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EAU Guidelines View

European Association of Urology Guidelines on Renal Cell Carcinoma: The 2025 Update

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Abstract

Background and objective: The European Association of Urology (EAU) renal cell carcinoma (RCC) guideline panel has updated their evidence-based guidelines and recommendations for the management of RCC. Here we present a summary of the 2025 RCC guidelines updated with standardised methodology to provide reproducible evidence for the management of RCC.

Methods: For the 2025 update, a literature search was performed covering the period from May 1, 2023 to May 1, 2024 using the Medline, EMBASE, and Cochrane Libraries. The data search focused on meta-analyses, systematic reviews, randomised controlled trials (RCTs), and retrospective or controlled comparator-arm studies. Evidence was synthesised as outlined for all EAU guidelines.

Key findings and limitations: Clinical practise recommendations were updated in all chapters of the RCC guidelines on the basis of a structured literature search. The studies included were predominantly retrospective with matched or unmatched cohorts based

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Systemic therapy
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on single- or multi-institutional data. Several prospective studies and RCTs provided data that resulted in recommendations based on higher levels of evidence. Specifically, updates include new recommendations on stereotactic body radiotherapy for localised RCC, adjuvant therapy, systemic therapy for clear-cell RCC in later lines, other subtypes, and a new chapter on hereditary RCC.

Conclusions and clinical implications: The 2025 RCC guidelines have been updated by a multidisciplinary panel of experts using methodological standards to provide a contemporary evidence base for the management of RCC.

1. Introduction

The European Association of Urology (EAU) renal cell carcinoma (RCC) guidelines were first published in 2000 to provide clinicians with evidence-based management recommendations for kidney cancer [1]. A multidisciplinary RCC panel that includes urologists, medical oncologists, a pathologist, a methodologist, and a patient advocate update the EAU RCC guidelines yearly [1]. For the 2025 update, a comprehensive and structured literature review was performed and new recommendations were issued on the basis of relevant data. The full version of the current RCC guidelines is available on the EAU website [2].

2. Methods

For the 2025 RCC guidelines, new and relevant evidence was identified, collated, and appraised via a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the RCC guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering the time frame from May 1, 2023 to May 1, 2024. After deduplication, a total of 1781 unique records were identified, retrieved, and screened for relevance (https://uroweb.org/guidelines/renal-cell-carcinoma/publications-appendices). Where practice-changing evidence emerged beyond this period, relevant articles were considered to ensure that the guideline recommendations reflect the latest available data. The most relevant updated recommendations are summarised in Table 1.

Recommendations were assigned a level of evidence (LE) according to the 2009 Oxford Centre for Evidence-based Medicine scheme [3]. Most studies were retrospective analyses that included some larger multicentre or well-designed controlled comparative studies, apart from the topic of systemic treatment of high-risk localised and metastatic RCC, for which data from several randomised controlled trials (RCTs) have been published, resulting in a higher LE. Recommendations in the guidelines were developed by the expert panel to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. A transparent and reproducible strength rating derived from integration of evidence certainty, effect magnitude, and patient values and preferences accompanies each guideline recommendation [3,4]. The panel members had heterogeneous opinions on adjuvant therapy, so formal consensus methods were used to achieve agreement on the final recommendation.

3. Guidelines

3.1. Epidemiology, aetiology, and screening

RCC accounts for approximately 2–3% of all cancers and the highest incidence occurs in Western countries [5]. In 2022, there were an estimated 434 840 new cases of RCC globally [6] and 155 953 deaths worldwide [7]. RCC is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. The male/female predominance is 1.5:1, with peak incidence at age 60–70 yr [8]. RCC comprises different subtypes with specific histopathological and genetic characteristics [9]. In Europe, the incidence of RCC was 145 721 in 2022, with 52 347 deaths [10]. Among 27 European countries, male RCC mortality was lowest in Luxembourg, Cyprus, and Finland. The highest mortality rates were in the Baltic countries, Czechia, and Slovakia [11].

Overall, the incidence of RCC is rising, but mortality trends vary. In Europe, 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 [12].

RCC aetiology includes lifestyle factors such as smoking (hazard ratio [HR] 1.23–1.58), obesity (body mass index >35 vs <25 kg/m^2; HR 1.71, 95% confidence interval [CI] 1.06–2.79), hypertension (HR 1.70, 95% CI 1.30–2.22), and metabolic syndrome (risk ratio 1.62, 95% CI 1.41–1.87) [13–19]. Some 50.2% of patients with RCC are current or former smokers [20]. 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 [15].

The most effective prophylaxis for RCC is to avoid cigarette smoking and reduce obesity [13–16]. The 2025 guidelines therefore include a specific recommendation to reduce weight and eliminate cigarette smoking (LE: 2a).

