, the curative therapy is RN including removal of the tumour-bearing kidney. Complete resection of the primary tumour by open- or laparoscopic surgery offers a reasonable chance of cure.

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of either RN or RN with, or without, ipsilateral adrenalectomy [228]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten years was seen, with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 interventions were for benign lesions [228]. Two small retrospective studies addressed RN with, or without ipsilateral adrenalectomy [229, 230], but only one study reported five-year CSS [229]. Neither study reported peri-operative or QoL outcomes. The low quality of both studies (small sample sizes, wide CIs, and short follow-up) does not allow any meaningful conclusions to be drawn.

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 [231]. The clinical assessment of LN status is based on the detection of an enlargement of LNs; either by CT/MRI or the intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [232]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [233]. For clinically positive LNs (cN+) see Section 7.2.2.

For patients with clinically negative LNs (cN0), six clinical trials have evaluated the clinical value of LND including one RCT [232] and five comparative studies [115, 234-237].

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive lymphadenectomy preferably in patients at high risk for lymphogenic spread. In a large retrospective study, the outcomes of RN with or without LND in patients with high-risk non-metastatic RCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, or cancer-specific or all-cause mortality. Neither eLND nor the extent of LND was associated with improved oncologic outcomes [238]. The number of LN metastases (< / > 4) as well as the intra- and extracapsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [233, 239-241]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extranodal extension. On the basis of a retrospective SEER database analysis of > 9,000 patients no effects of an extended LND on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [242]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of ten for the number of nodes dissected resulted in a 10% absolute increase in DSS. In addition, in a larger cohort of 1,983 patients Capitano *et al.* demonstrated that extended LND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [243]. As to morbidity related to eLND, a recent retrospective propensity score analysis from a large single centre database showed that eLND is not associated with an increased risk of Clavien grade ≥ 3 complications. Furthermore, LND was not associated with length of stay or estimated blood loss [244].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of only 4%, the risk of lymphatic spread appears to be very

low. Recognising the latter, only a staging effect was attributed to LND [232]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Additionally, only 25% of patients with pT3 tumours were subjected to a complete LND. The LN template used by the authors was also not clearly stated.

The optimal extent of LND remains controversial. Retrospective studies suggest that an extended LND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [233, 234, 245]. At least fifteen LNs should be removed [243, 246]. Sentinel LND is an investigational technique [247, 248].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [249, 250]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [251-253]. 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 renal cell cancer

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

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

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

7.1.3.1 Radical nephrectomy techniques

No RCTs have assessed oncological outcomes of laparoscopic vs. open RN. A cohort study [254] and retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher stage disease and locally more advanced tumours [255-257]. Based on a SR, less morbidity was found for laparoscopic vs. open RN [202].

Data from one RCT [256] and two NRSs [204, 258] 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 [258]. 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 [204, 256, 258]. 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 [204].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal tumours ≥ T2. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of hospital stay and convalescence compared to those who underwent open RN [257-259]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [257-259] (LE: 2b). Another multi-centre propensity matched analysis compared laparoscopic and open surgery for pT3a RCC, showing no significant

difference in three-year RFS between groups [260]. The best approach for RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [260, 261] and one quasi-randomised study [262]. Quality of life variables were similar for both approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [262] and one database review [225]. Estimated five-year OS, CSS, and RFS rates were comparable. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN cohort [225, 262]. However, the sample size was small.

A SR reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause cancer-specific mortality [263]. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [264, 265].

7.1.3.2 Partial nephrectomy techniques

Studies comparing laparoscopic and open PN found no difference in PFS [266-269] and OS [268, 269] in centres with laparoscopic expertise. The mean estimated blood loss was lower with the laparoscopic approach [266, 268, 270], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [266, 268]. Operative time is generally longer with the laparoscopic approach [267-269] and warm ischaemia time is shorter with the open approach [266, 268, 270, 271]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [269], but not after follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [271]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [272]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [273, 274].

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN than in open PN patients, but there was no significant difference in high Clavien grade complications. Glomerular filtration rate three months after operation was lower in the HALPN than in the open PN group [275].

The feasibility of off-clamp laparoscopic PN and laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm their safety and clinical role [276, 277].

Whereas oncological long-term data for conventional laparoscopic PN are available [266], the oncological safety of robot-assisted vs. open PN has, so far, only been addressed in studies with relatively limited follow-up. The Gill *et al.* study suggests comparable oncological efficacy even in case of higher stage tumours (pT1b/pT3a). However, the higher number of patients treated with open surgery in this series might reflect a selection bias by offering robotic surgery in case of a less complex anatomy [278]. 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 of creatinine levels, and pathologic margins were similar among the groups [279].

A recent multicentre French series from a prospective database compared the outcomes of 1,800 patients who underwent open PN and robot-assisted PN. Although the follow-up was shorter, there was a decreased morbidity in the robotic-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [280].

A meta-analysis, including a series of NSS with variable methodological quality compared the peri-operative outcomes of robot-assisted- and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of hospital stay. No significant difference was observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins [281].

7.1.3.3 Positive margins on histopathological specimens of resected tumours

A positive surgical margin is encountered in about 2-8% of PNs [281]. Studies comparing different resection techniques (open, laparoscopic, robotic) are inconclusive [282, 283]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite positive surgical margins [284]. A positive surgical margin status occurs more frequently in cases in which surgery is imperative (solitary kidney 27%

vs. 4% and bilateral disease 23% vs. 10.4%) and in patients with adverse pathological features (pT2a, pT3a, grade III-IV) [285-288]. The potential negative impact of a positive margin status on the oncologic outcome is still controversial [282]. The majority of retrospective analysis reported so far indicated that positive surgical margins do not translate into a higher tendency towards the development of metastases or a decreased CSS [286, 287]. Coupled with the fact that only a small percentage of patients with an uncertain margin status actually harbour residual malignancy, RN or re-resection of margins can result in overtreatment in many cases [289]. Local tumour bed recurrences were found in 16% in positive surgical margins compared with 3% in negative margins [285], Patients with positive surgical margins should be informed that they will be subjected to a more intense surveillance (imaging) programme and are at increased risk for secondary local therapies [286, 290]. However, protection from recurrence is not ensured by negative surgical margins [291].

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

Summary of evidence	LE
Laparoscopic radical nephrectomy has lower morbidity than open surgery.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open radical nephrectomy.	2a
Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with radical nephrectomy.	3

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

*7.1.4 **Therapeutic approaches as alternatives to surgery***

7.1.4.1 Surgical versus non-surgical treatment

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality in patients treated with surgery [215, 292, 293]. 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 [292]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [294-296].

