Guidelines

EAU Guidelines on Renal Cell Carcinoma: 2014 Update

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Article info

Abstract

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

Objectives: To provide an update of the 2010 RCC guideline based on a standardised methodology that is robust, transparent, reproducible, and reliable.

Evidence acquisition: For the 2014 update, the panel prioritised the following topics: percutaneous biopsy of renal masses, treatment of localised RCC (including surgical and nonsurgical management), lymph node dissection, management of venous thrombus, systemic therapy, and local treatment of metastases, for which evidence synthesis was undertaken based on systematic reviews adhering to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Relevant databases (Medline, Cochrane Library, trial registries, conference proceedings) were searched (January 2000 to November 2013) including randomised controlled trials (RCTs) and retrospective or controlled studies with a comparator arm. Risk of bias (RoB) assessment and qualitative and quantitative synthesis of the evidence were performed. The remaining sections of the document were updated following a structured literature assessment.

Evidence synthesis: All chapters of the RCC guideline were updated. For the various systematic reviews, the search identified a total of 10 862 articles. A total of 151 studies reporting on 78 792 patients were eligible for inclusion; where applicable, data from RCTs were included and meta-analyses were performed. For RCTs, there was low RoB across studies; however, clinical and methodological heterogeneity prevented data pooling for most studies. The majority of studies included were retrospective with matched or unmatched cohorts based on single or multi-institutional data or national registries. The exception was for systemic treatment of metastatic RCC, in which several RCTs have been performed, resulting in recommendations based on higher levels of evidence.

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Conclusions: The 2014 guideline has been updated by a multidisciplinary panel using the highest methodological standards, and provides the best and most reliable contemporary evidence base for RCC management.

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

1.　Introduction

The European Association of Urology (EAU) Renal Cell Carcinoma (RCC) Guideline Panel has compiled these clinical guidelines to 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 particular expertise in this field. To meet the requirements for a multidisciplinary approach, the panel has recently been reinforced by several experts, including a medical oncologist, pathologists, radiologists, a methodologist, biostatisticians, and members of patient advocacy groups. The EAU RCC guidelines were first published in 2000 [1], with a subsequent full update in 2006 and partial updates in 2007, 2008, 2009, 2010 [2], and 2013. The current 2014 document presents a full-text update and is fundamentally different from the versions published previously. The panel adopted Cochrane methodology and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [3] in undertaking systematic reviews (SRs) in 2011 to ensure that the evidence synthesis was performed in a robust, standardised, transparent, and reproducible manner. For the 2014 update, the panel has proceeded with the SR work in a stepwise fashion. The majority of sections have been updated based on SRs; however, a few sections of the document have been updated following a structured literature assessment, as shown in Table 1. As a result, the previous guideline has been completely revised and supplemented with a section on management of venous tumour thrombus. A detailed version of the current guideline including full references, level of evidence, and grade of recommendations is available at www.uroweb.org [4]. The focus for the next 2 yr is for the complete guidelines document to be based on SRs for evidence synthesis, as SRs represent the highest possible level of data work-up.

2.　Evidence acquisition

All chapters of the 2014 RCC Guidelines publication have been updated. As mentioned in Table 1, the consistency of the data work-up differed between sections. For the parts of the guideline that have been updated by SR, the review methodology is outlined in detail in several ensuing publications [5,6]. In brief, SRs of the literature were conducted in accordance with PRISMA guidelines [3]. Important topics and questions were prioritised by the panel for the present update. 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 to achieve consensus. Where relevant, confounding variables were identified for each question to facilitate the assessment of nonrandomised studies. Individual literature searches were conducted separately for each update question using the following databases: Medline, Medline In-Process, Embase, Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013), and the Latin American and Caribbean Center on Health Sciences Information (LILACS). In addition, SRs and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013). The SR protocols containing details of the review process and search strategies used have been published on www.uroweb.org [7]. In addition, the reference lists of all the studies included were scanned to identify additional potentially relevant studies, and reports identified by the panel served as an additional source for

Table 1 – Description of the update and summary of the review methodology for 2014

