



Guidelines

European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update

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Abstract

Context: The European Association of Urology Renal Cell Carcinoma (RCC) Guideline Panel has prepared evidence-based guidelines and recommendations for the management of RCC.

Objective: To provide an updated RCC guideline based on standardised methodology including systematic reviews, which is robust, transparent, reproducible, and reliable.

Evidence acquisition: For the 2019 update, evidence synthesis was undertaken based on a comprehensive and structured literature assessment for new and relevant data. Where necessary, formal systematic reviews adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were undertaken. Relevant databases (Medline, Cochrane Libraries, trial registries, conference proceedings) were searched until June 2018, including randomised controlled trials (RCTs) and retrospective or controlled studies with a comparator arm, systematic reviews, and meta-analyses. Where relevant, risk of bias (RoB) assessment, and qualitative and quantitative syntheses of the evidence were performed. The remaining sections of the document were updated following a structured literature assessment. Clinical practice recommendations were developed and issued based on the modified GRADE framework.

Evidence synthesis: All chapters of the RCC guidelines were updated based on a structured literature assessment, for prioritised topics based on the availability of robust

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data. For RCTs, RoB was low across studies. For most non-RCTs, clinical and methodological heterogeneity prevented pooling of data. The majority of included studies were retrospective with matched or unmatched cohorts, based on single- or multi-institutional data or national registries. The exception was for the treatment of metastatic RCC, for which there were several large RCTs, resulting in recommendations based on higher levels of evidence.

Conclusions: The 2019 RCC guidelines have been updated by the multidisciplinary panel using the highest methodological standards. These guidelines provide the most reliable contemporary evidence base for the management of RCC in 2019.

Patient summary: The European Association of Urology Renal Cell Carcinoma Guideline Panel has thoroughly evaluated the available research data on kidney cancer to establish international standards for the care of kidney cancer patients.

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1. Introduction

The European Association of Urology (EAU) renal cell cancer (RCC) guidelines provide clinicians with evidence-based information and recommendations for the management of patients with RCC. The RCC Panel is an international group consisting of clinicians with expertise in this field. The multidisciplinary panel includes urologists, medical oncologists, a pathologist, a radiologist, a methodologist, and a member of a patient advocacy group. The EAU RCC guidelines were first published in 2000 [1]. For the 2019 update, the entire guideline has been updated based on a comprehensive and structured literature assessment, with several sections requiring a formal systematic review (SR) based on the availability of data (Table 1). A detailed version of the current guideline including full references, level of evidence (LE), and grade of recommendations is available at <http://uroweb.org/guideline/renal-cell-carcinoma/> [2].

2. Evidence acquisition

All chapters of the 2019 RCC guideline publication were updated using a structured literature assessment [2]. Literature searches were conducted in the following databases: MEDLINE, MEDLINE In-Process, Embase, and Cochrane Database of Systematic Reviews and Controlled Trials Register. Additionally, a series of topics and questions were prioritised a priori, on which formal, protocol-driven SRs were undertaken, for which the review methodology has

been described elsewhere [3,4]. These were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [2,5]. For each SR, elements for inclusion and exclusion, including patient population, intervention, comparison, outcomes (PICO); study design; and search terms and restrictions were developed using an iterative process involving all members of the panel in a consensus model. Where relevant, confounding variables were identified for each question to facilitate the assessment of nonrandomised studies. The SR protocols containing details of the review process and the search strategies used, as well as, reference lists of all included studies are published on uroweb.org [2]. The search was conducted up to the end of June 2018. Two independent reviewers screened abstracts and full texts, carried out data abstraction, and assessed risk of bias (RoB). Data were assessed according to their level of scientific evidence (LE) based on the 2009 Oxford Centre for Evidence-based Medicine Levels of Evidence (<http://www.cebm.net/index.aspx?o=1025> [accessed date January 2019]). The majority of included studies were retrospective analyses that included some larger multicentre or well-designed controlled comparative studies, except for the topic of systemic treatment of metastatic RCC (mRCC), in which several practice-changing randomised controlled trials (RCTs) have been performed, resulting in a higher LE. Once the LE for a particular topic or question had been determined, a guideline recommendation was made using a transparent, reproducible, and reliable process modified