7.1.4.2 Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [297, 298]. 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 [299]. The concept of AS differs from the concept of watchful waiting. Watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and do not require follow-up imaging, unless clinically indicated.

In the largest reported series of AS the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [300, 301].

A single-institutional comparative study evaluating patients aged > 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours. However, a multi-variate analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [297]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [302].

Results from the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published [303]. This prospective, NRS enrolled 497 patients with solid renal masses < 4 cm in size 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 for AS in this study the overall median small renal mass growth rate was 0.09

cm/year with a median follow-up of 1.83 years. The growth rate and variability decreased with longer follow-up. No patients developed metastatic disease or died of RCC [304].

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 [303]. Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate for initially monitoring small renal masses, followed, if required, by treatment for progression [299-301, 305-308].

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 [309].

7.1.4.3 Ablative therapies

7.1.4.3.1 Cryoablation

Cryoablation is performed using either a percutaneous or a laparoscopic-assisted approach. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic and percutaneous cryoablation [310-312]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow up compared with 118 patients treated percutaneously with a shorter follow up [311]. A shorter average length of hospital stay was found with the percutaneous technique [311-313]. No studies are available comparing surveillance strategies to cryoablation.

A recent SR including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [314]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

7.1.4.3.2 Cryoablation versus partial nephrectomy

Studies compared open, laparoscopic or robotic PN with percutaneous or laparoscopic cryoablation. Oncological outcomes were mixed, with some studies showing no difference in OS, CSS, RFS, disease-free survival (DFS), local recurrence or progression to metastatic disease [315, 316], with some showing significant benefit for the PN techniques for some or all of these outcomes [317-320]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed an oncological benefit for cryoablation over PN.

Peri-operative outcomes, complication rates and other QoL measures were mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [315-317], whilst also finding no differences in other peri-operative outcomes such as recovery times, complication rates or post-operative serum creatinine levels. Two studies [319, 320] reported specific Clavien rates, with mostly non-significant differences, which were mixed for intra-operative vs. post-operative complications. Estimated GFRs were not significantly different in two of the studies, but in favour of cryoablation in a third [318-320]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [318], another strongly in favour of PN [319], and the third showing no difference [320]. One study compared PN with ablation therapy, either cryoablation or RFA [242], and showed significantly improved DSS at both five and ten years for PN.

A recent study compared 1,057 patients treated by PN to 180 treated by RFA and 187 treated by cryoablation for a cT1 tumour and found no difference regarding RFS between the three techniques. Metastasis-free survival was superior after PN and cryoablation compared to RFA for cT1a patients. However, follow-up of patients treated by thermal ablations was shorter [212].

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Four studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [321-324].

Complications occurred in up to 29% of patients but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously. One study with a limited number of patients found a higher rate of incomplete ablation in patients treated by percutaneous RFA [323]. However, no differences in recurrence or CSS were found in the three comparative studies.

7.1.4.3.4 Radiofrequency ablation versus partial nephrectomy

Most publications about RFA are retrospective cohort studies with a low number of patients and limited follow up. Three studies retrospectively compared RFA to surgery in patients with T1a tumours [325-327].

One study compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS [302]. Another study retrospectively reviewed 105 T1a patients treated

by percutaneous RFA or RN. Cancer-specific survival was 100% in both groups [325]. Overall survival was lower in the RFA group but patients treated with surgery were younger [325].

In a monocentric study that compared 34 RFA patients to sixteen open PN patients, a higher rate of complications and transfusions was shown in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [327].

A meta-analysis reported comparable complication rates and post-operative estimated glomerular filtration rates (eGFR) between RFA and PN [328]. The local tumour recurrence rate was higher in the RFA group than in the PN group (OR = 1.81) but there was no difference regarding the occurrence of distant metastasis.

A retrospective analysis of 264 patients treated with either percutaneous RFA or PN and a median follow up of 78 months showed that T1b ccRCC patients have less favourable outcomes for percutaneous RFA as compared to PN. However, percutaneous RFA provides comparable oncological outcomes to PN in patients with T1b non-ccRCC. The authors conclude that it may be necessary to take RCC subtypes into consideration when selecting either PN or percutaneous RFA as a surgical approach to treat T1b RCC [329].

A recent large SR and meta-analysis including 3,974 patients who had undergone an ablative procedure (RFA or cryoablation) or PN showed higher all-cause mortality and cancer-specific mortality rates for ablation than for PN (HR: 2.11 and 3.84, respectively). No statistically significant difference in local recurrence rates or risk of metastasis was seen. Complication rates were lower for ablation than for PN (13% vs. 17.6%, $p < 0.05$). A significantly greater decrease in eGFR was observed after PN vs. ablation therapy [330].

7.1.4.3.5 Cryoablation versus radiofrequency ablation

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

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

7.1.4.3.6 Other ablative techniques

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

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

Summary of evidence	**LE**
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for thermal ablation therapies compared to partial nephrectomy.	3

Recommendation	**Strength rating**
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	Weak

7.2 Treatment of locally advanced RCC

7.2.1 Introduction

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

7.2.2 Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified [28]. However, the extent of LND remains controversial [233]. A recent SR and meta-analysis attempted to evaluate the role of retroperitoneal LND in non-metastatic and mRCC [334]. The review included several studies which recruited patients at high risk of LN metastases, including cN1 patients. Lymph node dissection was not associated with any survival benefit. However, LND may provide additional staging information. A recent analysis also indicates that LND is not associated with improved oncologic outcomes in patients with radiographic lymphadenopathy (cN1) and across increasing probability thresholds of pN1 disease [238].

7.2.3 Management of locally advanced unresectable RCC

In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [251-253]. The use of systemic therapy to downsize tumours is experimental and cannot be recommended outside clinical trials.

7.2.4 Management of RCC with venous tumour thrombus

Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [335-343]. However, uncertainties remain as to the best approach for surgical treatment of these patients.

7.2.4.1 The evidence base for surgery in patients with venous tumour thrombus

Data whether patients with venous tumour thrombus should undergo surgery is derived from case series only. In one of the largest published studies a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis [340]. Thus, all patients with non-metastatic disease and venous tumour thrombus, and an acceptable PS, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation. The surgical technique and approach for each case should be selected based on the extent of tumour thrombus.