Despite growing interest in RCC screening programmes, there is a relative lack of studies on the efficacy, cost

Table 1 – Overview of the most relevant updated recommendations for 2025 [a]

Recommendation	Strengthrating
Epidemiology, aetiology, and screening	
Increase physical activity, eliminate cigarette smoking, and in obese patients reduce weight are the primary preventative measures to decrease the risk of RCC.	Strong
Treatment of localised RCC	
Use a shared decision-making approach when deciding on appropriate treatment for RCC	Strong
Do not attempt off-clamp partial nephrectomy unless indicated.	Weak
Offer SBRT to patients with growing, biopsy-proven, nonmetastatic RCC who are unfit for surgery.	Weak
Treatment of locally advanced RCC	
Adjuvant therapy	
Offer adjuvant pembrolizumab to patients with ccRCC, preferably within 12–16 wk after nephrectomy, with a recurrence risk as defined in the Keynote-564 trial:*Intermediate-high risk* • pT2, grade 4 or sarcomatoid, N0 M0 • pT3, any grade, N0, M0*High risk* • pT4, any grade, N0, M0 • any pT, any grade, N+, M0*M1 NED* • NED after resection of oligometastatic sites within 1 yr after nephrectomy	Strong
If adjuvant therapy is planned: • Discuss the contradictory results from adjuvant ICI trials with the patient to facilitate shared decision-making. • Inform the patient about the potential risk of overtreatment and immune-related side effects if adjuvant therapy is considered.	Strong
Do not offer ICI monotherapy or combination therapy to patients with recurrence during or within 6 mo after adjuvant pembrolizumab.	Weak
Local therapy for metastases in metastatic RCC	
Perform a confirmatory axial scan of disease status before metastasectomy to rule out rapid progressive metastatic disease that requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with the patient the option of a period of observation until progression is confirmed.	Weak
Systemic therapy for advanced/metastatic RCC	
ccRCC	
Offer pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib, or nivolumab and cabozantinib, or nivolumab plus ipilimumab, or sunitinib, or pazopanib for IMDC favourable-risk disease.	Weak
Do not offer PD-L1 combination therapy after progression on an ICI combination.	Weak
Offer belzutifan as an alternative to everolimus to patients previously treated with second- to fourth-line therapy for ccRCC	Weak
Offer immune checkpoint inhibitor combination therapy for advanced metastatic ccRCC with sarcomatoid features.	Weak
Non-ccRCC	
Offer lenvatinib plus pembrolizumab to patients with non-ccRCC subtypes.	Weak
Offer cabozantinib and nivolumab to patients with non-ccRCC subtypes other than chromophobe RCC.	Weak
Offer nivolumab plus ipilimumab to patients with non-ccRCC.	Weak
Hereditary and syndrome-specific RCC	
Offer belzutifan to patients with VHL-related renal and other tumours who are not surgical candidates	Weak
Follow up for RCC	
Base stratification of the risk of recurrence on validated subtype-specific models such as the Leibovich score for ccRCC, or the University of California-Los Angeles integrated staging system for non-ccRCC.	Weak

ICI = immune checkpoint inhibitor; IMDC = International Metastatic RCC Database Consortium; NED = no evidence of disease; RCC = renal cell carcinoma; ccRCC = clear-cell RCC; SBRT = stereotactic body radiotherapy; VHL = von Hippel-Lindau.

[a] The full version of the guidelines containing all recommendations is on the European Association of Urology website (https://uroweb.org/guidelines/renal-cell-carcinoma).

effectiveness, and optimal modality for RCC screening. Targeting high-risk individuals and/or combining detection of RCC with other routine health screens may represent pragmatic options to improve the cost effectiveness and reduce the potential harms of RCC screening [21–24]. There is currently no evidence to support primary screening in the general population.

3.2. Diagnosis and staging

3.2.1. Symptoms

Fewer patients with RCC now present with symptomatic disease (bone pain, deterioration of performance status [PS], or persistent cough) at advanced stages [25] (LE: 3). The majority of RCC cases are detected incidentally via imaging for other reasons [26]. In a cohort study, RCC diagnosis for 60% of patients overall, 87% of patients with T1a stage, and 36% of patients with stage III or IV RCC was incidental [27]. The former triad of flank pain, visible haematuria, and a palpable abdominal mass is uncommon today [8] (LE: 3) and the proportion of patients presenting with primary metastatic RCC (mRCC) is declining (18%) [28].

3.2.2. Imaging

Imaging modalities for detection and characterisation of renal masses include contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) [25]. Contrast-enhanced US (CEUS) can be helpful in specific cases [29] (LE: 3). Importantly, CT, MRI, US, and CEUS are unable to reliably distinguish benign entities such as oncocytoma, fat-poor angiomyolipoma, and metanephric adenoma from malignant renal neoplasms (LE: 3). Positron emission tomography (PET) is currently not a standard investigation in patients with clear-cell RCC (ccRCC) despite recent encouraging results with zirconium-labelled girentuximab PET [30]. Chest CT remains the most accurate investigation for diagnosing lung metastases or enlarged mediastinal lymph nodes (LNs) (LE: 3)

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and is strongly recommended, except for cT1a renal tumours, which have a low risk of pulmonary metastases [31]. Since most bone and brain metastases cause symptoms that lead to diagnosis, routine bone or brain imaging is not indicated in localised disease, but can be useful in patients with mRCC, for whom brain imaging is recommended before any medical or surgical intervention [32] (LE: 3).