Table 1 – Description of guideline 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 traditional narrative review, based on a structured literature assessment. |
| 4. Staging and grading classification systems | This chapter was updated by a traditional narrative review, based on a structured literature assessment. |
| 5. Diagnostic evaluation | Diagnostic imaging was revised based on an SR. The remainder of the chapter was updated by a structured literature assessment. |
| 6. Prognosis | This chapter was updated by a traditional narrative review, based on a structured literature assessment. |
| 7. Treatment (disease management) | Treatment of localised and locally advanced disease was revised based on an updated SR. Non-clear-cell cancer was updated by the means of an SR. The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease was updated by SRs. |
| 8. Surveillance following radical or partial nephrectomy or ablative therapies | This chapter was updated by a traditional narrative review, based on a structured literature assessment. |

SR = systematic review.

from the GRADE framework [6]. This approach allows the integration of the LE with other essential elements, including certainty of the evidence, magnitude of effects, balance between consequences, and patient values and preferences [7], in order to issue clinical practice recommendations [2,6]. Where there was heterogeneity of opinions amongst panel members, formal consensus methods were used to arrive at the final recommendation [8].

3. Evidence synthesis

3.1. Epidemiology and aetiology

RCC represents approximately 3% of all cancers, with the highest incidence occurring in Western countries [9]. Generally, during the last 2 decades, there has been an annual increase of 2% in incidence both worldwide and in Europe, leading to approximately 99 200 new RCC cases and 39 100 kidney cancer-related deaths within the European Union in 2018 [9]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilising or declining thereafter [10]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, and Slovakia), mortality rates still show an upward trend [9,10]. RCC is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. There is a 1.5:1 predominance in men over women, with a peak incidence at 60–70 yr of age [11]. It comprises different RCC subtypes with specific histopathological and genetic characteristics [12]

Aetiology includes lifestyle factors such as smoking, obesity, and hypertension [13]. Having a first-degree relative with RCC is also associated with an increased risk. A number of other factors have been suggested to be associated with a higher or lower risk of RCC. These include specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [13,14]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [15]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [13].

3.2. Diagnosis and staging

3.2.1. Symptoms

Many patients with renal masses (RMs) remain asymptomatic until the late stages. Today, >60% of RCCs are detected incidentally with abdominal ultrasound (US) or computed tomography (CT) performed for other reasons (LE: 3). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare today, and correlates with advanced disease and subtypes associated with poor prognosis (LE: 3) [11]. Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (LE: 4). A few patients present with symptoms caused by mRCC, such as

bone pain, deterioration of performance status (PS), or persistent cough (LE: 3) [16].

The EAU RCC guideline recommendations for diagnostic procedures of RMs are shown in Table 2.

3.2.2. Imaging

CT, US, and magnetic resonance imaging (MRI) are the imaging modalities used to detect and characterise RMs [17]. RMs can be classified as solid or cystic on the basis of the imaging findings. With solid RMs, the most important criterion for differentiating malignant lesions is the presence of contrast enhancement or restriction (LE: 3) [18]. Contrast-enhanced US (CEUS) can be helpful in specific cases (LE: 3) [17]). However, CT and MRI cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (LE: 3). Positron emission tomography is not currently a standard investigation (LE: 3) [19]. In patients with RCC, chest CT is the most accurate investigation to diagnose lung metastases or enlarged mediastinal lymph nodes (LNs) (LE: 3) [20]. Since most bone and brain metastases are symptomatic at diagnosis, bone or brain imaging is performed on indication (LE: 3) [21]. In the case of a renal cystic mass, the Bosniak classification distinguishes five categories based on CT presentation, can predict the risk of malignancy (LE: 3), and provides guidance for management [22]. MRI and CEUS show higher sensitivity and specificity than CT, and both are recommended to evaluate unclear cystic lesions, especially Bosniak III cysts [23]. Bosniak I, II, IIF, III, and IV cysts are malignant in around 0%, 0%, 10%, 50%, and 100% of surgically

Table 2 – Recommendations for the diagnostic assessment of renal cell carcinoma

| | Strength rating |
|--|-----------------|
| Use multiphasic 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 nonionising 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 |

RCC = renal cell carcinoma.

treated cases, respectively [24]. Cautious surveillance of Bosniak III cysts is a reasonable option to the conventional management [24].

