European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update

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Abstract

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

Objective: To present a summary of the 2022 RCC guideline, which is based on a standardised methodology including systematic reviews (SRs) and provides transparent and reliable evidence for the management of RCC.

Evidence acquisition: For the 2022 update, a new literature search was carried out with a cutoff date of May 28, 2021, covering the Medline, EMBASE, and Cochrane databases. The data search focused on randomised controlled trials (RCTs) and retrospective or controlled comparator-arm studies, SRs, and meta-analyses. Evidence synthesis was conducted using modified GRADE criteria as outlined for all the EAU guidelines.

Evidence synthesis: All chapters of the RCC guideline were updated on the basis of a structured literature assessment, and clinical practice recommendations were developed. The majority of the studies included were retrospective with matched or unmatched cohorts and were based on single- or multi-institution data or national registries. The exception was systemic treatment of metastatic RCC, for which there

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are several large RCTs, resulting in recommendations that are based on higher levels of evidence.

**Conclusions:** The 2022 RCC guidelines have been updated by a multidisciplinary panel of experts using the highest methodological standards. These guidelines provide the most reliable contemporary evidence base for the management of RCC in 2022.

**Patient summary:** The European Association of Urology panel for guidelines on kidney cancer has thoroughly evaluated the research data available to establish up-to-date international standards for the care of patients with kidney cancer.

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1. Introduction

The European Association of Urology (EAU) guidelines on renal cell carcinoma (RCC) provide clinicians with evidence-based information and recommendations for the management of patients with RCC. The multidisciplinary EAU RCC panel includes urologists, medical oncologists, a pathologist, a radiologist, a methodologist, and a patient advocate. The EAU RCC guidelines were first published in 2000 and have been updated yearly since then [1]. For the 2022 update, a comprehensive and structured literature assessment was carried out, with several sections requiring a formal systematic review (SR) according to the availability of data. A detailed version of the current RCC guideline is available on the EAU website [2].

2. Evidence acquisition

Literature searches were conducted in the following databases: MEDLINE, MEDLINE In-Process, Embase, and Cochrane Libraries of Systematic Reviews (SRs) and Controlled Trials Register. In addition, a series of topics and questions were prioritised a priori for which formal, protocol-driven SRs were undertaken, as described elsewhere [3,4]. These were conducted in accordance with the PRISMA guidelines [2,5]. For each SR, elements for the inclusion and exclusion of patients, 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 assessment of nonrandomised studies. The SR protocols contain details of the review process and the search strategies used, and the reference lists of all studies included are published on the EAU website [2]. The search was conducted up to the end of May 2021. Two independent reviewers screened abstracts and full texts, carried out data abstraction, and assessed the risk of bias (RoB). Data were evaluated according to their level of scientific evidence in line with the 2009 Oxford Centre for Evidence-based Medicine levels of evidence (LE) [6]. Most 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), for which several practice-changing randomised controlled trials (RCTs) have been published, resulting in a higher LE. Once the LE for a particular topic or question had been determined, a guideline recommendation was developed using a transparent, reproducible, and reliable process following a modified GRADE framework [7]. This approach allows integration of the LE with other essential elements, including the certainty of the evidence, the magnitude of the effects, the balance between desirable and undesirable consequences, and patient values and preferences, to issue clinical recommendations [2,7,8]. In cases with heterogeneous opinions among panel members, formal consensus methods were used to arrive at the final recommendation. In particular, the section on follow-up was also revised on the basis of accumulating data from a large prospective registry set up by the panel.

3. Evidence synthesis

3.1. Epidemiology and aetiology

RCC represents approximately 3% of all cancers, with the highest incidence occurring in Western countries [9]. 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 for men over women, with peak RCC incidence at 60–70 yr of age [10]. RCC comprises different subtypes with specific histopathological and genetic characteristics [11]. During the past two decades there has been an annual increase of 2% in RCC incidence both worldwide and in Europe, with approximately 99 200 new RCC cases and 39 100 kidney cancer–related deaths in the EU in 2018 [9]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilising or declining thereafter [12].

RCC aetiology includes lifestyle factors such as smoking, obesity, and hypertension [13]. Having a first-degree relative with RCC is also associated with higher risk. Other factors include specific dietary habits, diabetes, and occupational exposure to specific carcinogens, but the literature is inconclusive [13]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [15]. Preventative measures include elimination of cigarette smoking and reducing obesity [13].