7.2.4.2 The evidence base for different surgical strategies

A SR was undertaken which included only comparative studies on the management of venous tumour thrombus in non-metastatic RCC [344, 345]. Only five studies were eligible for final inclusion, with high risk of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [346, 347]. Pre-operative embolisation [348] was associated with increased operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.

No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support [349].

No surgical method was shown to be superior for the excision of venous tumour thrombus. The surgical method selected depended on the level of tumour thrombus and the grade of occlusion of the IVC [344, 346, 347, 349]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 *Summary of evidence and recommendations for the management of RCC with venous tumour thrombus*

Summary of evidence	LE
In patients with locally advanced disease due to clinically enlarged lymph nodes (LNs), the survival benefit of lymph node dissection is unproven but LN dissection adds staging information.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3
Tumour embolisation or inferior vena cava filter do not appear to offer any benefits.	3

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong

7.2.5 ***Adjuvant therapy***

There is currently no evidence from randomised phase III trials that adjuvant therapy offers a survival benefit. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [350-354] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) did not show a survival benefit [355]. Heat shock protein-peptide complex-96 (vitespen) [356], may have a benefit in a subgroup of patients but the overall data from phase III trials were negative. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [357]. No difference in DFS was observed in the overall trial analysis, but a subgroup evaluation of patients with high CAIX expression suggests a potential benefit of girentuximab in this population. Several trials investigating adjuvant sunitinib, sorafenib or pazopanib have reported whilst studies investigating sorafenib, axitinib and everolimus have completed accrual and are expected to report in the next years.

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, three RCTs comparing VEGFR-TKI vs. placebo have been published. One of the largest adjuvant trials compared sunitinib vs. sorafenib vs. placebo (ASSURE). Its interim results published in 2015 demonstrated no significant differences in DFS or OS between the experimental arms and placebo [358]. The study published its updated analysis on a subset of high-risk patients in 2018, which demonstrated five-year DFS rates of 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo (HR: 0.94 for sunitinib vs. placebo; and HR: 0.90, 97.5% CI: 0.71-1.14 for sorafenib vs. placebo), and five-year OS of 75.2%, 80.2%, and 76.5% (HR: 1.06, 97.5% CI: 0.78-1.45, p = 0.66, sunitinib vs. placebo; and HR: 0.80; 97.5% CI: 0.58-1.11, p = 0.12 for sorafenib vs. placebo). The results indicated that adjuvant therapy with sunitinib or sorafenib should not be given [174].

The PROTECT study included 1,135 patients between pazopanib (n = 571) and placebo (n = 564) in a 1:1 randomisation [359]. The primary endpoint was amended after 403 patients were included on pazopanib 800 mg vs. placebo, to DFS with pazopanib 600 mg. The primary analysis results of DFS in the intention-to-treat (ITT) pazopanib 600 mg arm were not significant (HR: 0.86; 95% CI: 0.7-1.06, p = 0.16). DFS in the ITT pazopanib 800 mg population was improved (HR: 0.69; 95% CI: 0.61 0.94, 1.06, p = 0.02). No benefit in OS was seen in the ITT pazopanib 600 mg population: HR: 0.79 (0.57-1.09, p = 0.16). There is data suggesting that full-dose therapy is associated with improved DFS in subset analysis across these studies. Furthermore, no strong association of DFS with OS has been established for RCC [360, 361].

In contrast, the S-TRAC study included 615 patients randomised to either sunitinib or placebo [362]. The results showed a benefit of sunitinib over placebo for DFS (HR: 0.76; 95% CI: 0.59-0.98, p = 0.03) but data for OS remained immature. Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in QoL for loss of appetite and diarrhoea. The study published its updated results in 2018; the results for DFS had not changed significantly (HR: 0.74; 95% CI: 0.55-0.99, p = 0.04), and median OS was not reached in either arm (HR: 0.92, 95% CI: 0.66-1.28, p = 0.6).

In summary, there is conflicting data in the three available studies of adjuvant therapy. A recent SR and meta-analysis combined the results of all three RCTs [363]. The pooled analysis of VEGFR-TKIs vs. placebo demonstrated that VEGFR-targeted therapy was not statistically significantly associated with improved DFS (HR: 0.92, 95% CI: 0.82-1.03, p = 0.16) nor OS (HR: 0.98, 95% CI: 0.84-1.15, p = 0.84) compared with placebo. The adjuvant therapy group experienced significantly higher odds of grade 3-4 adverse events (OR: 5.89, 95% CI: 4.85-7.15, p < 0.001). In summary, there is currently a lack of proven benefits of adjuvant therapy with VEGFR-TKIs for patients with high-risk RCC after nephrectomy.

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

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

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

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

7.3 Advanced/metastatic RCC

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

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN+ immunotherapy vs. immunotherapy only, increased long-term survival was found in patients treated with CN [364]. The role and sequence of CN in the era of targeted therapy has been investigated by two RCTs (CARMENA, NCT00930033, EORTC 30073 SURTIME; NCT01099423). 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 [365]. 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 was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82; 95% CI: 0.67-1.00). The clinical benefit rate, defined as disease control beyond 12 weeks was 36.6% with CN and 47.9% with sunitinib alone (p = 0.022). Of note, 38 patients in the sunitinib only arm required secondary CN due to acute symptoms or for complete or near-complete response. The median time from randomisation to secondary CN was 11.1 months.

The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS (HR: [95% CI]: 0.88 [0.59-1.37], p = 0.569). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 (14.5-65.3) months in the deferred CN arm vs. 15.0 (9.3-29.5) months in the immediate CN arm (HR: [95% CI] 0.57 [0.34-0.95], p = 0.032). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy. This confirms previous findings from single-arm phase II studies [366]. Moreover, deferred CN and surgery appears safe after sunitinib which supports the findings, with some caution, of the only available RCT.

In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended [367]. These data are confirmed by CARMENA [365].

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 [251-253] (see recommendations Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic renal cell cancer

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

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

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

A SR of the local treatment of metastases from RCC in any organ was undertaken [368]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [369]. 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 [370-377]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [378-380], two in the brain [381, 382] and one each in the liver [383] lung [384] and pancreas [385]. Three studies were published as abstracts only [374, 376, 384]. Data were too heterogeneous to meta-analyse. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 Complete versus no/incomplete metastasectomy

An SR, including only eight studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [370-377]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [373]. Non-surgical modalities were not applied. Six studies [370, 372-374, 376, 377] 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 [371] showed no significant difference in CSS between complete and no metastasectomy, and one [375] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [384], liver [383], and pancreas [385], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical

therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and five-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [380]. Single-dose IGRT (≥ 24 Gy) had a significantly better three-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [378]. A significantly higher five-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multi-variate analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases to the spine [379]. Pain, objective response rate (ORR), time-to-pain relief and duration of pain relief were similar.