Chapter	Description of review methodology
1. Introduction	Not applicable
2. Epidemiology and aetiology	Updated using a structured data assessment
3. Diagnosis and staging	Updated using a systematic review on tumour biopsy and a traditional narrative review for the other aspects of diagnosis and staging
4. Classification and prognostic factors	Updated using a structured data assessment
5. Other renal tumours	Updated using a traditional narrative review, based on a structured literature search; of particular note is the inclusion of the new Vancouver Classification in the Histology section
6. Treatment of localised disease	Updated using systematic reviews for management of small renal masses, lymph node dissection, and local treatment of metastases A new section, Management of RCC with venous thrombus, has been added that is based on a systematic review
7. Systemic therapy for metastatic disease	Updated using a systematic review
8. Surveillance following radical or partial nephrectomy or ablative therapies	Updated based on a traditional narrative review, based on a structured data search

studies. In most instances the search was conducted up to the end of November 2013. Two independent reviewers screened abstracts and full texts, carried out data abstraction, and assessed the risk of bias (RoB). The results were presented in tables showing baseline characteristics and summaries of findings. Meta-analyses were performed only for randomised controlled trials (RCTs) if consistency and homogeneity of data were demonstrated. When this was not possible, a narrative synthesis of the evidence was provided. The remaining parts of the guideline have been updated using a traditional narrative review strategy.

References were assessed according to their level of scientific evidence (LE), and guideline recommendations were graded according to the 2009 Oxford Centre for Evidence-based Medicine Levels of Evidence (http://www.cebm.net/index.aspx?o=1025).

3. Evidence synthesis

The majority of the studies included in this guideline update are retrospective analyses that include some larger multi-centre studies and well-designed controlled studies. As only a few RCTs are available, most of the data are not based on high levels of evidence. The exception was for systemic treatment of metastatic RCC (mRCC), for which several RCTs have been performed, resulting in recommendations based on higher levels of evidence.

3.1. Epidemiology and aetiology

RCC represents 2–3% of all cancers, with the highest incidence occurring in Western countries. In general, during the last two decades there has been an annual increase of approximately 2% in incidence both worldwide and in Europe until recently, with approximately 84 400 new RCC cases and 34 700 kidney cancer-related deaths within the European Union in 2012 [8]. In Europe, overall mortality rates for RCC increased up until the early 1990s, with rates generally stabilising or declining thereafter [9]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend. with increasing rates [9]. RCC is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics [10]. There is a 1.5:1 predominance in men over women, with peak incidence occurring between 60 and 70 yr of age. Aetiological factors include lifestyle variables such as smoking, obesity, and hypertension [11]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. A number of other factors have been suggested as being associated with higher or lower risk of RCC, but have not been confirmed. These include specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [12]. Moderate alcohol consumption appears to have a protective effect

for reasons not yet known [13]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity. Currently, more than 50% of RCCs are detected incidentally when abdominal ultrasound (US) or computed tomography (CT) is carried out for other medical reasons (LE 3). This has led to an increase in the incidence of small renal masses (RMs), defined as contrast-enhancing masses with a greatest dimension of 4 cm or less on abdominal imaging [14].

3.2. Diagnosis and staging

3.2.1. Symptoms
Many patients with RMs remain asymptomatic until the late stages of the disease. It has been reported that the prevalence of the classic triad of flank pain, gross haematuria, and a palpable abdominal mass in some parts of the world is lower than previously observed (now 6–10%) and correlates with advanced disease and subtypes associated with poor prognosis (LE 3) [15]. 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].

3.2.2. Imaging
The traditional approaches for detecting and characterising RMs are US, CT, and magnetic resonance imaging (MRI; Table 2). RMs can be classified as solid or cystic on the basis of the imaging findings. For solid RMs, the most important criterion for differentiating malignant lesions is the presence of contrast enhancement or restriction on MRI (LE 3) [17]. Most RMs can be diagnosed accurately using imaging alone. Contrast-enhanced US can be helpful in specific cases (eg, chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis) (LE 3) [18]. However, CT and MRI features cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms (LE 3) [19,20]. Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored in RM assessment [21]. Positron emission tomography (PET) is not currently a standard investigation (LE 3) [22]. In patients with RCC, chest CT is the most accurate investigation to diagnose lung metastases or enlarged mediastinal lymph nodes (LE 3) [23]. Since most bone and brain metastases mostly are symptomatic at diagnosis routine bone or brain imaging is only performed on indication (LE 3) [24]. In the case of a renal cystic mass, the Bosniak classification distinguishes five categories according to CT presentation. Bosniak classification can predict the risk of malignancy (LE 3) and provide guidance for management [25]. Bosniak 1, 2, 2F, 3, and 4 cysts are malignant in 0%, 0%, 25%, 54%, and 100% of cases, respectively [26].