3.2. Diagnosis and staging

3.2.1. Symptoms

Many patients with RCC only present with symptomatic disease (bone pain, deterioration of performance status, or persistent cough) in advanced stages [16] (LE: 3). The
majority of RCCs are detected incidentally via noninvasive imaging for investigation of various nonspecific symptoms and other abdominal diseases. In a recent cohort study, 60% of patients overall, 87% of patients with T1a stage, and 36% of RCC patients with stage 3 or 4 disease were incidentally diagnosed [17]. The classic triad of flank pain, visible haematuria, and a palpable abdominal mass is rare today and generally correlates with aggressive disease [10] (LE: 3).

3.2.2. Imaging
Computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) are the imaging modalities used to detect and characterise renal masses (RMs) as solid or cystic [18]. For solid RMs, the most important criterion for malignant lesions is the presence of contrast enhancement or restriction [19] (LE: 3). Contrast-enhanced US can be helpful in specific cases [18] (LE: 3). Furthermore, CT and MRI cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (LE: 3). Positron emission tomography (PET) is increasingly being used in papillary RCC (pRCC), but PET is currently not a standard investigation in patients with clear-cell RCC (ccRCC) [20,21] (LE: 3). Chest CT is the most accurate investigation for diagnosing lung metastases or enlarged mediastinal lymph nodes (LN) (LE: 3) and is strongly recommended except in cT1a renal tumours, for which the probability of positive chest CT is low [22]. Since most bone and brain metastases are symptomatic at diagnosis, bone or brain imaging is performed if indicated, with the exception of patients with mRCC, for whom brain imaging is recommended [23] (LE: 3).

For renal cystic masses, the Bosniak classification (updated in 2019) distinguishes five categories on the basis of CT or MRI diagnostic criteria [24]. This classification can predict the risk of malignancy and provide guidance for management, especially for Bosniak III cysts [24,25] (LE: 3). Bosniak I, II, IIF, III, and IV cysts are malignant in approximately 0%, 0%, 10%, 50%, and 100% of surgically treated cases, respectively [25]. Cautious surveillance of Bosniak III cysts is a reasonable alternative to primary surgery, as surgery for Bosniak III cysts constitutes overtreatment in 49% of the cases because many of these lesions have low malignant potential [25].

3.2.3. Renal biopsy
Percutaneous tumour biopsies are increasingly used for histological diagnosis to avoid unnecessary surgery for benign lesions, to select patients for surveillance, and to obtain histology before ablative and primary systemic treatment [26] (LE: 3). Needle core biopsies are preferable for solid RMs rather than fine needle aspiration (LE: 2b). Core biopsies with a coaxial technique should be used to minimise the risk of seeding [27] (LE: 2b). Core biopsies of solid RMs have a diagnostic yield of 78–97% and high specificity (98–100%) and sensitivity (86–100%) for diagnosis of malignancy [26] (LE: 2b). If a biopsy is nondiagnostic, a second biopsy or surgical resection should be considered [27] (LE: 4). Core biopsies are not recommended for cystic RMs owing to their low diagnostic yield unless areas with a solid pattern are present (Bosniak IV cysts) [26] (LE: 2b).

3.2.4. Histological diagnosis
RCCs comprise a broad spectrum of histological entities described in the 2016 World Health Organization (WHO) classification [11]. There are three main RCC types: ccRCC (70–80%), pRCC (types I and II, 10-15%, of which 60–70% are type I), and chromophobe RCC (4–5%). There are differences in tumour stage and grade and cancer-specific survival (CSS) between the RCC subtypes, with an impact on prognosis. The four-tiered WHO/International Society of Urological Pathology grading system has replaced the Fuhrman scheme [11]. Sarcomatoid differentiation can be found in all RCC subtypes and denotes high-grade and very aggressive tumours.

Besides the common RCC subtypes described in the 2016 WHO classification [11], the remaining 10% include renal pelvis carcinoma and a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described, as well as a group of unclassified RCCs. Table 1 summarises the malignant potential of some of these rare renal tumours and lists recommendations for treatment. Additional details are provided in the full RCC guidelines [2].