Complex cystic lesions are classified according to the 2019 Bosniak scheme that distinguishes five categories according to CT or MRI diagnostic criteria predicting the risk of malignancy, which provides guidance for management [33,34] (LE: 3). The rate of malignancy is low for Bosniak I/II cysts and increases to 84% for Bosniak IV cysts [35].

Active surveillance (AS) of Bosniak III cysts is recommended as an alternative to primary surgery, as only 51% of these lesions are malignant and have low malignant potential [34] (LE: 2).

3.2.3. *Renal biopsy*

Percutaneous renal mass biopsy (RMB) avoids unnecessary interventions for benign lesions and supports selection of patients for surveillance and systemic treatment in mRCC [36] (LE: 3). Needle core biopsies are preferred for solid renal masses rather than fine needle aspiration (LE: 2b). Core biopsies sampled via a coaxial technique minimise the risk of seeding [37] (LE: 2b). Core biopsies of solid renal masses have a diagnostic yield of 78–97% and high specificity (98–100%) and sensitivity (86–100%) for diagnosis of malignancy [36] (LE: 2b). If a biopsy is nondiagnostic, a second biopsy or surgical resection should be considered [37] (LE: 4). Core biopsies are not recommended for cystic renal masses because of their low diagnostic yield unless there are focal solid areas amenable to biopsy present (Bosniak IV cysts) [36] (LE: 2b).

3.2.4. *Histological diagnosis*

RCC and other renal tumours comprise a broad spectrum of histopathological entities described in the updated 5th edition of the World Health Organization (WHO) classification of urogenital tumours published in 2022 [38–40], which is now included in the guidelines. In comparison to the 2016 classification, the 2022 edition presents updated standard morphological diagnostic criteria, combined with immunohistochemistry and relevant molecular tests [9]. The global application of next-generation sequencing has resulted in a diagnostic shift from morphological to molecular classification. Therefore, a molecular-driven renal tumour classification has been introduced in addition to morphology-based categorisation of renal tumours (Table 2), including *SMARCB1*-deficient renal medullary carcinoma, *TFE3*- and *TFEB*-rearranged RCC, *ALK*-rearranged RCC, and *ELOC*-mutated RCC. The most profound changes in the 2022 WHO classification mainly relate to rare kidney tumours. There remain three main RCC types: ccRCC, papillary RCC (pRCC; no longer divided into types I and II), and chromophobe RCC [2].

Table 2 – World Health Organization 2022 classification of renal tumours [38,39]

1. Renal cell tumours	
01.I	Clear-cell renal tumours
	Clear-cell RCC
	Multilocular cystic renal neoplasm of low malignant potential
01.II	Papillary renal tumours
	Papillary adenoma
	Papillary RCC
01.III	Oncocytic and chromophobe renal tumours
	Oncocytoma of the kidney
	Chromophobe RCC
	Other oncocytic tumours of the kidney
01.IV	Collecting duct tumours
	Collecting duct carcinoma
01.V	Other renal tumours
	Clear-cell papillary renal cell tumour
	Mucinous tubular and spindle cell carcinoma
	Tubulocystic RCC
	Acquired cystic disease–associated RCC
	Eosinophilic solid and cystic RCC
	RCC not otherwise specified
01.VI	Molecularly defined renal tumours
	TFE3-rearranged RCCs
	TFEB-altered RCC (*TFEB*-rearranged RCC and *TFEB*-amplified RCC)
	ELOC (formerly *TCEB1*)-mutated RCC
	Fumarate hydratase–deficient RCC
	Succinate dehydrogenase–deficient RCC
	ALK-rearranged RCCs
	SMARCB1-deficient renal medullary carcinoma
2. Metanephric tumours	
	Metanephric adenoma
	Metanephric adenofibroma
	Metanephric stromal tumour
3. Mixed epithelial and stromal tumour family	
	Mixed epithelial and stromal tumour
	Adult cystic nephroma
4. Renal mesenchymal tumours	
04.I	Adult renal mesenchymal tumours
	Classic angiomyolipoma/PEComa of the kidney
	Epitheloid angiomyolipoma/epithelioid PEComa of the kidney
	Renal haemangioblastoma
	Juxtaglomerular cell tumour
	Renomedullary interstitial cell tumour
04.II	Paediatric renal mesenchymal tumours
	Ossifying renal tumour of infancy
	Congenial mesoblastic nephroma
	Rhabdoid tumour of kidney
	Clear-cell sarcoma of kidney
5. Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Paediatric cystic nephroma
	Cystic partially differentiated nephroblastoma
	Nephroblastoma
6. Miscellaneous tumours	
Germ cell tumours of the kidney	

PEComa = perivascular epithelioid cell tumour; RCC = renal cell carcinoma.