3.2.3. Renal tumour biopsy

Percutaneous renal tumour biopsies are increasingly used for histological diagnosis in order to avoid unnecessary surgery in the event of a benign lesion, to select patients for surveillance, and to obtain histology before ablative treatment. Tumour biopsies are also used in mRCC for the selection of medical and surgical treatment (LE: 3) [25]. Core biopsies are preferable to fine needle aspiration for solid RMs (LE: 2b) and are not recommended for cystic RMs due to their low diagnostic yield, unless areas with a solid pattern are present (Bosniak IV cysts; LE: 2b) [25].

A core biopsy should be performed with 18G needle and a coaxial technique to minimise the risk of seeding (LE: 2b) [26]. At least two quality cores (nonfragmented, >10 mm in length) should be obtained, and necrotic areas should be avoided in order to maximise diagnostic accuracy (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid central necrosis (LE: 2b). In experienced centres, percutaneous core biopsies have low morbidity, a high diagnostic yield, and accuracy for the diagnosis of malignancy and RCC type (LE: 2b) [25]. However, they are nondiagnostic in 2.5–22% of cases (LE: 2b) [26]. If a biopsy is nondiagnostic, a second biopsy or surgical exploration should be considered (LE: 4).

3.2.4. Histological diagnosis

Renal neoplasms comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [12]. There are three main RCC types: clear-cell RCC (ccRCC; 80–90%), papillary RCC (pRCC—types I and II; 10–15%, of which 60–70% are type I), and chromophobe RCC (4–5%). Differences in tumour stage, grade, and cancer-specific survival (CSS) exist between RCC subtypes, and they have an impact on prognosis. Histological diagnosis includes, besides RCC type, evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, invasion of the collecting system and perirenal fat, and LN status. The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [27]. Sarcomatoid differentiation can be found in all RCC subtypes, and denotes high grade and very aggressive tumours. Collecting duct carcinoma and other infrequent renal tumours are shown in Table 3.

3.3. Classification and prognostic factors

3.3.1. Tumour-node-metastasis stage classification

The 2017 version of the tumour-node-metastasis (TNM) classification should be used for clinical and scientific staging. The prognostic value of the TNM classification has been validated in both single- and multi-institutional studies [28].

3.3.2. Prognostic factors

Anatomical, histological, clinical, and molecular factors give prognostic information. Anatomical factors are reflected in the TNM classification, providing the most reliable information. In addition, complexity scores such as the R.E.N.A.L. nephrometry score, amongst others, aim to standardise renal tumours and aid in the comparison of treatment strategies [29]. Histological factors include nuclear grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Although affected by intra- and interobserver variability, grade remains an independent prognostic factor [27]. Comparing RCC subtypes, pRCC type 1 has a significantly reduced risk of death compared with ccRCC and pRCC type 2 in non-mRCC [30]. Postoperative prognostic nomograms have externally been validated to predict survival, but none have been fully validated in the contemporary patient population (LE: 3) [31].

Numerous molecular markers, including CAIX, PTEN, and CXCR4, as well as gene expression profiling, and deep and whole genome wide sequencing (GWAS) have been investigated, but none of these techniques has yet yielded profiles that improve the current prognostic systems [32].

The expression of the *BAP1* and *PBRM1* genes, situated on chromosome 3p in a region that is deleted in >90% of ccRCCs, have shown to be independent predictive factors for tumour recurrence [33]. Published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes than patients with *PBRM1*-mutant tumours. A 16-gene signature can predict relapse and was validated in adjuvant trials [34]. This signature may be introduced in the clinical setting.

Prognostic information on cytokines and blockade of immune-inhibitory molecules such as PD-L1 have shown promising therapeutic results, but their use in RCC treatment remains to be explored [35].

Emerging data on chromosomal alterations, through GWAS, miRNA, single nucleotide polymorphisms, and gene methylations, all contribute to improving diagnostic and prognostic information. A number of studies have confirmed prognostic information based on the 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 predict survival in ccRCC independently [36].

3.4. Other renal tumours

Besides the common RCC types, described in the 2016 WHO classification [12,32], the remaining 10% include renal pelvis carcinoma; a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described; and a group of unclassified carcinomas. Table 3 summarises the malignant potential of these rare renal tumours, with recommendations for treatment. Additional details are provided in the full guidelines [2].