7.3.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study [381] compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus WBRT.

Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS and WBRT in a subgroup analysis of RPA class I showed significantly better two-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [382]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with metastasectomy plus conventional radiotherapy.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [386]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [387] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Summary of evidence and recommendations for local therapy of metastases in metastatic renal cell cancer

Summary of evidence	**LE**
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	**Strength rating**
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone or brain metastases for local control and symptom relief.	Weak

7.4 Systemic therapy for advanced/metastatic renal cell cancer

*7.4.1 **Chemotherapy***

Chemotherapy is moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents [388]. However, in one study IFN-α showed equivalent efficacy to IFN-α plus IL-2 plus 5-FU [389]. A combination of gemcitabine and doxorubicin could be an option in sarcomatoid and rapidly progressive RCC [73, 390].

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

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

Recommendation	Strength rating
Do not offer chemotherapy as first-line therapy in patients with clear-cell mRCC.	Strong

*7.4.2 **Immunotherapy***

7.4.2.1 IFN-α monotherapy and combined with bevacizumab

Conflicting results exist for IFN-α in clear-cell-mRCC. Several studies showed that IFN-α in mRCC has a survival advantage similar to that of hormonal therapy [391]. Interferon-α resulted in response rates of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [392, 393]. However, patients with intermediate-risk disease failed to confirm this benefit [394].

Interferon-α may only be effective in some patient subgroups, including patients with ccRCC favourable-risk criteria, as defined by the MSKCC and lung metastases only [391]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [393]. Bevacizumab plus IFN-α increased response rates and PFS in first-line therapy compared with IFN-α monotherapy [394]. All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab plus IFN-α, and temsirolimus [394-397]. Interferon-α has been superseded by targeted therapy in clear-cell-mRCC.

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

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

**The MSKCC (Motzer) criteria are also widely used in this setting [392].*

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

7.4.2.2 Interleukin-2

Interleukin-2 has been used to treat mRCC since 1985 with response rates ranging from 7-27% [397, 399, 400]. Complete and durable responses have been achieved with high-dose bolus IL-2, however, IL-2 remains the only drug to date that can cure a small percentage of RCC patients [401]. The toxicity of IL-2 is substantially greater than that of IFN-α [393].

7.4.2.3 Vaccines and targeted immunotherapy

A vaccine trial with tumour antigen 5T4 plus first-line standard therapy (i.e. sunitinib, IL-2 or IFN-α) showed no survival benefit compared with placebo and first-line standard therapy [402]. Several vaccination studies are ongoing. Monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-L1), which have efficacy and acceptable toxicity in patients with RCC [403] are currently being investigated in phase III trials.

7.4.2.4 Immune checkpoint blockade

Immune checkpoint blockade with monoclonal antibodies targets and blocks the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)-signalling to restore tumour-specific T-cell immunity [404]. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [179, 184, 405]. Nivolumab has superior OS to everolimus (HR: 0.73, 95% CI: 0.57-0.93, p < 0.002) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus (LE: 1b). Patients who had failed multiple lines of VEGF-targeted therapy were included in this trial making the results broadly applicable. The trial included 15% MSKCC poor-risk patients. There was no PFS advantage with nivolumab despite the OS advantage. Currently the PD-L1 biomarkers are not used to select patients for this therapy.

The phase III trial CheckMate 214 (NCT 02231749) investigated the combination of nivolumab and ipilimumab vs. sunitinib in first-line treatment of treatment-naïve advanced or clear-cell-mRCC. Patients ineligible for immune checkpoint inhibitors or VEGF-targeted therapy were not included. The trial had triple co-primary endpoints of response rate, PFS and OS in intermediate- and poor-risk groups as defined by IMDC. Outcomes in the unselected population (ITT) was a secondary endpoint, 1,096 patients were randomised in the ITT population, 847 of which had intermediate- or poor-risk disease. Twenty-three percent, 61% and 17% of patients had favourable-, intermediate- and poor-risk disease, respectively [406]. Two percent of the ITT population and 28% of the intermediate/poor-risk population with quantifiable PD-L1 expression were biomarker positive (> 1% of tumour cell staining with 288 antibody). The study successfully achieved the primary endpoints of RR and OS (Table 7.2). It failed to achieve the third endpoint of PFS.

Secondary endpoints included investigating RR and OS in the ITT population. Results showed that a combination of ipilimumab and nivolumab was associated with a significant advantage for both RR and OS. Again, a higher proportion of the patients treated with nivolumab plus ipilimumab achieved durable remissions, justifying their use in unselected patients (including favourable-risk disease). Health-related QoL assessment, based on the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), was performed and favoured the immunotherapy combination.

Exploratory endpoints included outcomes in favourable-risk patients and by tumour PD-L1 expression level. Results in the favourable-risk population showed response rates of 29% (95% CI: 21-38%) vs. 52% (95% CI: 43%-61%) and a median PFS of 15.3 months (95% CI: 9.7-20.3) vs. 25 (95% CI: 20.9-NE) for nivolumab plus ipilimumab and sunitinib, respectively (PFS HR: 2.18 [95% CI: 1.29-3.68]). Due to the exploratory nature of these analyses, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn.

Table 7.2: Summary of Checkmate 214 data [406]

	IMDC intermediate and poor risk			**ITT population (secondary endpoint)**		
	IPI/NIVO	**sunitinib**	**HR**	**IPI/NIVO**	**sunitinib**	**HR**
n	425	422		550	546	
RR **95% CI**	42 (37-47)	27 (22-31)		39 35-43	32 28-36	
PFS **99.1 CI**	11.6 (8.5-15.5)	8.4 (7.0-10.8)	0.82 (0.64-1.05)	12.4 (9.9-16.5)	12.3 (9.8-15.2)	0.98 (0.79-1.23*)
OS **99.8 CI**	NR (28.2-NR)	26.0 (22-NR)	0.63 (0.44-0.82	NE (NE-NE)	32.9 (NE-NE)	0.68 (0.49-0.95)

CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention to treat; n = number of patients; NE = neutral effect; NIVO = nivolumab; NR = not reported; OS = overall survival; PFS = progression-free survival; RR = relative risk.