3.3. *Classification and prognostic factors*

3.3.1. *TNM classification system*

The 2016 TNM classification [41] is recommended for clinical and pathological staging. While the prognostic value of the TNM classification has been validated in both single- and multi-institutional studies, it should not be considered as the only criterion for clinical decision-making. The patient's condition, comorbidities, and wishes are of fundamental importance in selecting the most appropriate treatment. A clinically guided RCC staging classification was proposed in 2022 by the EAU RCC guidelines panel on the basis of changes observed for the management of small renal masses and locally advanced and metastatic disease [42].

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3.3.2. Anatomic classification

Complexity metrics such as the RENAL and PADUA nephrometry scores catalogue anatomic features with an impact on surgery to help in comparing treatment strategies [43–45].

3.3.3. Prognostic factors

Prognostic information is derived from anatomic, histological, clinical, and molecular factors. Postoperative prognostic nomograms that predict survival have been externally validated, but none has yet been prospectively compared [2] (LE: 3). Establishment of reliable prognostic factors for predicting recurrence beyond the clinical prognostic models and TNM classification is needed to better define patients who are likely to benefit from adjuvant therapy. KIM-1 is emerging as a potential prognostic and predictive biomarker in this setting [46].

3.4. Treatment of RCC

3.4.1. Patient involvement in RCC management

A global survey of 1983 patients with RCC from 43 countries has prompted an updated recommendation to use a shared decision-making approach when deciding on appropriate treatment for RCC. The survey identified geographic variations in patient education, experience, awareness, access to care, best practices, quality of life, and unmet psychosocial needs [47]. The survey results revealed that at diagnosis, 43% of all respondents had no understanding of their RCC subtype, and 29% reported no involvement in their treatment decision.

3.4.2. Treatment of localised RCC and local treatment of mRCC

3.4.2.1. Surgical treatment. For localised RCC, surgery remains the primary curative treatment. On the basis of renal function, oncological outcomes, and quality of life (QoL), the recommended preferred management option for localised cT1 RCC is partial nephrectomy (PN) rather than radical nephrectomy (RN) if technically feasible, irrespective of the surgical approach [2] (LE: 1b). Most studies comparing oncological outcomes of PN and RN are retrospective and include cohorts of varied and limited size [48,49]. Only one prospective RCT including patients with organ-confined RCC of limited size (cT1b <5 cm), which was prematurely closed, has been published. The results showed noninferior cancer-specific survival (CSS) for PN versus RN (HR 2.06, 95% CI 0.62–6.84) [50].

PN is associated with better preservation of kidney function in comparison to RN, which reduces the risk of cardiovascular or metabolic disorders [48,51]. In retrospective studies addressing pT1b RCC, no significant CSS differences were observed between PN and RN [48,52,53].

For cT2 and T3 tumours, the evidence for PN remains poor. A meta-analysis of nine studies involving 1278 patients who underwent PN and 2113 who underwent RN for pT3a RCC showed no differences in CSS, overall survival (OS), or recurrence-free survival, indicating that PN can be used for functional benefits [54].

Irrespective of the data available, treatment decisions should be individualised for frail and comorbid patients, weighing the risks and benefits of PN versus RN.

3.4.2.2. RN techniques. No RCT has assessed the oncological outcomes of conventional or robot-assisted laparoscopic RN versus open RN. According to two systematic reviews, laparoscopic or robotic RN was associated with less morbidity and shorter hospital stays in comparison to open RN, but this advantage was lost when comparing robotic to laparoscopic RN [48,55] (LE: 1b). Similar oncological outcomes were reported for retroperitoneal versus transperitoneal laparoscopic approaches in a large multi-institutional cohort [56]. There are no reliable comparative data regarding manually assisted single-port robotic versus conventional laparoscopic approaches.

3.4.2.3. PN techniques. Retrospective studies on laparoscopic PN versus open PN (OPN) found no difference in PFS or OS between the two techniques in centres with laparoscopic expertise [57,58]. Retroperitoneal and transperitoneal laparoscopic PN approaches had similar perioperative outcomes.

Regarding robot-assisted PN (RAPN) versus OPN, analysis of a multicentre French prospective database of 1800 patients revealed lower morbidity in the RAPN group, as well as fewer overall and major complications, fewer transfusions, and shorter hospital stays [59]. A systematic review and meta-analysis comparing RAPN and OPN demonstrated similar short-term functional outcomes [60]. OPERA, a prospective RCT comparing OPN versus RAPN for intermediate- or high-complexity renal tumours (RENAL score $\geq$7), showed no significant difference in the 30-d postoperative complication rate, which was the primary endpoint. The trial was prematurely closed and full results have not yet been published [61].

The single-centre, open-label ROBOCOP II feasibility RCT randomised patients with suspected localised disease in a 1:1 ratio to RAPN or OPN [62]. In a cohort of 50 patients (accrual rate 65%), RAPN was associated with lower blood loss, less need for opioids, and fewer complications according to the mean Comprehensive Complication Index in comparison to OPN. OPN had shorter operative and warm ischaemia times, with no differences in postoperative functional outcomes. Considering the limitations of both prospective trials, the clinical impact of RAPN remains controversial.