Table 3 – Other renal cortical tumours and recommendations for treatment [2]

| 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; sunitinib, gemcitabine plus doxorubicin is also an option |
| Multilocular cystic renal neoplasm of low malignant potential | Formerly multilocular cystic RCC | Benign | 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 CSS in comparison with ccRCC is 4.49 | High, very aggressive Median survival 30 mo | Surgery; response to targeted therapies is poor |
| Renal medullary carcinoma | Very rare; mainly young black men with sickle cell trait | High, very aggressive, median survival is 5 mo | Surgery; different chemotherapy regimes, radiosensitive |
| Translocation RCC Xp11.2 | Rare, mainly younger patients <40 yr, more common in females It constitutes with TRCC 6p21 MiT translocation RCCs | High | Surgery; 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 | 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 | 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 is used as well; imaging—Bosniak type III or II/IV | Low/benign | Surgery, NSS |
| Oncocytoma | 3–7% of all renal tumours Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC Histopathological diagnosis remains the reference standard | Benign | Observation (when histologically confirmed) NSS |
| 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 |

ccRCC = clear-cell RCC; CSS = cancer-specific survival; NSS = nephron-sparing surgery; RCC = renal cell carcinoma; TRCC = translocation RCC; VEGF = vascular endothelial growth factor; WHO = World Health Organization.

3.5. Treatment of localised RCC and local treatment of mRCC

The EAU RCC guideline recommendations for the treatment of localised RCC and local treatment of mRCC are given in Table 4.

3.5.1. Surgical treatment

Surgery is the only curative treatment for localised RCC. Based on oncological and functional outcomes, localised T1a-b tumours are best managed by partial nephrectomy (PN) rather than by radical nephrectomy (RN), irrespective of the surgical approach (LE: 1b). Multiple retrospective series as well as one prospective RCT including patients

with organ-confined RCC of limited size have demonstrated comparable CSS for PN versus RN [37]. PN better preserved general kidney function than RN, thereby lowering the risk of development of metabolic or cardiovascular disorders [3,38]. Many retrospective studies compared PN versus RN (open or laparoscopic) for RCCs of ≤ 4 cm [39], demonstrating an association of RN with increased cardiovascular events and mortality from any cause after adjusting for patient characteristics. In studies analysing RCCs of 4–7 cm, no CSS differences were shown between PN and RN [37,40,41]. In clinically localised RCCs of ≤ 4 cm, an SR concluded that compared with RN, PN was associated with equal or better survival, whereas serious adverse event

Table 4 – Recommendations for treatment of localised RCC and local treatment of mRCC

| Recommendations | Strength rating |
|--|-----------------|
| Treatment of localised RCC | |
| 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 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 |
| Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy. | Strong |
| Do not perform minimally invasive radical nephrectomy in patients with T1 tumours for whom a partial nephrectomy is feasible by any approach, including open. | Strong |
| Do not perform minimally invasive surgery if this approach may compromise oncological, functional, and perioperative outcomes. | Strong |
| Offer active surveillance, radiofrequency ablation, and cryoablation to elderly and/or comorbid patients with small renal masses. | Weak |
| Treatment of patients with RCC and clinically positive lymph nodes | |
| In patients with clinically enlarged lymph nodes, perform lymph node dissection for staging purposes or local control. | Weak |
| Management of RCC with venous tumour thrombus | |
| Remove the renal tumour and thrombus in case of venous involvement in nonmetastatic disease. | Strong |
| Recommendations for adjuvant therapy | |
| 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 |
| Recommendations for cytoreductive nephrectomy | |
| Do not perform 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 VEGFR-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 |
| Recommendations for local therapy of metastases in mRCC | |
| 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 |
| CN = cytoreductive nephrectomy; mRCC = metastatic RCC; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor. | |

rates, CSS, and time to recurrence were similar for both groups [3]. One study reported on radiofrequency ablation (RFA) versus RN or PN for T1a RCC, resulting in almost 100% CSS at 7 yr of for all three treatment groups [39].

3.5.1.1. Techniques of RN. Some cohort studies assessing oncological outcomes of laparoscopic versus open RN show similar oncological outcomes even for locally more advanced tumours [39,40]. No significant differences in CSS, progression-free survival (PFS), and overall survival (OS) were reported. Based on an SR, less morbidity was found for laparoscopic versus open RN [37,41]. These studies showed significantly shorter hospital stay, less perioperative blood loss, and lower analgesic requirements for the laparoscopic RN-treated group than the open RN group (LE: 1b). Similar oncological outcomes were reported for retroperitoneal versus transperitoneal approaches in the two RCTs and one quasirandomised study [42]. No reliable comparative data exist with regard to hand-assisted, robotic, and LESS laparoscopic nephrectomy versus conventional laparoscopic approach. There was no difference in complications, but operation time was significantly shorter in the open RN arm. Postoperative quality of life (QoL) scores were similar [3].