Tumours which overexpressed the PD-L1 biomarker at baseline were associated with a better RR and PFS with nivolumab plus ipilimumab than sunitinib (PFS HR: 0.48 95% CI: 0.28-0.82). This was not the case in the PD-L1-negative cohort, where PFS was almost identical (HR: 1.0 95% CI: 0.74-1.36). Therefore, the PD-L1 biomarker appears predictive for PFS. However, due to the exploratory nature of this work significance cannot be drawn. As no group receiving combination immunotherapy appear to have a worse outcome compared to sunitinib and patient-reported outcomes favoured nivolumab plus ipilimumab, the Guidelines Panel do not currently recommend selection based on the PD-L1 biomarker (> 1% expression using 288 antibody). Further data will be needed before a recommendation can be made.

Nivolumab plus ipilimumab was associated with 15% grade 3-5 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). Nivolumab plus ipilimumab should not be offered outside of the first-line setting. The PD-L1 biomarker currently is not used to select patients for therapy.

Recently, EMA revoked the initial decision made by their Committee for Medicinal Products for Human Use (CHMP) and approved the combination of nivolumab and ipilimumab as a first-line treatment option in adult patients with IMDC intermediate- and poor-risk advanced RCC (https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo).

Patients who stop nivolumab plus ipilimumab because of toxicity should not be re-challenged with the same drugs in the future without expert guidance and support from a multidisciplinary team (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 (LE: 1). Nivolumab plus ipilimumab should not be combined with other agents outside of a clinical trial.

Further combinations of VEGF-targeted therapy and immune therapy are being compared in phase III trials against sunitinib and may change treatment recommendations soon. These include:

- Javelin Renal 101 - NCT02684006;
- IMmotion151 - NCT02420821: co-primary PFS data were positive, no further recommendation can be provided, awaiting mature data;
- pembrolizumab plus axitinib - NCT02133742;
- lenvatinib plus everolimus or pembrolizumab - NCT02811861.

7.4.2.5 Summary of evidence and recommendations for immunotherapy in metastatic renal cell cancer

Summary of evidence	**LE**
Interferon-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
Interleukin-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only).	2a
Interleukin-2 has more side-effects than IFN-α.	2b
High-dose (HD)-IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve, low-risk and intermediate-risk ccRCC.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b
The combination of nivolumab and ipilimumab in treatment-naïve patients with clear-cell-mRCC of IMDC intermediate- and poor-risk leads to superior survival compared to sunitinib.	1b
The combination of nivolumab and ipilimumab in the ITT population of treatment-naïve unselected patients with clear-cell-mRCC leads to superior survival compared to sunitinib.	2b
Due to the exploratory nature of PD-L1 tumour expression, the small sample size, the lack of OS data and the premature results in this subpopulation, definitive conclusions cannot be drawn relative to the usefulness of PD-L1 expression.	2b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths.	1b

Recommendations	Strength rating
Offer ipilimumab plus nivolumab to treatment-naïve patients with clear-cell-mRCC of IMDC intermediate and poor risk.	Strong
Administer nivolumab plus ipilimumab in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	Weak
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in mRCC.	Strong
Do not offer monotherapy with interferon (INF)-α or high-dose bolus interleukin-2 as first-line therapy in mRCC.	Weak
Do not offer bevacizumab plus IFN-α to treatment-naïve clear-cell favourable- and intermediate-risk RCC patients.	Weak
Do not use PD-L1 tumour expression as a predictive biomarker.	Weak
Do not re-challenge patients who stop nivolumab plus ipilimumab because of toxicity, with the same drugs in the future without expert guidance and support from a multidisciplinary team.	Strong

*7.4.3 **Targeted therapies***

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL-inactivation results in over-expression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [407-409]. 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 MSKCC risk model [391] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to aid accurate prognosis of patients treated in the era of targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors while lactate dehydrogenase (LDH) has been removed [398].

The IMDC published data on conditional survival which may be used in patient counselling [410]. The IMDC risk model has been validated and compared with the Cleveland Clinic Foundation (CCF) model, the French model, the MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The IMDC model did not differ from the other models, indicating that a ceiling has been reached in predicting prognosis based solely on clinical factors [411]. Both the MSKCC and IMDC developed models for second-line treatment in the era of targeted therapy based, in part, on their risk models for treatment-naïve patients [412].

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

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

** Based on [411]; ** based on [398]*
CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; n = number of patients; OS = overall survival.

7.4.3.1 Tyrosine kinase inhibitors

7.4.3.1.1 Sorafenib

Sorafenib is an oral multi-kinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [413] (HR: 0.44; 95% CI: 0.35-0.55, $p < 0.01$). Overall survival improved in patients initially assigned to placebo who were censored at crossover [414]. In patients with previously untreated mRCC sorafenib was not superior to IFN-α (phase II study). A number of studies have used sorafenib as the control arm in sunitinib-refractory disease vs. axitinib, dovitinib and temsirolimus. None showed superior survival for the study drug compared to sorafenib.

7.4.3.1.2 Sunitinib

Sunitinib is an oral TKI inhibitor and has anti-tumour and anti-angiogenic activity. Sunitinib as second-line monotherapy (after cytokines) in patients with mRCC demonstrated a partial response in 34-40% and stable disease at > 3 months in 27-29% of patients [415]). First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4 months) vs. INF-α (21.8 months) despite crossover [416].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear-cell-mRCC [417]. Median time to progression (TTP) with sunitinib 50 mg was numerically longer than the 37.5 mg arm (9.9 vs. 7.1 months). No significant differences in OS were seen (23.1 vs. 23.5 months, p = 0.615). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer TTP with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [418, 419].

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [420]. Median PFS with pazopanib compared with placebo was:

- 9.2 vs. 4.2 months in the overall study population;
- 11.1 vs. 2.8 months for the treatment-naïve subpopulation;
- 7.4 vs. 4.2 months for the cytokine-pre-treated subpopulation.

A trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as another first-line option. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles, and QoL was better with pazopanib [421]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, p < 0.05) due to symptomatic toxicity [422]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial, axitinib was compared to sorafenib in patients who had previously failed cytokine treatment or targeted agents (mainly sunitinib) [423].