Off-clamp PN should not be attempted unless imperative to minimise or avoid warm ischaemia time and improve functional outcomes (LE: 1b). This recommendation is based on the randomised CLOCK trial, which demonstrated a comparable safety profile for off-clamp versus on-clamp PN in terms of intraoperative and perioperative complications, as well as comparable absolute variation in the estimated glomerular filtration rate and split renal function at 6 mo after surgery in patients with regular baseline function and two kidneys. However, of the patients randomised to the off-clamp group, 40% were converted to an on-clamp approach intraoperatively (median ischaemia time of 15 min) [63,64]. Owing to the selective inclusion criteria of the RCT, an off-clamp technique may still be an option for imperative indications such as chronic kidney disease, a solitary kidney, and multifocal disease [65,66].

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3.4.2.4. Positive surgical margins after PN. A positive surgical margin (PSM) occurs in approximately 2–8% of PN cases. Studies comparing different resection techniques (OPN, laparoscopic PN, RAPN) are inconclusive. PSM status occurs more frequently for imperative PN indications (solitary kidney, bilateral disease) and for patients with adverse pathological features as in stage pT3a disease.

A systematic review suggested that PSM after PN in patients with pT1 RCC is associated with a higher risk of local recurrence [67]. However, only a certain proportion of patients with an uncertain margin status actually harbour residual malignancy. The incidence of local tumour-bed recurrences was 16% for patients with PSMs versus 3% for patients with negative margins [68], Therefore, RN or repeat resection of margins can result in overtreatment in many cases (LE: 3). Patients with PSMs should be informed that they will need more intense surveillance (imaging) follow-up and that they are at higher risk of needing secondary local therapies (LE: 3) [69,70]. However, negative surgical margins are not a guarantee of freedom from recurrence [67,71].

3.4.2.5. Adrenalectomy. A systematic review revealed no evidence of an oncological difference between RN with and without adrenalectomy. No meta-analysis was conducted because of diverse study designs and data heterogeneity [72]. There was no difference in OS between RN with and without adrenalectomy (LE: 3).

3.4.2.6. LN dissection for clinically negative LNs (cN0). The indication for LN dissection (LND) along with PN or RN is still controversial [72]. Clinical assessment of LN status is based on detection of LN enlargement via either CT/MRI or intraoperative palpability of enlarged nodes. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [73].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far, and did not find a survival advantage (LE: 2b). As the incidence of LN involvement is only 4%, the risk of lymphatic spread appears to be very low. In recognition of this incidence, only a staging benefit was attributed to LND [74,75]. In a trial that included a very high percentage of patients with pT2 tumours, who are not at higher risk of LN metastases, only 25% of patients with pT3 tumours underwent a complete LND [74]. Nevertheless, the data seem to be further supported by a large retrospective study in which outcomes of RN with or without LND in patients with high-risk non-mRCC were compared using a propensity score analysis. LND was not significantly associated with lower risk of distant metastases, cancer-specific mortality, or all-cause mortality. LND extent was not associated with better oncological outcomes [75]. The guideline panel therefore recommends not offering extended LND to patients with organ-confined disease (LE: 2b).

3.4.2.7. LND for clinically positive LNs (cN1). For cN1 disease the probability of identifying pathologically confirmed LN metastases ranges between 10.3% for cT1 tumours and 54.5% for locally advanced RCC. LND in cN1 disease that involve removal of visible and palpable nodes can be helpful [76] for staging, prognosis, adjuvant therapy, and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [75,77]. The extent of LND remains controversial. Retrospective data for resected isolated macroscopic LN metastasis (pN1) showed that the median time to systemic progression was 4.2 mo [78], suggesting that systemic therapy should be discussed if there is evidence of LN invasion.

3.4.2.8. Management of RCC with venous tumour thrombus. A systematic review that included 14 studies concluded that no surgical method was superior to another for venous tumour thrombus (VTT) excision, and the impact on oncological outcomes remains uncertain [79]. 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 surgery with versus without cardiopulmonary bypass showed no differences in oncological outcomes. Overall, the studies included had high risks of bias and confounding [79].

The surgical method used depends on the level of VTT. The relative benefits and harms of the several strategies and approaches have not been prospectively studied. Nevertheless, the findings support the recommendation that surgical intervention should be considered for all patients with nonmetastatic disease and VTT, irrespective of the extent of VTT at presentation [80] (LE: 3). PS can significantly improve after VTT removal; therefore, PS deterioration due to VTT should not be an exclusion criterion for surgery. Neoadjuvant strategies for VTT downsizing are currently being investigated in prospective studies but cannot be recommended outside clinical trials. A phase 2 trial of preoperative axitinib in patients with VTT demonstrated a reduction in VTT level in 35% of patients (seven of 20) [81].

3.4.2.9. Therapeutic approaches as alternatives to surgery.

3.4.2.9.1. Embolisation. In patients unfit for surgery with symptoms of recurrent haematuria or flank pain, embolisation can be a beneficial palliative intervention [82] (LE: 3).