3.5.1.2. Techniques of PN. Whereas oncological long-term data for conventional laparoscopic PN are available, oncological safety of robot-assisted versus open PN has only been addressed in studies with limited follow-up. Studies comparing laparoscopic PN and open PN found no difference in PFS or OS between the two techniques in centres with laparoscopic expertise [43,44]. The Gill et al. [45] study suggests comparable oncological efficacy even in case of higher-stage tumours (pT1b/pT3a). The higher number of patients treated with open surgery might reflect a selection bias by offering robotic surgery in case of a less complex anatomy. 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 pathological margins were similar amongst the groups [46].

In a matched-pair comparison, the decline in estimated glomerular filtration rate was greater in the laparoscopic PN group in the immediate postoperative period, but not after a follow-up of 3.6 yr [43]. Retroperitoneal and transperitoneal laparoscopic PNs were found to have similar perioperative outcomes. A prospective comparison of surgical outcomes obtained after robotic or pure laparoscopic PN in moderate-to-complex renal tumours showed significantly lower estimated blood loss and a shorter warm ischemia time in the robotic group [47]. A meta-analysis found comparable perioperative outcomes comparing surgery and ablation [39]. In conclusion, PN can be performed, with an open, pure laparoscopic, or robot-assisted approach, based on surgeon's expertise, skills, and availability of equipment (LE: 2b).

A positive surgical margin occurs in about 2–8% of PNs. Studies comparing different resection techniques (open, laparoscopic, robotic) are inconclusive. A positive surgical

margin status occurs more frequently in cases in which surgery is imperative (solitary kidney, bilateral disease) and in patients with adverse pathological features (pT2a, pT3a, grade III–IV). Local tumour recurrence was found in 16% in positive surgical margins compared with 3% in negative margins [48]. Patients with positive surgical margins are not indicated immediately to any reintervention but to a more intense surveillance.

3.5.1.3. Adrenalectomy. One nonrandomised study on PN and two small studies on RN compared the outcomes with, or without, ipsilateral adrenalectomy [4,49]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS was seen with or without adrenalectomy. Adrenalectomy was justified using criteria based on radiographic and intraoperative findings. Only 48 of 2065 patients underwent concurrent ipsilateral adrenalectomy, of whom 42 were for benign lesions [49].

3.5.1.4. LN dissection for clinically negative LNs (cN0). Clinical assessment of LN status is based on the detection of LN enlargement either by CT/MRI or by intraoperative palpation of enlarged nodes. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [4]. For patients with clinically negative LNs (cN0), LN dissection (LND) was not associated with a reduced risk of distant metastases, or cancer-specific or all-cause mortality [50,51]. Neither did LND improve oncological outcomes amongst patients at a high risk of radiographic cN1 [51].

3.5.2. Management of RCC with venous tumour thrombus

An SR on the management of venous tumour thrombus (VTT), in non-mRCC, included only five studies with a high RoB across all studies [52]. Minimal-access techniques resulted in significantly shorter operating time compared with sternotomy. Preoperative embolisation was associated with increased operating time, blood loss, hospital stay, and perioperative mortality. 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. No surgical method was shown to be superior for the excision of VTT. The surgical method was dependent on the upper level of tumour thrombus. The relative benefits and harms of other strategies and approaches regarding access to the inferior vena cava (IVC), and the role of IVC filters and bypass procedures remain uncertain with non-mRCC. Nevertheless, the findings support that all patients with nonmetastatic disease and VTT should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation (LE: 3) [53]. PS can significantly improve after removal; therefore, deterioration of PS due to thrombus should not be an exclusion for surgery,

3.5.3. Therapeutic approaches as alternative to surgery

3.5.3.1. Embolisation. Before a routine nephrectomy, there is no benefit in performing tumour embolisation. In patients

unfit for surgery and suffering from massive haematuria or flank pain, embolisation can be a beneficial palliative intervention (LE: 3).