The overall median PFS was greater for axitinib than sorafenib. The difference in PFS was greatest in patients in whom cytokine treatment had failed. For those in whom sunitinib had failed, axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21% of patients. Overall survival was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between axitinib or sorafenib [424, 425]. In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naïve clear-cell-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated [426]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.3.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinase (TK), including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to VEGFR and mTOR inhibitors demonstrating objective responses and disease control [183]. Based on these results a randomised phase III trial investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [63, 427]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease by 42% (HR: 0.58 95% CI: 0.45-0.75) [63] (LE: 1b). The median PFS for cabozantinib was 7.4 months (95% CI: 5.6-9.1) vs. 3.8 months (95% CI: 3.7-5.4) for everolimus. The trial recruited 658 patients although PFS was assessed on the first 375 patients. The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI: 14.7-18.8) with everolimus in VEGF-resistant RCC. The HR for death was 0.66 (95% CI: 0.53-0.83, p = 0.0003) [427]. Grade 3 or 4 adverse events were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib. Discontinuation due to toxicity was not significantly different for the two drugs. The trial included 16% MSKCC poor-risk patients.

The Alliance A031203 CABOSUN phase II trial comparing cabozatinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [428, 429]. Compared with sunitinib, cabozantinib treatment significantly increased median PFS (8.2 vs. 5.6 months) and

was associated with a 34% reduction in rate of progression or death (adjusted HR: 0.66; 95% CI: 0.46 to 0.95; one-sided p = 0.012). Objective response rate was 46% (95% CI: 34-57) for cabozantinib vs. 18% (95% CI: 10-28) for sunitinib. All-causality grade 3 or 4 adverse events were similar for cabozantinib and sunitinib. Due to limitations of the statistical analyses within this trial the evidence is inferior over existing choices.

7.4.3.1.6 Lenvatinib

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

7.4.3.1.7 Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1, VEGFR2, and VEGFR3 and was compared in a phase III trial with sorafenib as initial targeted therapy in patients with mRCC [430]. Tivozanib was approved by the EMA in front-line mRCC. It can therefore be prescribed in the European Union.

However, the Panel feels that it remains an inferior option as compared to other TKIs in this setting without further randomised data.

*7.4.4 **Monoclonal antibody against circulating VEGF***

7.4.4.1 Bevacizumab monotherapy and bevacizumab plus IFN-α

Bevacizumab is a humanised monoclonal antibody. The double-blind AVOREN study compared bevacizumab plus IFN-α with INF-α monotherapy in mRCC. Overall response was higher in the bevacizumab plus IFN-α group. Median PFS increased from 5.4 months with IFN-α to 10.2 months with bevacizumab plus IFN-α. No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab/IFN-α group (23.3 vs. 21.3 months) [431].

An open-label trial (CALGB 90206) [432, 433] of bevacizumab plus IFN-α vs. IFN-α showed a higher median PFS for the combination group. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab plus IFN-α, with significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria.

*7.4.5 **mTOR inhibitors***

7.4.5.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [434]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN-α monotherapy, or a combination of both [396]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus plus IFN-α group was not significantly superior to IFN-α alone [396]. Interferon-α toxicity was marked, partly due to the high doses used. The INTORSECT trial investigated temsirolimus vs. sorafenib in patients who had previously failed sunitinib. Although no benefit in PFS was observed, a significant OS benefit for sorafenib was noted [435]. Based on these results, temsirolimus is not recommended in patients with VEFG TKI-refractory disease.

7.4.5.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus plus best supportive care (BSC) vs. placebo plus BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [436]. The initial data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [436]. This was extended to 4.9 months in the final analysis (HR: 0.33) [437]. Subset analysis of PFS for patients receiving only one previous VEFG TKI was 5.4 months [438]. This included some patients who were intolerant rather than progressed on therapy (PFS was also 5.4 months) [438]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in a third- and fourth-line setting [436].

The RECORD-3 randomised phase II study of sequential first-line sunitinib and second-line everolimus vs. sequential first-line everolimus and second-line sunitinib in treatment-naïve mRCC reported a higher median PFS for first-line treatment in the sunitinib group [439]. Primary endpoint was to assess PFS non-inferiority of first-line everolimus to first-line sunitinib. A large number of the crossover patients did not receive the planned subsequent therapy making further analysis complex and underpowered.

*7.4.6 **Therapeutic strategies***

7.4.6.1 Therapy for treatment-naïve patients with clear-cell metastatic RCC

The combination of nivolumab and ipilimumab is the standard of care in IMDC intermediate- and poor-risk patients (figure 7.1). Alternative agents such as sunitinib, pazopanib and cabozantinib should be considered

where nivolumab plus ipilimumab is not safe or feasible. In view of the non-inferiority of pazopanib compared to sunitinib (COMPARZ) this is also included in the Guidelines for this subgroup of patients. Sunitinib or pazopanib therefore remain the preferred agents in favourable-risk patients. Key trials have established bevacizumab plus IFN-α as another first-line treatment option in treatment-naïve patients with clear-cell-mRCC and a favourable-to-intermediate risk score. However, it has not been tested against nivolumab plus ipilimumab and the evidence for subsequent therapies is unclear. The same arguments apply for temsirolimus in poor-risk patients. It is therefore more appealing to treat patients with sunitinib or pazopanib, both of which were tested in all three risk groups in pivotal trials, where nivolumab plus ipilimumab is not safe or feasible.

Recent phase II data, comparing cabozantinib and sunitinib in intermediate- and poor-risk disease, favoured cabozantinib for RR and PFS, but not OS [428]. This underpins the activity of cabozantinib but the lack of a randomised phase III study means it cannot be supported above alternative VEGF-TKIs such as sunitinib or pazopanib.

7.4.6.1.1 Sequencing systemic therapy in clear-cell RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [430]. Nivolumab plus ipilimumab is a new standard of care for front line therapy. Its impact on subsequent therapies is unclear, although OS with nivolumab plus ipilimumab in the CheckMate 214 trial is longer than one would predict from PFS, suggesting significant activity of subsequent agents. The Guidelines Panel provide recommendations in Section 7.6.4.3. The level of evidence is weak due to a lack of data.