3.4.2.9.2. Surveillance. For elderly and comorbid patients with incidentally detected small renal masses, RCC-specific mortality is relatively low in comparison to significant competing-cause mortality [83]. In contrast to watchful waiting, AS is defined as initial monitoring of tumour size via serial abdominal imaging (US, CT, or MRI), with delayed intervention reserved for patients who show clinical progression during follow-up. A renal biopsy is recommended before AS (LE: 3), but only in patients for whom treatment will be considered if there is abnormal tumour growth. In the largest AS series reported, the mean growth rate of the renal mass was 3 mm/yr and progression to mRCC was rare (1–2%) [83] (LE: 3). The imaging schedule in this study consisted of CT, MRI, or US at 3 and 6 mo, then every 6 mo up to 3 yr, and annually thereafter (LE: 3).

3.4.2.9.3. Ablative therapies. Ablative techniques for RCC include percutaneous radiofrequency ablation (RFA), cryoablation (CA), microwave ablation, and stereotactic ablative radiotherapy (SABR). Indications for thermal abla-

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tion include a small renal mass (cT1a) in elderly, comorbid patients considered unfit for surgery, recurrence after previous surgery, patients with a genetic predisposition for the development of multiple tumours, bilateral tumours, and patients with a solitary kidney who are at high risk of deterioration of renal function after PN.

Larger tumours (>3–4 cm) and tumours located at the hilum or near the proximal ureter should not be treated using ablative therapies if other treatment options are available. One cohort-embedded RCT investigated the feasibility of randomising patients to CA or PN, but the study was not powered for comparison of oncological outcomes [84]. Owing to limitations in the studies available, a systematic review could not reliably compare outcomes between ablation and PN [85]. Low-quality studies suggest a higher local recurrence rate for thermal ablation in comparison to PN (LE: 3). The quality of the data available does not allow any definitive conclusions regarding morbidity and oncological outcomes for RFA and CA [86] (LE: 3). On the basis of these data, the panel recommends that RFA should not be routinely offered for tumours >3 cm, or CA for tumours >4 cm, and that the harms and benefits regarding oncological outcomes and complications should be discussed with the patient. Importantly, retrospective data support the recommendation to perform percutaneous RMB before rather than concomitantly with ablation [87] (LE: 3).

SABR is emerging as a treatment option for patients with localised cT1a or cT1b tumours who are medically unfit for surgery [88,89].

Recent results from a prospective phase 2 trial revealed a 1-yr local control rate of 100% for T1–2a tumours at median follow-up of 43 mo [90]. Viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [91]. Grade 3–4 toxicities occurred in 0–9.1% of patients across studies [89]. On the basis of these data, the guideline panel has issued a weak recommendation to offer stereotactic body radiotherapy (SBRT) to patients with biopsy-proven nonmetastatic RCC who are unfit for surgery (LE: 3).

3.4.2.9.4. Neoadjuvant therapy. Neoadjuvant therapy is currently under investigation and available in clinical trials. In the preoperative setting, response rates to neoadjuvant tyrosine kinase inhibitor (TKI) and immune checkpoint inhibitor (ICI) therapy varied between 7% and 59% in retrospective series and some phase 2 trials [81,92,93].

There is currently no evidence that neoadjuvant treatment prolongs OS, and the data do not currently support its use outside clinical trials.

3.4.2.9.5. Adjuvant therapy. Phase 3 trials from the TKI monotherapy era provided no evidence that adjuvant TKIs offer an OS benefit, although the S-TRAC study showed a disease-free survival (DFS) benefit of sunitinib over placebo, but with a high grade 3–4 toxicity rate [94] (LE: 1a). ICIs have shown substantial efficacy in mRCC and have been investigated as adjuvant therapy for patients with localised RCC at risk of recurrence [95]. Among adjuvant trials of several ICIs, only adjuvant pembrolizumab, a PD-1 antibody, significantly improved DFS and OS in localised ccRCC with a high risk of relapse. At 57.2-mo follow-up, the results for OS reached statistical significance (HR 0.62, 95% CI 0.44–0.87; p = 0.005) [96]. With OS data now available, the guidelines panel reassessed the new results in relation to recommendations for adjuvant therapy, and now issues a strong recommendation for adjuvant pembrolizumab (LE:1b) [97]. In addition, the TiNivo and CONTACT-03 trials have reported results for subsequent therapy after mRCC progression on ICI therapy [98,99], leading to a new recommendation of subsequent therapy after recurrence on or after adjuvant ICI therapy. ICI monotherapy or combination therapy is not recommended for patients with recurrence during or shortly after adjuvant pembrolizumab (LE: 4).