3.5.3.2. Surveillance. Elderly and comorbid patients with incidentally detected small RMs have relatively low RCC-specific mortality and significant competing-cause mortality [54]. Active surveillance (AS) can be offered to this category of patients and is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI), with delayed intervention reserved for those tumours that show clinical progression during follow-up. A renal biopsy is recommended prior to surveillance (LE: 3). In the largest reported prospective series of AS, the growth rate of the RM was slow in most cases and progression to mRCC occurred in 1.1% of patients (LE: 3) [54]. Frequency of serial imaging in this study consisted of CT, MRI, or US at months 3 and 6, every 6 mo until 3 yr, and annually thereafter (LE: 3). In a large prospective nonrandomised study comparing AS or primary active intervention for small RMs, OS and CSS were not significantly different in the two treatment groups [55].

3.5.3.3. Ablative therapies. The most commonly performed ablative therapies for renal tumours are percutaneous RFA, and laparoscopically assisted or percutaneous cryoablation (CA). Microwave ablation, stereotactic radiosurgery, laser ablation, and high-intensity focused US ablation are considered experimental. Indications for thermal ablation include elderly, comorbid patients with a small RM who are considered unfit for surgery; patients with a genetic predisposition to develop multiple tumours; and patients with bilateral tumours or with a solitary kidney, and a high risk of complete loss of renal function following PN. Larger tumours or those located at the hilum or near the proximal ureter are not recommended for ablation. There are no RCTs comparing RFA or CA with PN [37]. Low-quality studies suggest a higher local recurrence rate for thermal ablation compared with PN (LE: 3). The quality of the available data does not allow any definitive conclusions regarding morbidity and oncological outcomes for RFA and CA (LE: 3) [56].

3.5.4. Adjuvant therapy

There is currently no evidence from randomised phase III trials that adjuvant therapy offers an OS benefit. Besides tumour vaccination, CAIX, and adjuvant Interferon therapy, recent evidence is based on adjuvant trials with targeted therapies in high-risk patients. These included the ASSURE study comparing sunitinib versus sorafenib versus placebo, the PROTECT study comparing pazopanib and placebo, and the S-TRAC study comparing sunitinib with placebo [57]. The results showed a benefit of sunitinib over placebo for disease-free survival (DFS) in the S-TRAC study ($p = 0.03$), but in 2018, data for OS remained immature since median OS was not reached in either arm. Grade 3/4 toxicity in the study was 61% for patients receiving sunitinib and 21% for patients on placebo. A pooled analysis of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) versus placebo demonstrated

that VEGFR-targeted therapy was not statistically significantly associated with improved DFS or OS compared with placebo [58]. In addition, the ATLAS study comparing axitinib with placebo did not meet its primary endpoint [59]. In summary, there is currently a lack of proven benefit of adjuvant therapy with VEGFR-TKIs for patients with high-risk RCC after nephrectomy, and their use is not recommended (LE: 1a).

3.5.5. Surgical treatment of mRCC

Most patients with mRCC require systemic therapy, and the role and sequence of cytoreductive nephrectomy (CN) has been investigated in two RCTs. In the previous cytokine era, increased long-term survival was found in patients treated with CN + immunotherapy [60]. The SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS. The trial accrued poorly, and the results are mainly exploratory. In secondary endpoint analysis, a strong OS benefit was observed in favour of the deferred CN approach in the intent-to-treat (ITT) population, with median OS of 32.4 mo in the deferred CN arm versus 15.0 mo in the immediate CN arm. The CARMENA study showed that sunitinib alone was not inferior to immediate CN followed by sunitinib with regard to OS [8]. In an ITT analysis, median OS was 13.9 mo with CN versus 18.4 mo with sunitinib alone. This noninferiority study did not reach the full accrual of planned (450 out of 576) patients. Thirty-eight patients in the sunitinib-only arm (17%) required secondary CN due to acute symptoms or for complete or near-complete response.

In summary, immediate CN is not recommended in Memorial Sloan Kettering Cancer Center (MSKCC) intermediate- and high-risk patients requiring sunitinib, or an equivalent VEGFR-TKI (LE: 1b). Those patients are recommended immediate sunitinib, and weak evidence from both CARMENA and SURTIME supports performing a deferred CN at 3 mo, or later, in patients who do not progress on VEGFR-TKI therapy (LE: 2b).

Neither CARMENA nor SURTIME answered the question of CN in patients with low-volume metastatic disease, good PS, and a favourable and intermediate risk, who do not require immediate VEGFR-TKI treatment but may be observed instead [8]. In these patients, immediate CN retains its role, since observation until progression requiring systemic treatment can result in substantial time to onset of VEGF-targeted therapy (LE: 2b) [61].