Subsequent therapy for patients with disease refractory to nivolumab plus ipilimumab in first-line has not been prospectively tested. However, progression of disease while receiving nivolumab plus ipilimumab should result in subsequent sequencing of targeted therapy (Figure 7.1). Vascular endothelital growth factor-targeted therapies have the most robust efficacy record of activity in mRCC [440]. These agents should be prioritised initially. The Guidelines Panel was unable to specify which VEGF-targeted therapy to use. Axitinib has positive data in VEGF- and cytokine-refractory disease for PFS [441]. Cabozantinib has positive trials in multiple settings in mRCC, including OS [423]. Sunitinib and pazopanib were the standard first-line VEGF-targeted therapies in unselected patients, justifying their use [442]. Tivozanib, sorafenib and bevacizumab/interferon are less favoured and not widely used [440]. The Panel do not favour the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated as they have been outperformed by other VEGF-targeted therapies in mRCC [440]. The combination of bevacizumab and INF-α would involve re-challenge with immune therapy which requires further data prior to being able to provide a positive recommendation [63]. Drug choice in the third-line setting, after nivolumab plus ipilimumab 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 nivolumab. Cabozantinib is the only agent in VEGF-refractory disease with a survival advantage in a randomised phase III trial and should be used preferentially [423]. 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 [440]. Lenvatinib and everolimus have been granted regulatory approval based on randomised phase II data and are an alternative despite only phase II data [443].

There is no evidence for sequencing of immune therapies, which remains within the realms of clinical trials. Patients should receive individual immune checkpoint inhibition only once in the opinion of the Panel. Re-challenge with nivolumab or a combination of ipilimumab and nivolumab is not recommended at this stage. While data on the combination of VEGF-targeted therapy and immune checkpoint inhibition is promising, further randomised data is required prior to any recommendations being made.

7.4.6.2 Non-clear-cell renal cancer

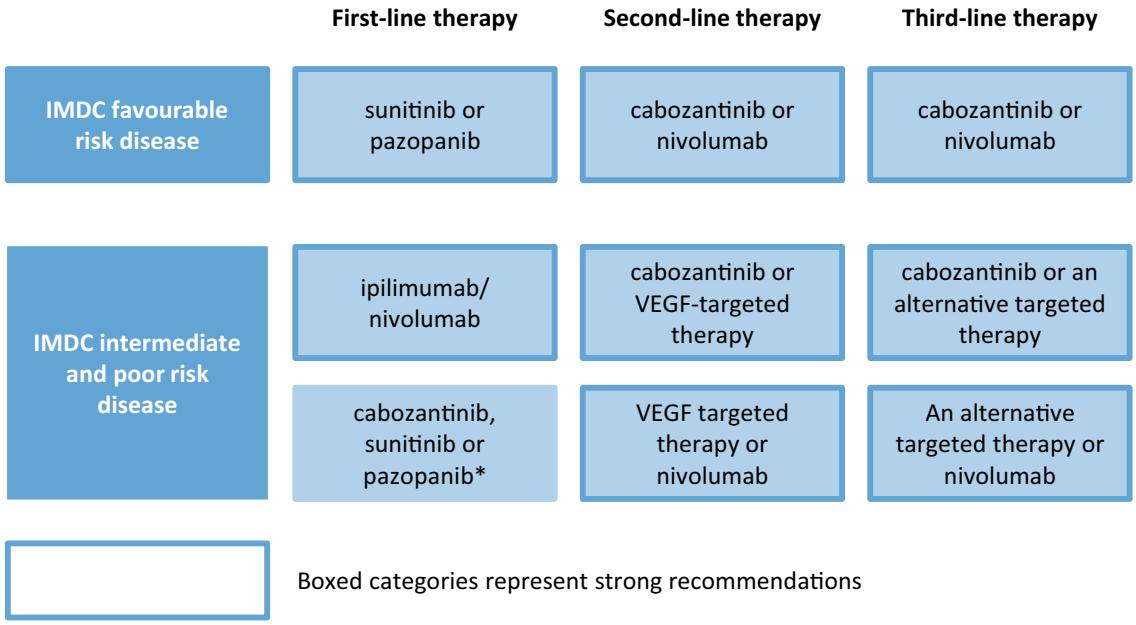
No phase III trials of patients with non-ccRCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-ccRCC has focused on temsirolimus, everolimus, sorafenib and sunitinib [396, 444-446].

The most common non-clear-cell subtypes are papillary type I and non-type I papillary RCCs. There are small single-arm trials for sunitinib and everolimus [446-449]. A trial of both types of pRCC treated with everolimus (RAPTOR) [449], showed a median PFS of 3.7 months per central review in the ITT population with a median OS of 21.0 months.

Another trial investigated foretinib (a dual MET/VEGFR2 inhibitor) in patients with pRCC. Toxicity was acceptable with a high relative risk in patients with germline MET mutations [450]. However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-clear-cell-mRCC including 73 patients (27 with pRCC) was stopped after a futility analysis for PFS and OS [451]. The final results presented at the 2014 annual meeting of the American Society of Clinical Oncology showed a non-significant trend

favouring sunitinib (6.1 vs. 4.1 months). Based on a SR including subgroup analysis of the ESPN, RECORD-3 and another phase II trial (ASPEN) sunitinib and everolimus remain options in this population, with a preference for sunitinib [8, 147, 452]. Patients with non-clear-cell-mRCC should be referred to a clinical trial, where appropriate. Collecting-duct cancers are resistant to systemic therapy. There is a lack of data to support specific therapy in these patients.

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



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium;
VEGF = vascular endothelial growth factor.
**pazopanib for intermediate risk only.*

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

Summary of evidence	LE
VEGF-targeted therapies increase PFS and/or OS as both first-line and second-line treatments for patients with clear-cell mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naïve clear-cell RCC leads to better response rates and PFS but not OS when compared to sunitinib.	1b
Tivozanib has recently been approved, but the evidence is still considered inferior over existing choices.	3
Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
In treatment-naïve patients, bevacizumab in combination with IFN-α has not been tested against nivolumab plus ipilimumab and the evidence for subsequent therapies is unclear.	3
Pazopanib is superior to placebo in both treatment-naïve mRCC patients and post-cytokine patients.	1b
First-line pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN-α in treatment-naïve poor-risk mRCC.	1b
In treatment-naïve patients temsirolimus has not been tested against nivolumab plus ipilimumab and the evidence for subsequent therapies is unclear.	3
Cabozantinib is superior to everolimus in terms of PFS and OS in patients after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo or when the patient cannot tolerate these therapies.	1b
Sorafenib has broad activity in a spectrum of settings in ccRCC patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) have limited oncological efficacy in non-clear cell RCC. There is a non-significant trend for improved oncological outcomes for sunitinib, over everolimus.	2a
Lenvatinib in combination with everolimus modestly improved PFS over everolimus alone.	2a