3.3. Classification and prognostic factors

3.3.1. TNM classification system
The 2017 TNM classification is recommended for clinical and scientific staging. The prognostic value of the TNM classification has been validated in both single- and multi-institution 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. (radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior, location relative to polar lines) nephrometry score, among others, aim to standardise renal tumours and aid comparison of treatment strategies [29]. Histological factors include RCC subtype, tumour grade, sarcomatoid features, vascular invasion, tumour necrosis, invasion of the collecting system, and perirenal fat [28]. Comparing different RCC subtypes, pRCC type I has a significantly lower risk of death in comparison to ccRCC and pRCC type II in the nonmetastatic setting [30]. Postoperative prognostic nomograms to predict survival have been externally validated, but none has yet been fully validated [2,29] (LE: 3).

Numerous molecular markers including CAIX, PTEN, and CXCX4, as well as gene expression profiling, gene mutations, and methylisation status, have been investigated for treatment selection in mRCC, but none of these techniques has yet yielded profiles that improve the current prognostic systems [31].

It has been shown that expression levels of the BAP1 and PBRM1 genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, are independent predictive factors for tumour recurrence [32]. Results 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 [33].

Furthermore, data on chromosomal alterations from genome-wide association studies and analyses of miRNAs, single-nucleotide polymorphisms, and gene methylation all contribute to improve diagnostic and prognostic information. Several studies have confirmed prognostic information from 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 [34]. Prognostic information on cytokines and blockade of immune-inhibitory molecules such as PD-L1 have led to promising therapeutic results, but their use in RCC treatment has yet to be explored [35].

### 3.4. Treatment of RCC

#### 3.4.1. Treatment of localised RCC and local treatment of mRCC

The EAU RCC guideline recommendations for treatment of localised RCC are shown in Table 2.

#### 3.4.1.1. Surgical treatment

For localised RCC, surgery is still the only curative treatment. According to renal functional, oncological, and quality of life (QoL) outcomes, localised T1 RCCs are best managed with partial nephrectomy (PN) rather than radical nephrectomy (RN), irrespective of the surgical approach [2] (LE: 1b). Multiple retrospective series and one RCT including patients with organ-confined RCC have demonstrated comparable CSS for PN versus RN [36]. PN resulted in better preservation of general kidney function than RN did, thereby lowering the risk of developing metabolic or cardiovascular disorders [3,37]. Several retrospective studies comparing PN versus RN for RCCs <4 cm demonstrated an association of RN with higher rates of cardiovascular events and mortality from any cause after adjusting for patient characteristics [38]. In addition, studies addressing T1b RCC revealed no significant CSS differences between PN and RN [36,39,40]. One SR found that PN for clinically localised RCC was associated with lower overall survival (OS) in comparison to RN, whereas serious adverse event (AE) rates, CSS, and time to recurrence were similar for the two groups [3]. One trial reported on
radiofrequency ablation (RFA) versus RN or PN for T1a RCC, revealing similar CSS at 7 yr for each of the three treatments [38].

Irrespective of the data available, treatment decisions for frail patients should be individualised, weighing the risks and benefits of PN versus RN, the higher risk of perioperative complications, and the risk of developing or worsening chronic kidney disease postoperatively.

3.4.1.1. Techniques for RN. So far, no RCT has assessed the oncological outcomes of laparoscopic versus open RN. A cohort study and retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher-stage disease and locally advanced tumours [41,42]. No significant differences in CSS, progression-free survival (PFS), or OS were reported. One SR revealed less morbidity for laparoscopic than for open RN, with shorter hospital stays, less perioperative blood loss, and lower analgesic requirements for the laparoscopic RN group [36] (LE: 1b). Similar oncological outcomes were reported for retroperitoneal versus transperitoneal laparoscopic approaches in a large multi-institutional cohort [42]. There are no reliable comparative data on hand-assisted, robot-assisted, or laparoendoscopic single-site RN versus the conventional laparoscopic approach. There was no difference in complications, but operation time was significantly shorter for open RN and postoperative QoL scores were similar [3]. In a large SR and meta-analysis on robot-assisted versus laparoscopic RN versus open RN, robot-assisted RN did not have a higher risk of any or major complications, but had longer operating time and higher hospital costs in comparison to laparoscopic RN [43]. An SR and meta-analysis of seven studies (n = 1832 patients) confirmed that there were no differences between robot-assisted and laparoscopic RN in perioperative outcomes, including operative time, blood loss, conversion rates, and complications [44]. Similar results were seen in observational cohort studies comparing "portless" and three-port laparoscopic RN [45].