Table 2 – Key recommendations on diagnosis, staging, classification, and prognosis in patients with renal tumours

Recommendation	GR
Contrast-enhanced multiphase abdominal CT and MRI are recommended for work-up of patients with RCC and are considered equal for both staging and diagnosis	B
Contrast-enhanced multiphase abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterisation and staging before surgery	C
A chest CT is recommended for staging assessment of the lungs and mediastinum	C
A bone scan is not routinely recommended	C
A renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology	C
A percutaneous biopsy is recommended in patients in whom active surveillance is pursued	C
A percutaneous renal tumour biopsy should be obtained with a coaxial technique	C
Use of the current TNM classification system is recommended.	B
Grading systems and classification of RCC subtype should be used	B
Prognostic risk models should be used in the metastatic setting	B

CT = computed tomography; GR = grade of recommendation; MRI = magnetic resonance imaging: RCC = renal cell carcinoma.

3.2.3. Renal biopsy

Percutaneous renal tumour biopsies are increasingly being used (1) for histological diagnosis of radiologically indeterminate RMs to avoid surgery in the event of benign lesions; (2) to select patients with small RMs for surveillance approaches; (3) to obtain histology before ablative treatments; and (4) to select the most suitable medical and surgical treatment strategy in the setting of mRCC (LE 3) [27–29]. Needle core biopsies are preferable for solid RMs in comparison with fine needle aspiration (LE 2b). Core biopsies should be performed with 18G needles and a coaxial technique to minimise the risk of complications and seeding (LE 2b) [28,30,31]. Either a US- or CT-guided approach can be used according to tumour and patient characteristics (LE 2b) [28,30]. At least two quality cores (nonfragmented, >10 mm in length) should be obtained, and necrotic areas should be avoided to maximise diagnostic accuracy (LE 4) [30,32]. Peripheral biopsies are preferable for larger tumours to avoid the central necrosis (LE 2b) [33]. Core biopsies of solid RMs have shown a diagnostic yield of 78–97%, with high specificity (98–100%) and high sensitivity (86–100%) for the diagnosis of malignancy (LE 2b) [34]. However, it has been reported that core biopsies are nondiagnostic in 2.5–22.0% of cases (LE 2b) [34]. If a biopsy is nondiagnostic but there are radiological findings suspicious for malignancy, a further biopsy or surgical exploration should always be considered (LE 4). Owing to the high diagnostic accuracy of current imaging, a biopsy is not necessary in the setting of localised or locally advanced disease before surgical treatment in fit patients with a long life expectancy and a highly suspicious, contrast-enhancing RM on CT or MRI (LE 4). Core biopsies should not be recommended for cystic RMs, unless areas with a solid pattern are present (Bosniak 4 cysts; LE 2b) [28,30].

3.2.4. Histological diagnosis

Renal neoplasms comprise a broad spectrum of histopathological entities described in the 2004 WHO classification and modified by the International Society of Urological Pathology (ISUP) Vancouver Classification (Section 3.4) [35]. From a clinical viewpoint, three main RCC subtypes are important: 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 (chRCC; 4–5%). There are differences in tumour stage, grade, and cancer-specific survival (CSS) between RCC subtypes, and they have an impact on prognosis (Section 3.3). The 5-yr overall survival (OS) for all RCC subtypes is 49%, which has further improved since 2006, probably because of an increase in incidentally detected RCCs and the introduction of targeted therapies [36]. Sarcomatoid differentiation can be found in all RCC subtypes and is equivalent to high-grade and very aggressive tumours (Section 3.4). Collecting duct carcinoma and other infrequent renal tumours are discussed in Section 3.4 (Table 3).

3.3. Classification and prognostic factors

3.3.1. TNM stage classification

The latest version of the TNM classification was published in 2010 and should be used for clinical and scientific staging purposes. The prognostic value of the 2010 TNM classification has been validated in both single- and multiinstitutional studies [37]. However, the subclassification of T1 tumours using a cutoff of 4 cm might not be optimal with the widening indication for nephron-sparing surgery for localised RCC. In addition, the value of size stratification of T2 tumours has been questioned [38]. In comparison to the 2009 version, there is no longer any distinction between N1 metastasis in a single regional lymph node and N2 metastases in more than one regional lymph node. Instead, N1 comprises metastasis in regional lymph node(s) [37].