3.4.3. Treatment of mRCC

3.4.3.1. Surgical treatment. Surgery is only potentially curative if all tumour deposits are excised. This includes patients with the primary tumour in situ and single-metastasis or oligometastatic resectable disease for which adjuvant therapy may be an option. However, for most patients with mRCC, cytoreductive nephrectomy (CN) is palliative and systemic therapy is required. In the recent TKI era, the CARMENA study demonstrated that sunitinib alone was not inferior to immediate CN followed by sunitinib in terms of OS [100]. In an intention-to-treat (ITT) analysis, median OS was 13.9 mo for CN versus 18.4 mo for sunitinib alone. Thirty-eight patients in the sunitinib-only arm (17%) underwent deferred CN, mainly because of a major response at metastatic sites. In addition, the SURTIME trial, which had poor accrual and investigated the sequence of CN and sunitinib revealed a strong OS benefit in favour of deferred CN in the ITT population, with median OS of 32.4 versus 15.0 mo in the immediate CN group [100]. Meanwhile, ICI therapy has replaced VEGFR-targeted TKI agents as the first-line standard of care in International Metastatic RCC Database Consortium (IMDC) intermediate-risk and poor-risk mRCC. However, as patients with primary mRCC included in the pivotal ICI trials had the primary tumour in place, the guideline panel continues to recommend immediate systemic treatment in patients with an indication for first-line therapy until higher-level evidence is available (LE: 2b). For patients with durable responses, deferred CN can be offered. Real-world data have demonstrated durable responses and surgical safety for this strategy, but long-term surveillance data are lacking [101–103]. RCTs in this setting are ongoing [104].

For patients with low-volume metastatic disease, good PS, and intermediate IMDC risk, as well as patients who do not require immediate systemic treatment, upfront CN is still indicated, as observation until progression before commencing systemic treatment can result in substantial gains in the treatment-free interval [105] (LE: 2b).

3.4.3.2. Local therapy for metastases in mRCC. A systematic review assessing treatment of RCC oligometastases before the introduction of ICIs into the treatment paradigm included only retrospective nonrandomised comparative studies with a high risk of bias [106,107]. The interventions assessed included metastasectomy, various radiotherapy strategies, and no local treatment. The outcomes assessed included survival (OS, CSS and PFS), local symptom control, and adverse events. Apart from brain metastases, and possi-

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bly bone metastases, which are frequently treated with SBRT, metastasectomy by default remained an appropriate local treatment for most metastatic sites. Margin-free metastasectomy is associated with longer OS and CSS, and delay of systemic therapy. Radiotherapy, especially SBRT, targeted at bone and brain metastases can induce significant relief from local symptoms [107] (all LE: 3). Owing to its noninvasive nature, SBRT is of increasing interest in this setting. SBRT has been used in oligometastatic and progressive RCC. Two systematic reviews of single-arm studies have been conducted [108,109], and local control rates and delay of systemic treatment are promising.

Adjuvant therapy after surgical metastasectomy is controversial. KEYNOTE-564 included a small percentage of patients who underwent nephrectomy and complete metastasectomy within 1 yr after primary diagnosis (6%) [110,111], excluding brain and bone metastases. Metachronous recurrence at <1 yr is an adverse prognostic factor according to the IMDC classification [112,113]. Systemic therapy with ICI combinations has stronger levels of evidence than surgery in this intermediate/advanced disease setting [95]. In addition, TKI-driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [114,115]. On the basis of current data, it cannot be concluded that metastasectomy within 1 yr of initial diagnosis of the primary tumour and subsequent adjuvant pembrolizumab is superior to a period of observation and dual IO-based combination first-line therapy on progression for patients with oligorecurrent disease.

Results from TKI studies suggest that patients with initial oligometastatic disease can be observed for up to a median of 15 mo until systemic therapy is initiated (LE: 2a) [105].

Therefore, the guideline panel does not recommend metastasectomy and adjuvant pembrolizumab in this population with recurrent disease within 1 yr after primary surgery. A careful reassessment of disease status to rule out rapid progressive disease should be performed (LE: 4).

3.4.3.3. Systemic therapy for mRCC.

3.4.3.3.1. ccRCC. The IMDC risk model was established to aid in assessment of prognosis and to guide therapeutic decisions [116]. The previous targeting agents such as TKIs, TOR inhibitors, and a VEGF antibody (bevacizumab) have been replaced by ICI combination therapy in the first line, although indications for sunitinib and pazopanib remain for patients with IMDC favourable risk and those for whom ICI therapy is not an option. Fig. 1 summarises the recommendations for first-line treatment. A detailed description of the agents and combinations available is provided in the full guideline (https://uroweb.org/guideline/renal-cell-carcinoma/) [2].

ICIs targeting PD-1, complemented by a TKI or a second ICI directed against CTLA-4, are now the backbone of therapy for treatment-naive metastatic ccRCC [95]. Eight phase 3 RCTs of dual ICI combinations, two of which are only available in China, have shown superiority over sunitinib, which was a previous standard of care. There is currently no role for a triple ICI combination outside of clinical trial settings. COSMIC-313 was the first RCT to evaluate cabozantinib + nivolumab + ipilimumab versus nivolumab + ipilimumab [117]. Although the primary endpoint of PFS was met, the incidence of treatment-related adverse events was high, with a high treatment discontinuation rate, and OS was not significantly prolonged by the triplet combination [118].