3.4.1.2. Techniques for PN. Whereas long-term oncological data are available for conventional laparoscopic PN, the 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 [46,47]. A study by Gill et al [45] suggests comparable oncological efficacy even for higher-stage tumours (pT1b/pT3a). The higher number of patients treated with open surgery might reflect a selection bias if robotic surgery is offered to cases with less complex anatomy. Robot-assisted RN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate, early, and short-term complications, variation in creatinine levels, and pathological margins were similar among the groups. A multicentre prospective database compared outcomes for 1800 patients who underwent open or robot-assisted PN. Although follow-up was short, lower morbidity with fewer overall complications, fewer major complications, fewer transfusions, and shorter hospital stays were observed in the robot-assisted PN group [48].

In a matched-pair comparison, the decline in estimated glomerular filtration rate was greater after laparoscopic
PN than after open PN in the immediate postoperative period [48], but not after follow-up of 3.6 yr. Retroperitoneal and transperitoneal laparoscopic PN were found to have similar perioperative outcomes. A prospective comparison of surgical outcomes after robotic or pure laparoscopic PN for moderate-to-complex renal tumours showed significantly lower estimated blood loss and shorter warm ischaemia time in the robotic group [49]. In conclusion, PN can be performed using either an open, pure laparoscopic, or robot-assisted approach according to the surgeon’s expertise and skills and the availability of equipment (LE: 2b).

3.4.1.1.3. Positive surgical margins after PN. A positive surgical margin occurs in approximately 2–8% of PN cases. 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 for patients with adverse pathological features, as in stage pT3a. In a large single-site cohort, 16% of patients with local tumour recurrence had positive surgical margins compared to 3% of patients without local recurrence [50]. Most retrospective analyses indicate that positive surgical margins do not translate into a higher risk of metastases or lower CSS, but in a retrospective analysis of a large National Cancer Data Base cohort, positive surgical margins were associated with a 31% increase in all-cause mortality (hazard ratio [HR] 1.31; p < 0.001), which persisted in a subanalysis of patients with a Charlson comorbidity index of 0 (HR 1.25; p < 0.001) [51]. Patients with positive surgical margins need not undergo an immediate reintervention since only a proportion of these patients will harbour residual malignancy, but more intense surveillance and a repeat resection strategy in the recurrence setting will be required.

3.4.1.1.4. Adrenalectomy. One consecutive nonrandomised study compared the outcomes of nephrectomy with or without ipsilateral adrenalectomy [52]. 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 for radiographic and intraoperative findings. Only 48 of 2065 patients underwent concurrent ipsilateral adrenalectomy, of which 42 cases were for benign lesions. In an SR there was no evidence of an oncological difference between RN with adrenalectomy and RN without adrenalectomy. A meta-analysis was not conducted because of diverse study designs and data heterogeneity [4].

3.4.1.1.5. LN dissection for clinically negative LNs (cN0). Clinical assessment of LN status is based on detection of LN enlargement, either via CT/MRI or the intraoperative palpability of enlarged nodes. Owing to the low quality of the evidence available and potentially biased results, an SR including 252 publications could not address oncological outcomes for patients undergoing concomitant LN dissection or ipsilateral adrenalectomy in comparison to patients undergoing RN alone for cT3–T4N0M0 RCC [4]. Among patients with clinically negative LNs (cN0), LN dissection was not significantly associated with a lower risk of distant metastases or with cancer-specific or all-cause mortality [53]. Depending on the clinicopathological group, grade, and tumour size, 5-yr survival for patients with LN metastases at primary diagnosis ranges from 13% to 43%. Patients with resected occult LN involvement (cN0/pN1 cM0) have the best prognosis and a considerable chance of long-term survival [53].

3.4.1.1.6. Management of RCC with venous thrombus. An SR that included 14 studies (n = 2262 patients) concluded that no surgical method was superior to another for excision of vena caval thrombus (VCT) [54]. Minimal access techniques appeared to have better perioperative and recovery outcomes over traditional median sternotomy, but the impact on oncological outcomes could not be assessed. Preoperative renal artery embolisation did not offer any oncological benefits and instead resulted in significantly worse perioperative and recovery outcomes, including possibly higher perioperative mortality. Comparison of groups with and without cardiopulmonary bypass showed no differences in oncological outcomes between these groups. Overall, there were high risks of bias and confounding [54].