3.3.2. Prognostic factors

Prognosis is influenced by anatomical, histological, clinical, and molecular factors. Anatomical factors are reflected in the TNM classification and provide the most reliable prognostic information. In addition, objective anatomical classification systems such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the RENAL nephrometry score, and the C-index have been proposed to standardise the description of renal tumours and aid in comparing nephron-sparing treatment strategies [39–41]. Histological factors include nuclear grade, RCC subtype, sarcomatoid features, microvascular

Table 3 – Summary of other renal tumours with an indication of malignant potential and recommendation for treatment (all grade C)

Entity	Malignant potential	Treatment of localised tumour
Sarcomatoid variants of RCC	High	Surgery
Multilocular clear cell RCC	Low, no metastasis	Surgery, NSS
Carcinoma of the collecting ducts of Bellini	High, very aggressive	Surgery, discussable for M+ tumours
Renal medullary carcinoma	High, very aggressive	Surgery
Translocation RCC Xp11.2	High	Surgery
Translocation RCC t(6;11)	Low	Surgery, NSS
Tubulocystic RCC	Low	Surgery, NSS
Mucinous tubular and spindle cell carcinoma	Intermediate	Surgery, NSS
Acquired cystic disease-associated RCC	Low	Surgery
Clear cell (tubulo) papillary RCC	Low	Surgery, NSS
Hybrid oncocytic chromophobe tumour	Low	Surgery, NSS
Metanephric tumours	Benign	Surgery, NSS
Cystic nephroma/mixed epithelial and stromal tumour	Low/benign	Surgery, NSS
Oncocytoma	Benign	Observation (when histologically confirmed)/surgery, NSS
Hereditary kidney tumours	High	Surgery, NSS
Angiomyolipoma	Benign	Consider treatment only in very well-selected patients
Unclassified RCC	Variable	Surgery, NSS

NSS = nephron-sparing surgery; RCC = renal cell carcinoma.

invasion, tumour necrosis, and invasion of the collecting system. Although affected by intra- and interobserver discrepancies, grade remains an independent prognostic factor [42]. At the ISUP conference, a simplified nuclear grading system, based only on the size and shape of nucleoli, was proposed to replace the Fuhrman grading system [35]. Regarding RCC subtypes, there is a trend in univariate analysis towards better prognosis for patients with chRCC versus pRCC (with pRCC type II worse than ccRCC) versus ccRCC [43]. However, the prognostic information provided by RCC subtype is lost when stratified to tumour stage (LE 3) [43]. For localised RCC, several risk scores and nomograms can be used, including the Stage, Size, Grade, and Necrosis Score (SSIGN) [44], a modified version of the SSIGN score (Leibovich score) [45], the University of California Los Angeles Integrated Staging System (UISS) [46], and Karakiewicz's nomogram (LE 3) [47]; Section 3.7 provides further details. Clinical factors include patient PS, localised symptoms, cachexia, anaemia, elevated neutrophil and platelet counts, and other laboratory parameters, and are predominantly used in prognostic risk models in mRCC (LE 3) [48,49]. Numerous molecular markers including gene expression profiling and deep and whole-genome–wide sequencing have been investigated, but none of these techniques has yet yielded markers or profiles that improve the predictive accuracy of current prognostic systems. Their use is therefore not recommended in routine practice. There is hope that molecular techniques will augment the current pre- and postoperative prognostic nomograms and the risk scores for mRCC, which have C-indices of 0.63–0.84 and have reached a plateau in accuracy based on histological and clinical factors [49].

3.4. Other renal tumours

A revised histopathological classification was published in 2013 as the ISUP Vancouver classification of renal neoplasia [35]. This classification will probably constitute the basis of the new WHO classification to replace the 2004 version.

The common RCC subtypes (Section 3.2.4.) account for 85–90% of renal malignancies. The remaining 10–15% of renal tumours include renal pelvis carcinoma and a variety of uncommon, sporadic, and familial carcinomas, some of which have recently been described, and a group of unclassified carcinomas. For these generally rare renal tumours, Table 3 summarises their malignant potential and universal grade C recommendations for treatment, if localised. Extensive details are provided in the full guidelines [4].

3.5. Treatment of localised RCC and local treatment of mRCC

Six SRs underpin the recommendations of this section (Supplementary Table 1) [7]. These reviews included all relevant published literature comparing surgical management of localised RCC (T1–2N0M0) [50,51], different strategies for small RMs, lymphadenectomy and adrenalectomy [6], caval venous thrombus, and local therapy of metastases from RCC. Owing to the very limited number of RCTs, nonrandomised studies (NRSs), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Studies with no comparator group (eg, case series), unmatched retrospective studies, and chart reviews were excluded because of their inherent RoB.