However, due to a paradigm change in first-line treatment for intermediate- and poor-risk patients shown in the CheckMate 214 study [62], the role and sequence of CN in the era of immunotherapy need to be reinvestigated.

3.5.6. Local therapy of metastases in RCC

An SR of comparative studies evaluated local treatment of metastases from RCC in any organ [63]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were survival (OS, CSS, and PFS), local symptom control, and adverse events. All included studies were retrospective, nonrandomised, comparative studies showing a high RoB

associated with nonrandomisation, attrition, and selective reporting. With the exception of brain and possibly bone metastases frequently treated by stereotactic radiotherapy, metastasectomy remained, by default, an appropriate local treatment for most sites. Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS, and delay of systemic therapy. Radiotherapy, especially stereotactic radiotherapy, to bone and brain metastases from RCC can induce significant relief from local symptoms (all LE: 3) [63].

3.6. Systemic therapy for mRCC

3.6.1. Targeted therapies

Until targeted therapies were introduced in 2006, the treatment of mRCC was generally based on immunotherapies such as interferon- α (IFN- α) and interleukin-2. With the introduction of targeting agents, stabilisation of the disease and prolonged survival was achieved. Several targeting drugs have been approved for the treatment of mRCC: sunitinib, sorafenib, pazopanib, axitinib, tivozanib, cabozantinib, the mTOR inhibitors everolimus and temsirinolimus, as well as bevacizumab combined with IFN- α . Treatment recommendations on first-line treatment and subsequent treatment lines are based on RCTs with a high LE. A detailed description of the targeting agents can be found in the RCC guideline text at www.uroweb.org[2]. For treatment recommendations, see Fig. 1 and SRs [2,64].

Most published trials have selected ccRCCs only; thus, the robust evidence-based recommendations are applicable only for ccRCC.

The International Metastatic Renal Cancer Database Consortium risk model has been established and validated to aid in an accurate prognosis of patients treated with targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while serum lactate dehydrogenase has been removed [65].

3.6.2. Immunotherapy

Immunotherapy trials using immune checkpoint blockade with monoclonal antibodies blocking the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) signalling to restore tumour-specific T-cell immunity have been conducted. The CheckMate 214 study reported superiority of nivolumab and ipilimumab over sunitinib in intermediate- and poor-risk patients, leading to a paradigm shift in the first-line management of mRCC patients. OS with nivolumab plus ipilimumab in both intermediate- and poor-risk patients is longer than one would predict for PFS, suggesting significant activity of subsequent agents [62]. Results showed that a combination of ipilimumab and nivolumab was associated with the achievement of durable remissions in a higher proportion of patients. These findings resulted in an updated recommendation of the systemic treatment of mRCC patients, as shown in Figure 1. The impact on subsequent therapies is unclear, since therapy for patients with disease refractory to nivolumab plus ipilimumab in a first-line setting has not been tested. A phase III trial of nivolumab versus everolimus