The surgical method used depends on the upper level of the 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. Nevertheless, the findings support that surgical intervention should be considered for all patients with nonmetastatic disease and VCT, irrespective of the extent of tumour thrombus at presentation [55] (LE: 3). Performance status can significantly improve after VCT removal; therefore, deterioration in performance status due to thrombus should not be an exclusion criterion for surgery.

3.4.1.2. Therapeutic approaches as alternatives to surgery. 3.4.1.2.1. Embolisation. Before a routine RN, 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 [56] (LE: 3).

3.4.1.2.2. Surveillance. Elderly and comorbid patients with incidentally detected small RMs have relatively low RCC-specific mortality and significant competing-cause mortality [57]. Active surveillance is defined as initial monitoring of tumour size via serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for those who show clinical progression during follow-up. A renal biopsy is recommended before surveillance (LE: 3). In the largest series of active surveillance cases reported, the RM growth rate (mean 3 mm/yr) was slow in most cases and progression to mRCC was rare (1–2%) [57] (LE: 3). The serial imaging frequency in this study was CT, MRI, or US at 3 and 6 mo, then every 6 mo up to 3 yr, and annually thereafter (LE: 3).

3.4.1.2.3. Ablative therapies. The minimally invasive ablative approaches performed most often include percutaneous RFA, cryoablation, microwave ablation, stereotactic radiosurgery, laser ablation, and high-intensity focused US ablation. Indications for thermal ablation include a small
RM in elderly, comorbid patients considered unfit for surgery, those with a genetic predisposition to develop multiple tumours with recurrences after previous surgery, patients with bilateral tumours or a solitary kidney, and those at high risk of complete loss of renal function following PN. Larger tumours of >3–4 cm and those located at the hilum or near the proximal ureter should not be treated with ablative therapies. There are no RCTs comparing RFA or cryoablation with PN [58]. Owing to limitations in the studies available, an SR could not reliably compare outcomes between ablation and PN [59]. Low-quality studies suggest a higher local recurrence rate after thermal ablation than after PN (LE:3). The quality of the data available does not allow any definitive conclusions regarding morbidity and oncological outcomes for RFA and cryoablation [60] (LE: 3).

3.4.1.2.4. Adjuvant therapy. There is no evidence from phase 3 RCTs that adjuvant tyrosine kinase inhibitors (TKIs) offer an OS benefit, although the S-TRAC study showed a disease-free survival (DFS) benefit with sunitinib over placebo, but with a high rate of grade 3/4 toxicity [61] (LE: 1a). The EAU guidelines panel do not recommend adjuvant sunitinib despite positive DFS data in one of the adjuvant studies in the absence of OS benefit.

It has recently been shown that immune checkpoint inhibitors (ICIs) designed to restore and enhance immune activity have substantial efficacy in mRCC [62]. The clinical success of these drugs inspired several ongoing adjuvant studies based on ICIs, with results expected in the coming years. Keynote-564, the first ICI adjuvant trial, reported better DFS after 1 yr of pembrolizumab therapy versus placebo (HR 0.68, 95% confidence interval 0.53–0.87; \( p = 0.001 \)) [63]. The 2-yr OS rate was 97% for pembrolizumab and 94% for placebo, with grade 3–5 AEs occurring in 32% versus 18% of cases, respectively. QoL assessment showed similar QoL or symptom scores for the two groups. After GRADE assessment the panel issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk ccRCC until final OS results are available [61].