3.5.1. Surgical treatment

For localised RCC, surgery is the only curative treatment with high-quality evidence. According to oncological and quality-of-life outcomes, localised T1a–b tumours are best managed by partial nephrectomy (PN) rather than radical nephrectomy (RN), if technically feasible, irrespective of the surgical approach (LE 1b; Table 4). A prospective RCT compared RN with PN in solitary T1a–b N0M0 renal tumours <5 cm with normal contralateral kidney function and WHO PS 0–2. At 9.3-yr follow-up, 198 patients (72.5%) were alive after RN and 173 (64.4%) after PN, with CSS of 98.5% and 97%, respectively. Local recurrence occurred in

Table 4 – Key recommendations for treatment of localised RCC and local treatment of metastatic RCC

Recommendation	GR
Nephron-sparing surgery is recommended in patients with T1a tumours	A
Nephron-sparing surgery should be favoured over radical nephrectomy in patients with T1b tumours when technically feasible	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland	B
Lymph node dissection is not recommended for localised tumours without clinical evidence of lymph node invasion	A
In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control	C
Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localised renal masses not treatable by nephron-sparing surgery	B
Owing to the low quality of the available data, no recommendation can be made on radiofrequency ablation or cryoablation	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation, and cryoablation can be offered	C
Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC	C
Bosniak cysts greater than type III should be regarded as RCC and be treated accordingly	C

GR = grade of recommendation; RCC = renal cell carcinoma.

one patient in the RN group and six patients in the PN group [52]. Many retrospective studies compared PN to RN (open or laparoscopic) for RCC <4 cm [4,50,53] and demonstrated an association between RN and 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 observed between PN and RN [50]. No prospective comparative studies were identified reporting on oncological outcomes for minimally invasive ablative procedures compared with RN. One trial reported on radiofrequency ablation (RFA) versus RN or PN for T1a RCC; CSS of 100% was observed for each of the three treatment modalities [50]. If PN is not feasible, the curative therapy remains RN, which includes removal of the tumour-bearing kidney. Complete resection of the primary tumour with PN or RN performed via either open or laparoscopic surgery offers a reasonable chance of cure. Ipsilateral adrenalectomy during RN or PN does not provide a survival advantage (LE 3). In patients with localised disease and no clinical evidence of lymph node metastases, there is no proof of any survival advantage of lymph node dissection (LE 1b). In patients with localised disease and clinically enlarged lymph nodes, the survival benefit of lymph node dissection is not demonstrated. However, such dissection can be performed for staging purposes (LE 3).

3.5.2. RN techniques

There are no RCTs assessing oncological outcomes of laparoscopic RN versus open RN. A prospective cohort study and several retrospective database reviews are available, mostly of low methodological quality. These studies showed similar oncological outcomes for laparoscopic versus open RN, but a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic compared with the open group [50,51]. On the basis of these data, laparoscopic RN has lower morbidity compared to open surgery (LE 1b). Similar oncological outcomes were reported for both retroperitoneal and transperitoneal approaches in two RCTs and one quasi-randomised study [54]. No reliable comparative data exist with regard to hand-assisted, robotic, and laparoendoscopic single-site nephrectomy versus the conventional laparoscopic approach.

3.5.3. PN techniques

Studies comparing laparoscopic PN and open PN found no difference in progression-free survival (PFS) or OS between the techniques in centres with laparoscopic expertise [55–57]. The mean estimated blood loss was generally lower with the laparoscopic approach, but warm ischaemia time (WIT) was prolonged [56]. In a matched-pair comparison, the decline in glomerular filtration rate was greater in the laparoscopic PN group in the immediate postoperative period [55], but not after a follow-up of 3.6 yr. Retroperitoneal and transperitoneal laparoscopic PN yielded similar perioperative outcomes. In a large, retrospective, multicentre comparative study, simple tumour enucleation had similar PFS and CSS rates to standard PN and RN [58]. At present, no study has compared the oncological outcomes of robot-assisted versus laparoscopic PN. 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 shorter WIT in the robotic group [59]. Meta-analyses of relatively small series found comparable perioperative outcomes and shorter WIT for robot-assisted PN [60]. In conclusion, PN can be performed, either with an open, pure laparoscopic, or robot-assisted approach, according to the surgeon's expertise and skills and equipment availability (LE 2b).