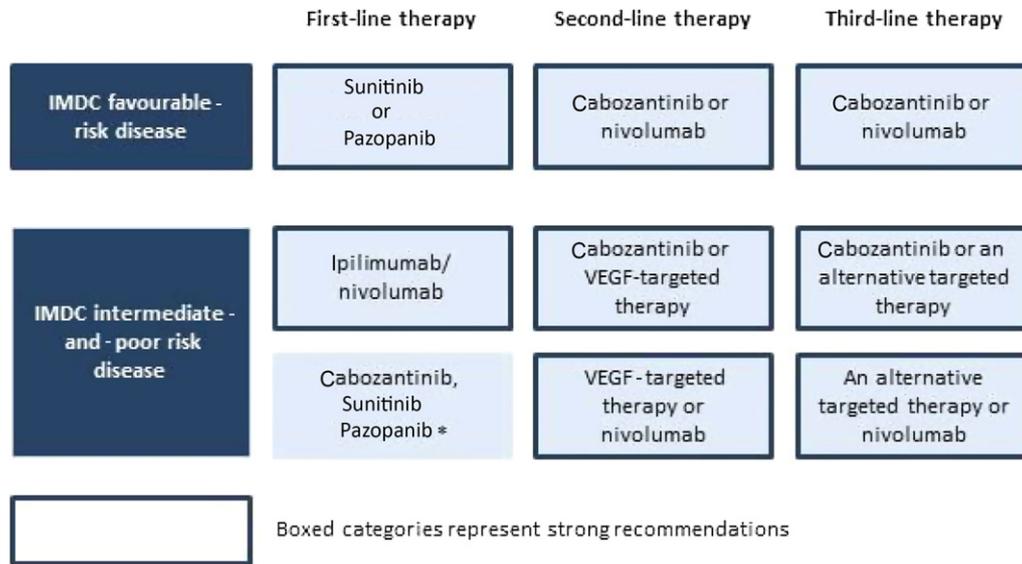


Fig. 1 – Updated European Association of Urology guideline recommendations 2019, for the systemic treatment of metastatic clear-cell renal cell carcinoma. IMDC = International Metastatic Renal Cancer Database Consortium; VEGF = vascular endothelial growth factor.

after one line or two lines of VEGF-targeted therapy reported longer OS, better QoL, and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [66]. Patients who 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.

3.6.3. Non-clear-cell mRCC

Only a few trials on systemic treatment in patients with non-clear-cell mRCC have been reported, showing modest efficacy only [67]. In randomised phase II trials comparing everolimus versus Sunitinib, superior efficacy of sunitinib in terms of PFS was suggested [67]. The most common non-clear-cell subtypes are type 1 and non-type 1 pRCCs (LE: 2b). A trial of both types of pRCCs treated with everolimus (RAPTOR) showed median PFS of 3.7 mo in the ITT population, with median OS of 21 mo [68]. Patients with non-clear-cell mRCC should be referred to a clinical trial, where appropriate.

3.7. Follow-up surveillance following nephrectomy or ablative therapies

Surveillance after treatment for RCC allows the clinician to monitor or identify postoperative complications, renal function, local recurrence after PN or ablation, recurrence in the contralateral kidney, and development of metastases. Although there is no randomised evidence, large studies have examined prognostic factors with a long follow-up (LE: 4) [69,70]. One study has shown a survival benefit for patients who were followed within a structured surveillance protocol versus patients who were not [69]. Patients undergoing follow-up seem to have longer OS than those not undergoing routine follow-up [70]. There is no

consensus on the surveillance schedule after RCC treatment, and there is no evidence that early versus later diagnosis of recurrences improves survival. The outcome after surgery for T1a low-grade tumours is almost always excellent [71]. It is therefore reasonable to stratify the follow-up, taking into account the risk of developing recurrence or metastases. This should include patients with a positive margin after PN since the risk of local recurrence is higher than in patients without positive margin.

An individualised, risk-based approach to RCC surveillance was recently proposed. The authors use competing risk models, incorporating patient age, pathological stage, relapse location, and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [72]. For patients with low-stage disease but with a Charlson comorbidity index of >2, the risk of non-RCC death exceeded that of abdominal recurrence risk already 1 mo after surgery, regardless of patient age [72]. The RECUR database reports similar results supporting a risk-based approach, but also shows that intense imaging, exceeding the frequency proposed by the EAU RCC Guideline Panel, does not improve patient survival

Table 5 – Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (expert opinion)

| Risk profile | Surveillance | | | | |
|-------------------|--------------|------|------|------|--|
| | 6 mo | 1 yr | 2 yr | 3 yr | >3 yr |
| Low | US | CT | US | CT | CT once every 2 yr; counsel about recurrence risk of 10% |
| Intermediate/high | CT | CT | CT | CT | CT once every 2 yr |

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

[73,74]. In the future, genetic profiling may refine the existing prognostic scores, and so far, external validation in datasets from adjuvant trials was promising. A proposed follow-up surveillance schedule following treatment for RCC is presented in Table 5.

4. Conclusions

The updated 2019 RCC guidelines provide the current evidence base for the management of RCC according to the most robust and reliable standards. A multidisciplinary panel prioritised the clinical questions for which evidence syntheses were performed based on SR methods. For other topics and questions, the guidelines were updated by way of a comprehensive, structured literature assessment based on new and relevant data. Guideline recommendations were developed and issued using transparent, robust, and reproducible methods based on a modified GRADE framework. It is the panel's ambition that by strengthening the methodological quality of evidence synthesis, the overall quality of the guidelines and the panel's recommendations will be improved further, which in turn will enhance its dissemination, uptake, and impact on patients, clinicians, and healthcare organisations.

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