3.4.2. Surgical treatment of metastatic RCC

Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In the previous cytokine era, combined treatment with CN plus interferon-based immunotherapy versus interferon only showed greater survival for patients treated with CN [64]. By contrast, the CAR-MENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) study, which was closed prematurely, showed that sunitinib alone was not inferior to immediate CN followed by sunitinib for OS [65]. In an intent-to-treat (ITT) analysis, median OS was 13.9 mo for CN versus 18.4 mo for sunitinib alone. Of the patients in the sunitinib-only arm, 38 (17%) required secondary CN. In addition, the SURTIME (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer) study had poor accrual, was underpowered, and was terminated prematurely, but revealed that the sequencing for CN and sunitinib did not affect PFS; in the ITT population a strong OS benefit was shown in favour of deferred CN, with median OS of 32.4 mo versus 15.0 mo in the immediate CN arm [65]. On the basis of these studies, the panel recommends immediate systemic treatment in patients with M1 RCC with sunitinib or an equivalent TKI + immunotherapy-based combination (LE: 1b). A weak recommendation based on low-level evidence from both CAR-MENA and SURTIME supports deferred CN at 3 mo or later in patients who do not progress on vascular endothelial growth factor receptor (VEGFR)-TKI therapy (LE: 2b).

Neither CAR-MENA nor SURTIME answered the question regarding CN in patients with low-volume metastatic disease, good performance status, favourable and intermediate risk according to the Memorial Sloan Kettering Cancer Center (MSKCC) scheme, and patients who do not require immediate VEGFR-TKI treatment [66]. For these patients, immediate CN retains its role since observation until progression requiring systemic treatment can result in a substantial time to onset of VEGF-targeted therapy [67] (LE: 2b).

However, owing to a paradigm shift in first-line treatment for patients with intermediate- and poor-risk disease [62], the role of and sequencing for CN in the era of immunotherapy need to be reinvestigated. As patients with primary mRCC with the primary tumour in place were included in the pivotal ICI trials, the guideline panel recommends treating patients accordingly until a higher level of evidence is available.

3.4.3. Local therapy for metastases in RCC

An SR including retrospective nonrandomised comparative studies only with high RoB evaluated treatments for metastases [68,69]. Interventions assessed included metastasectomy, various radiotherapies, and no local treatment, with survival (OS, CSS, and PFS), local symptom control, and AE rates as the outcomes. Except for brain, and possibly bone, for which metastases are frequently treated with stereotactic radiotherapy, metastasectomy remained an appropriate local treatment for most metastatic sites by default. Results consistently point to a benefit from margin-free metastasectomy in mRCC in terms of OS, CSS, and delay of systemic therapy. Radiotherapy, especially stereotactic radiotherapy, to bone and brain metastases from RCC can provide significant relief from local symptoms [69] (all LE: 3). Results from TKI studies suggest that patients with oligometastatic disease recurrence can be observed for up to a median of 15 mo until initiation of systemic therapy, and this practice is common in real-world settings [67]. A careful reassessment of disease status to rule out rapid progression is judged important.

3.5. Systemic therapy for mRCC

3.5.1. Targeted therapies

With the introduction of targeting agents in 2006, disease stabilisation or regression and prolonged survival have been achieved in patients with mRCC. Several targeting drugs were approved for the treatment of mRCC, including TKIs,
mechanistic target of rapamycin (TOR) inhibitors, and a VEGF antibody (bevacizumab). A detailed description of the targeting agents can be found in the full RCC guidelines (https://uroweb.org/guideline/renal-cell-carcinoma/) [2]. After the introduction of ICIIs, the recommendations for first-line and later-line TKIs have changed substantially [2,62].

The International Metastatic RCC Database Consortium (IMDC) established and validated a risk model to aid in accurate prognosis for 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 [70].

3.5.2 Immunotherapy
The backbone for treatment-naïve metastatic ccRCC has changed to ICIs targeting PD-1, complemented by a TKI or a second ICI directed against CTLA-4. At present, six phase 3 RCTs on ICI combinations have shown superiority against sunitinib, a previous standard of care [62].

Results showed that ICI combinations are associated with a higher proportion of patients achieving durable remissions. These findings resulted in an updated recommendation for systemic treatment of mRCC [2], as shown in Figures 1 and 2.

Treatment choice in second- and third-line settings after ICI combinations and subsequent VEGF-targeted therapy is currently unknown. Most of the regimens explored were tested after sequential use of TKIs and single-agent PD-1 inhibition. The panel recommends a subsequent agent that is approved in the VEGF-refractory disease setting, except for rechallenge with immune checkpoint blockade as monotherapy [2,62]. The panel awaits for randomised data for second and subsequent treatment lines.