3.5.4. Management of RCC with venous thrombus

An RCC tumour thrombus in the inferior vena cava (IVC) is a significant adverse prognostic factor (Section 3.3.1.). Traditionally, patients with venous tumour thrombus (VTT) usually undergo RN and thrombectomy. Aggressive surgical resection is widely accepted as the default management for VTT [61]. However, uncertainties remain regarding the surgical treatment, especially in terms of comparative effectiveness and harms. There is variation in how the surgery is undertaken in terms of preoperative strategies (eg, use of IVC filter or preoperative embolisation), the surgical approach for IVC access, and bypass procedures to achieve vascular control (eg, venovenous bypass or cardiopulmonary bypass and deep hypothermic circulatory arrest). To determine the evidence base for these different strategies, an SR of the literature was undertaken, including

comparative studies only reporting on management of VTT in non-mRCC (nmRCC; Supplementary Table 1) [7]. Only five retrospective studies [4] were eligible for inclusion, all with significant RoB, none of which addressed the question of whether patients with nmRCC and VTT derive a benefit from surgery to remove the thrombus, and how thrombectomy influences prognosis from an oncological perspective. Nevertheless, the findings support the notion that all patients with nmRCC and VTT should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation (LE 3). PS can significantly improve after removal; therefore, deterioration of PS due to thrombus should not be an exclusion criterion for surgery, There is no distinct surgical method that seems superior for VTT excision, although the surgical method appears to depend on the VTT level and the grade of occlusion of the IVC. For adequate removal of the thrombus, caval vein control is key, which may require liver mobilisation and cardiac bypass. Preoperative embolisation does not seem to have any clinical value. The relative benefits and harms of other strategies and approaches regarding IVC access and the role of IVC filters and bypass procedures remain uncertain.

3.5.5. Therapeutic approaches as alternatives to surgery

3.5.5.1. Embolisation. Before a routine nephrectomy, there is no benefit in performing tumour embolisation [62]. In patients unfit for surgery and suffering from massive haematuria or flank pain, embolisation can be a beneficial palliative intervention (LE 3).

3.5.5.2. Surveillance. Elderly and comorbid patients with incidentally detected small RMs have relatively low RCC-specific mortality and significant competing-cause mortality [63]. Active surveillance can be offered to this category of patients and is defined as initial monitoring of tumour size via serial abdominal imaging (US, CT, or MRI), with delayed intervention reserved for tumours that show clinical progression during follow-up. As mentioned, a renal biopsy is recommended before inclusion of patients in surveillance approaches (LE 3). In the largest reported active surveillance series, RM growth was low (average 0.13 cm/yr) in most cases and progression to mRCC was rare (1–2%; LE 3) [63]. The frequency of serial imaging in this study consisted of CT, MRI, or US at 3 and 6 mo, then every 6 mo until 3 yr, and then annually (LE 3).

3.5.5.3. Ablative therapies. The most commonly performed minimally invasive approaches besides surgery include percutaneous RFA, laparoscopically assisted or percutaneous cryoablation (CA), microwave ablation, stereotactic radiosurgery, laser ablation, and high-intensity focused US ablation. With the exception of RFA and CA, most approaches are experimental. Indications for thermal ablation include small RMs in elderly comorbid patients considered unfit for surgery, those 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. 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 (LE3) [64].

3.5.6. Adjuvant therapy

Several phase 3 RCTs of adjuvant sunitinib, sorafenib, pazopanib, axitinib, and everolimus are ongoing. Until results from these studies are reported, there is no evidence to support the use of adjuvant therapy after RCC surgery. Prior RCTs with cytokines, chemotherapy, or vaccines were largely negative [65].

3.5.7. Surgical treatment of mRCC (cytoreductive nephrectomy)

RCC surgery is curative only if all the tumour burden can be removed. Retrospective data suggest that this goal is achievable in patients with single- or oligometastatic disease that is amenable to surgery. For most patients with mRCC, cytoreductive nephrectomy (CN) is palliative and systemic treatment is necessary. In a meta-analysis of two RCTs comparing CN plus immunotherapy versus immunotherapy alone, there was a significant increase in long-term survival in patients treated with CN [66]. At present, only retrospective data are available for comparison of CN combined with targeted agents to systemic therapy alone; these data suggest that patients with good PS or risk scores may benefit from surgery [67]. Results for the randomised phase 3 CARMENA and EORTC SURTIME studies are awaited. CN is currently recommended in mRCC patients with good PS, large primary tumours, and low metastatic volume. In patients with poor PS or International mRCC Database Consortium (IMDC) risk, those with small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended.