Recommendations	Strength rating
Offer sunitinib or pazopanib to treatment-naïve patients with clear-cell mRCC of IMDC favourable risk.	Strong
Offer cabozantinib to treatment-naïve patients with clear-cell mRCC of IMDC intermediate and poor risk.	Weak
Do not offer bevacizumab plus interferon-α to treatment-naïve clear-cell favourable- and intermediate-risk RCC patients.	Weak
Do not offer tivozanib to treatment-naïve clear-cell mRCC patients.	Weak
Do not offer temsirolimus to treatment-naïve clear-cell poor-risk RCC patients.	Weak
Offer vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs) as second-line to patients refractory to nivolumab plus ipilimumab.	Weak
Offer cabozantinib for ccRCC after one or two lines of VEGF-targeted therapy in mRCC.	Strong
Offer axitinib, everolimus or lenvatinib plus everolimus to ccRCC patients who failed VEGF-targeted therapy, and when nivolumab or cabozantinib are not safe, tolerable or available.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer sunitinib as first-line therapy for non-clear cell mRCC.	Weak
Do not offer sorafenib as first- or second-line treatment to patients with mRCC.	Weak

7.5 Recurrent RCC

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

After NSS for pT1 disease, recurrences within the remaining kidney occur in about 1.8-2.2% of patients [453, 454]. Although the impact of positive margins on the clinical prognosis is still unclear [291, 454, 455] the preferred management, when technically feasible, is repeat surgical intervention to avoid the potential risk for tumour recurrence.

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [456]. Whereas repeat ablation is still recommended as the preferred

therapeutic option after treatment failure, the most effective salvage procedure as an alternative to complete nephrectomy has not yet been defined.

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

Only retrospective and non-comparative data on the frequency and efficacy of available therapeutic options have been reported. One of the largest series including 2,945 patients treated with RN reported on 54 patients with recurrent disease localised in the renal fossa, the ipsilateral adrenal gland or the regional LNs as sole metastatic sites [457]. Another recent series identified 33 local recurrences within a cohort of 2,502 surgically treated patients, confirming the efficacy of surgical treatment vs. conservative approaches (observation, medical therapy).

In summary, the limited available evidence suggests that in selected patients surgical removal of locally recurrent disease can induce durable tumour control. Since local recurrences develop early, with a median time interval of 10-20 months after treatment of the primary tumour [458], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up).

Adverse prognostic parameters are a short time interval (< 3-12 months) since treatment of the primary tumour [459], sarcomatoid differentiation of the recurrent lesion and an incomplete surgical resection [457]. In case complete surgical removal is unlikely or significant comorbidities are present (especially when combined with poor prognostic tumour features), palliative therapeutic approaches including radiation therapy aimed at symptom control and prevention of local complications should be considered (see Sections 7.3 and 7.4).

7.5.1 Summary of evidence and recommendation for advanced/metastatic renal cell cancer

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

Recommendation	Strength rating
Offer surgical resection of locally recurrent disease when a complete resection is possible and significant comorbidities are absent.	Weak

8. FOLLOW-UP IN RCC

8.1 Introduction

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

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- development of metastases.

There is no consensus on surveillance after RCC treatment, and there is no evidence that early vs. later diagnosis of recurrences improves survival. Intensive radiological surveillance for all patients is not necessary. However, follow-up is important to increase the available information on RCC and should be performed by a urologist, who should record the time to recurrence or the development of metastases. The outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify follow

up, taking into account the risk of developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods [25, 460, 461] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol vs. patients who were not [462]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [462].

An individualised, risk-based, approach to RCC surveillance was recently proposed. The authors use competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [463]. For patients with low-stage disease but with a Charlson comorbidity index > 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age. The RECUR database consortium initiated by this Guideline Panel collects similar data with the aim to provide comparators for guideline recommendations. Preliminary data support a risk-based approach. In the near future, genetic profiles may refine the existing prognostic scores and external validation in datasets from adjuvant trials were promising [9, 464].

Renal function is assessed by the measurement of serum creatinine and eGFR. Repeated long-term monitoring of eGFR is indicated in case of impaired renal function before, or after, surgery. Renal function [465, 466] and non-cancer survival [208, 209, 467] can be optimised by performing NSS, whenever possible, for T1 and T2 tumours [468] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is surgery [469, 470]. Recurrence in the contralateral kidney is also rare (1-2%), can occur late (median 5-6 years), and might be related to positive margins, multifocality, and grade [471] (LE: 3). Surveillance can identify local recurrences or metastases at an early stage. In metastatic disease, extended tumour growth can limit the opportunity for surgical resection which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

- The sensitivity of chest radiography and US for small metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in histology controlled comparative trials [472-474].
- Surveillance with these imaging modalities are less sensitive [475].
- In low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used outside the thorax.
- When the risk of relapse is intermediate or high, CT of the chest, abdomen and pelvis should be performed.
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to their limited specificity and sensitivity.
- After injection of contrast medium, the risk of acute renal failure seems to be negligible in patients with a GFR > 20 mL/min and chronic renal impairment [476].

Controversy exists on the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after five years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with NSS if the tumours are detected early. For tumours < 4 cm, there is no difference between PN and RN with regard to recurrences during follow up [477] (LE: 3). Several authors have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death [194, 196, 478, 479]. These systems have been compared and validated [480] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed but none include ablative therapies [481, 482]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [191]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [200] (LE: 3).

A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk profile, but also efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the surveillance schedule according to suspected risk of recurrence. The most suitable approach to define high-risk patients is the utilisation of nomograms.

Data from adjuvant trials are generally based on the University of California Los Angeles integrated staging system (UISS) risk stratification which makes it the most widely used and validated system [174, 483].

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

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

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; US = ultrasound of abdomen, kidneys and renal bed.

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

Summary of evidence	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing surveillance have a better overall survival than patients not undergoing surveillance.	3
Repeated CT scans do not reduce renal function in chronic kidney disease patients.	3

Recommendations	Strength rating
Base follow-up after RCC on the risk of recurrence.	Strong
Intensify follow-up in patients after NSS for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Base risk stratification on pre-existing classification systems such as the University of California Los Angeles integrated staging system integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443).	Strong

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Further information should be sought at what time point restaging has the highest chance to detect recurrence. Prognostic markers at surgery should be investigated to determine the risk of relapse over time.

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10. CONFLICT OF INTEREST

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

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