3.5.3 Non–clear-cell mRCC
No phase 3 RCTs of patients with non–clear-cell mRCC have been performed. Only a few trials on systemic treatment that included patients with non–clear-cell mRCC have been reported and showed only modest efficacy in comparison to ccRCC [71]. A randomised phase 2 trial comparing everolimus to sunitinib suggested superior efficacy of sunitinib in terms of PFS [72]. A recent randomised phase 2 trial (PAP-MET) compared sunitinib to cabozantinib, crizotinib, and
savolitinib in 152 patients with papillary mRCC [73]. PFS was significantly longer for cabozantinib than for sunitinib and the other drugs studied; the HR for progression or death was 0.60 (95% confidence interval 0.37–0.97; one-sided p = 0.019). The response rate was 23% for cabozantinib versus 4% for sunitinib (p = 0.010). These results add cabozantinib as an option for patients with papillary mRCC on the basis of superior PFS in comparison to sunitinib. Patients with non–clear-cell mRCC should be referred to a clinical trial where appropriate, and further data are still required for ICI-based combinations.

### 3.6 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 the development of metastases. Although there is no evidence from randomised trials, large studies have examined prognostic factors with long follow-up [74,75] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol in comparison to patients who were not [69]. Patients undergoing follow-up seem to have longer OS when compared to patients not undergoing routine follow-up [76]. 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 mostly excellent. It is therefore reasonable to stratify follow-up according to the risk of developing recurrence or metastases. This should include patients with a positive margin after PN since their risk of local recurrence is higher than for patients without a positive margin. The type of surgery performed and histological RCC type also affect the risk of recurrent disease [77].

An individualised, risk-based approach to RCC surveillance was recently proposed. The authors used 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.

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 guidelines panel, seems not to improve patient survival [78]. In the future, genetic profiling may refine the existing prognostic scores, and external validation in data sets from adjuvant trials so far has been promising. A follow-up surveillance schedule following treatment for RCC is proposed in Table 3.

### 4. Conclusions

The updated 2022 EAU RCC guideline provides 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 using SR methods. For other topics and questions, the guideline was updated by way of a comprehensive, structured literature assessment of new and relevant data. Guideline recommendations were developed and issued using transparent, robust, and reproducible methods according to a modified GRADE framework. The panel believes that by strengthening the methodological quality of evidence synthesis, the overall quality of the guideline and its recommendations will be further improved, which in turn will enhance its dissemination and impact on patients, clinicians, and health care organisations.

**Author contributions:** Börje Ljungberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Ljungberg, Bex.

**Acquisition of data:** Ljungberg, Bex, Albiges, Bedke, Capitanio, Hora, Klatte, Marconi, Powles, Volpe, Giles, Abu-Ghanem, Dabestani, Fernández-Pello, Hofmann, Kuusk, Tahbaz.

**Analysis and interpretation of data:** Ljungberg, Bex, Albiges, Bedke, Capitanio, Hora, Klatte, Marconi, Powles, Volpe, Giles, Abu-Ghanem, Dabestani, Fernández-Pello, Hofmann, Kuusk, Tahbaz.

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**Analysis and interpretation of data:** Ljungberg, Bex, Albiges, Bedke, Capitanio, Hora, Klatte, Marconi, Powles, Volpe, Giles, Abu-Ghanem, Dabestani, Fernández-Pello, Hofmann, Kuusk, Tahbaz.

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Table 3 – Proposed surveillance schedule following treatment for RCC, considering the patient’s risk profile and treatment efficacy (expert opinion)

<table>
<thead>
<tr>
<th>Risk of recurrence</th>
<th>Surveillance schedule</th>
</tr>
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<tbody>
<tr>
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<td>3 mo</td>
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<tr>
<td>Low</td>
<td>CT</td>
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<tr>
<td>Intermediate</td>
<td>CT</td>
</tr>
<tr>
<td>High</td>
<td>CT</td>
</tr>
</tbody>
</table>

CT = computed tomography of chest and abdomen (alternatively, use magnetic resonance imaging for the abdomen); RCC = renal cell carcinoma.

* Leibovich score 0–2 = low risk, 3–5 = intermediate risk, >6 = high risk. For non–clear cell RCC: pT1NX–0 grade 1–2 is low risk; pT1b grade 3–4 is intermediate risk; and pT2–4 grade 1–4, or any pT of grade 1–4 with N1 is high risk.

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References