3.5.8. Local therapy of metastases in RCC

An SR was undertaken of all types of comparative study on local treatment of metastases from RCC in any organ (Supplementary Table 1) [68]. Relevant interventions included metastasectomy, various radiotherapy modalities, and no local treatment [7]. The outcomes were survival (OS, CSS, and PFS), local symptom control, and adverse events. All studies included were retrospective, nonrandomised, comparative studies, resulting in high RoB associated with nonrandomisation, attrition, and selective reporting [68]. With the exception of brain and possibly bone metastases frequently treated by stereotactic radiotherapy, metastasectomy remains 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, for bone and brain metastases from RCC can induce significant relief from local symptoms (all LE 3).

3.6. Systemic therapy for mRCC

An SR was undertaken to analyse evidence for first and subsequent lines of treatment, combinations, and RCC subtypes (Supplementary Table 1) [5,7].

3.6.1. Clear-cell mRCC

In patients with clear-cell (cc)-mRCC, chemotherapy is not effective. Recent advances in molecular biology have led to the development of several novel agents for treating mRCC (Table 5). As a consequence, monotherapy with interferon (IFN)-α or high-dose bolus interleukin (IL)-2 should no longer be routinely recommended as first-line therapy in mRCC, except in certain circumstances (eg, lung metastasis, cc-mRCC, long interval). In sporadic cc-mRCC, hypoxia-inducible factor (HIF) accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which promote neoangiogenesis [69]. This process substantially contributes to the development and progression of RCC. At present, there are seven targeted drugs approved in the USA and Europe for treating mRCC: sorafenib; sunitinib; bevacizumab combined with IFN-α; pazopanib; temsirolimus; everolimus; and axitinib. A detailed review of the registration trials is available in the online guideline [4]. Since the Memorial Sloan-Kettering Cancer Center (MSKCC) (Motzer) criteria were developed during the cytokine era [70], the IMDC has established and validated a risk model for patients treated in the era of targeted therapy that should be preferred. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while lactate dehydrogenase (LDH) has been removed [49]. To accurately select treatment for patients, risk stratification according to prognostic scores should be performed and the subtype should be established (LE 1b based on results of RCTs using risk stratification [5,71,72]). Pivotal phase 3 trials have established sunitinib and bevacizumab plus IFN-α as first-line treatment options in treatment-naïve patients with cc-mRCC and good to intermediate risk [71,72]. The COMPARZ study, which had a noninferiority design, demonstrated that pazopanib and sunitinib have similar efficacy but different toxicity profiles [73]. The study therefore firmly established pazopanib as another first-line option. On the basis of trial results and limitations in study design, axitinib is not approved for therapy of treatment-naïve mRCC. For patients with (modified) poor-risk mRCC, an RCT demonstrated longer PFS and OS for temsirolimus compared to IFN-α alone or combined with temsirolimus (LE 1b) [74]. Despite several attempts, combination therapy using currently approved targeted drugs did not demonstrate a benefit in comparison to single-agent use, mainly because of tolerability issues. Therefore, there is a need to sequence available agents according to RCT results [5]. Several phase 2 and 3 trials have investigated therapeutic options for patients who have progressed on cytokines and first-line VEGF-targeted therapy. Axitinib and everolimus both met their primary endpoints in randomised phase 3 trials (AXIS and RECORD-1) in the VEFG-resistant setting, and sorafenib is a reasonable treatment option. No firm recommendations can currently be made regarding the best sequence for targeted therapy [5]. The therapeutic recommendations and evidence base are summarised in Table 5. For a list of graded key recommendations, see Supplementary Table 2.

Table 5 – European Association of Urology 2014 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [70]	First line	LE [e]	Second line [a]	LE [e]	Third line [a]	LE [e]	Later lines	LE
Clear cell [a]	Favourable, intermediate, and poor	Sunitinib Pazopanib Bevacizumab + IFN (favourable-intermediate only)	1b 1b 1b	After VEGFR: Axitinib Sorafenib [d] Everolimus After cytokines: Sorafenib [d] Axitinib Pazopanib	 2a 2a 2a 1b 2a 2a	After VEGFR: everolimus After mTOR: sorafenib	 2a 1b	Any targeted agent	4
Clear cell [a]	Poor [c]	Temsirolimus	1b	Any targeted agent					
Nonclear cell [b]	Any	Sunitinib Everolimus Temsirolimus	2a 2b 2b	Any targeted agent	4				

IFN = interferon; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; mRCC = metastatic renal cell carcinoma; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.
[a] Doses: IFN-α9 MU three times per week subcutaneously; bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for a period of 4 wk, followed by 2 wk of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally; axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure >150/90 mm Hg, or the patient is taking antihypertensive medication; everolimus 10 mg daily orally.
[b] No standard treatment available. Patients should be treated in the framework of clinical trials. If a trial is not available, a decision can be made in consultation with the patient to perform treatment in line with clear-cell renal cell carcinoma.
[c] Poor risk criteria in the NCT00065468 trial consisted of MSKCC [70] risk plus metastases in multiple organs.
[d] Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS (34).
[e] Level of evidence was downgraded in instances when data was obtained from subgroup analysis within an RCT.

Table 6 – Proposed algorithm for risk-adapted surveillance following treatment for RCC

Risk profile	Treatment	Surveillance						
		6 mo	1 yr	2 yr	3 yr	4 yr	5 yr	>5 yr
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/CA/RFA	CT	CT	CT	US	CT	CT	CT once every 2 yr
High	RN/PN/CA/RFA	CT	CT	CT	CT	CT	CT	CT once every 2 yr

CA = cryoablation; CT = computed tomography of chest and abdomen; MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; US = ultrasound of abdomen, kidneys, and renal bed.

3.6.2. Non–clear-cell mRCC

No phase 3 trials on systemic treatment of patients with non–clear-cell (ncc)-mRCC have been reported. Expanded access programs and subset analysis from RCC studies suggest that the outcome of targeted therapy in these patients is inferior to that for cc-mRCC. Targeted treatment in ncc-mRCC has focused on temsirolimus, everolimus, sorafenib, and sunitinib, and data have been reported from single-arm phase 2 trials [5]. A randomised phase 2 trial of everolimus versus sunitinib with crossover design in ncc-mRCC included 73 patients (27 with pRCC) and was stopped after a futility analysis for PFS and OS. Median OS for everolimus was 10.5 mo but was not reached for sunitinib [75]. The final results presented at the 2014 annual meeting of the American Society of Clinical Oncology showed a nonsignificant trend favouring sunitinib. Both sunitinib and everolimus remain options in this population, with a preference for sunitinib. Patients with ncc-mRCC should be referred to a clinical trial where appropriate.

3.7. 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. Since the last guideline update was published in 2010, the evidence base for follow-up strategies has not changed [2]. There is a clear need for further research to determine whether follow-up benefits patient survival, to identify the time point at which restaging has the best chance of detecting recurrence, and to develop prognostic markers at surgery for the risk of relapse over time. The current conclusions are that the aim of surveillance is to detect either de novo lesions in the kidney or local recurrence or metastases while the patient is still surgically curable. In addition, renal function should be assessed. To tailor follow-up and avoid unnecessary intensive surveillance with imaging, risk stratification should be based on risk assessment scores. Despite validation, none of the proposed models or nomograms is 100% accurate, with C-indices ranging from 74% to 82.2% for assessment of recurrence and from 68% to 89% for assessment of cancer-specific mortality [76]. A commonly used model is the UISS integrated staging system using TNM stage, Eastern Cooperative Oncology Group PS, and nuclear grade [46,77]. The SSIGN score adds necrosis and tumour size and has been modified by Leibovich [44,45]. Overall, because of a lack of 100%

accuracy, historical differences in the use of TNM staging systems, and differences in assessments (OS, CSS, mortality, recurrence-free survival) and subtypes (ccRCC only vs all subtypes), no preference for a risk stratification model can be given. A plateau has been reached in accuracy and a certain error rate has to be accepted for all models. However, the risk groups established for low, intermediate, and high risk allow tailoring of follow-up protocols, and one of the models should be chosen for use in routine clinical practice. The following recommendations can be made based on LE 4: (1) for low-risk disease, cross-sectional imaging (CSI) with CT/MRI can be used infrequently; (2) in the intermediate-risk group, intensified follow-up should be performed, including CSI at regular intervals; and (3) in high-risk patients, follow-up examinations should include routine CSI in the first few years following treatment. There is an increased risk of intrarenal recurrence in larger (>7 cm) tumours treated with PN, or when there is a positive margin. Follow-up should be intensified in such patients. Table 6 proposes a risk-adapted follow-up algorithm.

4. Conclusions

These updated 2014 guidelines provide the current evidence base for the management of RCC according to the most robust and reliable standards. In contrast to previous versions, a multidisciplinary panel prioritised the importance of specific topics and questions, for which evidence synthesis was performed based on SRs. In addition, guideline recommendations were graded according to the 2009 Oxford Centre for Evidence-based Medicine Levels of Evidence. The aim of the panel is to strengthen the methodological quality of evidence synthesis to further improve the overall quality of the guideline and its recommendations, which in turn will enhance its dissemination and uptake and its impact on patients, clinicians, and health care organisations.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.01.005.

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