Updated results from CheckMate 214 after median follow-up of 67.7 mo demonstrated that ipilimumab + nivolumab in the IMDC favourable-risk group was associated with an OS HR of 0.94 (95% CI 0.65–1.37) and a better complete response rate (13% vs 6%) and durable response rate (59% vs 52% with an ongoing response at 5 yr) over sunitinib. These longer-term results led the guidelines panel to change the recommendation to include nivolumab + ipilimumab for the IMDC favourable-risk patient population (LE: 2b) [119].

Treatment choice in the second- and third-line settings after dual ICI combination or ICI + VEGF-targeted therapy remains challenging. Randomised data for patients with disease refractory to either nivolumab + ipilimumab or ICI + TKI in the first-line setting are limited. Sequencing of ICI therapy with atezolizumab and cabozantinib did not yield benefits in terms of the objective response rate (ORR), PFS, or OS over single-agent TKI in the CONTACT 03 trial [98,120]. In addition, the tivozanib + nivolumab combination did not improve PFS, OS, or ORR over tivozanib monotherapy in the TiNivo trial [99]. The guidelines panel therefore updated the recommendation not to offer rechallenge with PD-L1/PD-L1 combination therapy after progression on an ICI combination (LE: 1b).

Prospective data on cabozantinib, tivozanib [121], and axitinib are also available for patients progressing on immunotherapy, but these studies did not focus solely on the front-line setting, involved subset analyses, and were too small for definitive conclusions [122,123]. The most robust data available are for cabozantinib monotherapy after first-line PD-1 inhibitor–based combination therapy (LE: 2a). The randomised phase 3 LITESPARK-005 trial investigated belzutifan (a HIF-2α inhibitor) versus everolimus in patients with advanced ccRCC who received several lines of treatment, including ICI and angiogenesis inhibitors [124]. At 18 mo, the progression-free rate favoured belzutifan over everolimus (24.0% vs 8.3%; $p = 0.002$) as a later-line option (LE: 1b). Fig. 2 summarises the updated later-line recommendations.

3.4.3.3.2. Renal tumours with sarcomatoid features. Subset analyses have shown better results for PD-1/PD-L1 inhibitor combinations with a CTLA-4 inhibitor or VEGF-targeted therapy for renal tumours with sarcomatoid features. Ipilimumab + nivolumab, axitinib_pembrolizumab, cabozantinib + nivolumab, lenvatinib + pembrolizumab, and avelumab + axitinib are all recommended over VEFG-targeted TKI therapy alone. These options have OS advantages over sunitinib, sunitinib + gemcitabine, and superseded VEGF-targeted therapy. The updated guidelines include a recommendation to offer ICI combination therapy for advanced metastatic ccRCC with sarcomatoid features (LE: 2b).

3.4.3.3.3. Metastatic non-ccRCC. For historical purposes, the panel recognises use of the term "metastatic non-ccRCC", but the guidelines refer to the distinct subtype

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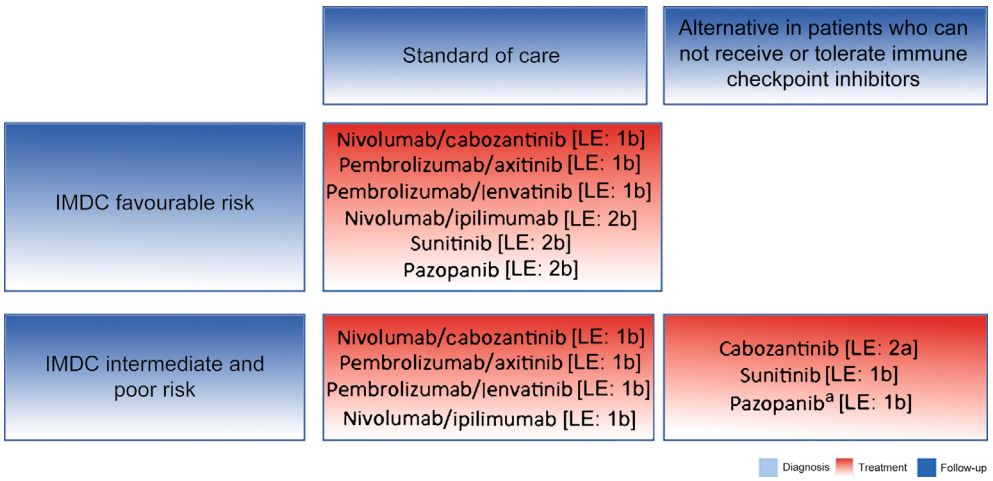

Fig. 1 – Updated guideline recommendations for first-line treatment of clear-cell metastatic renal cell carcinoma. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; LE = level of evidence; [LE: 1b] = evidence from one randomised controlled phase 3 trial; [LE: 2a] = evidence from a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial; [LE: 2b] = evidence from subgroup analysis of a randomised controlled phase 3 trial. [a] Pazopanib for intermediate-risk disease only.

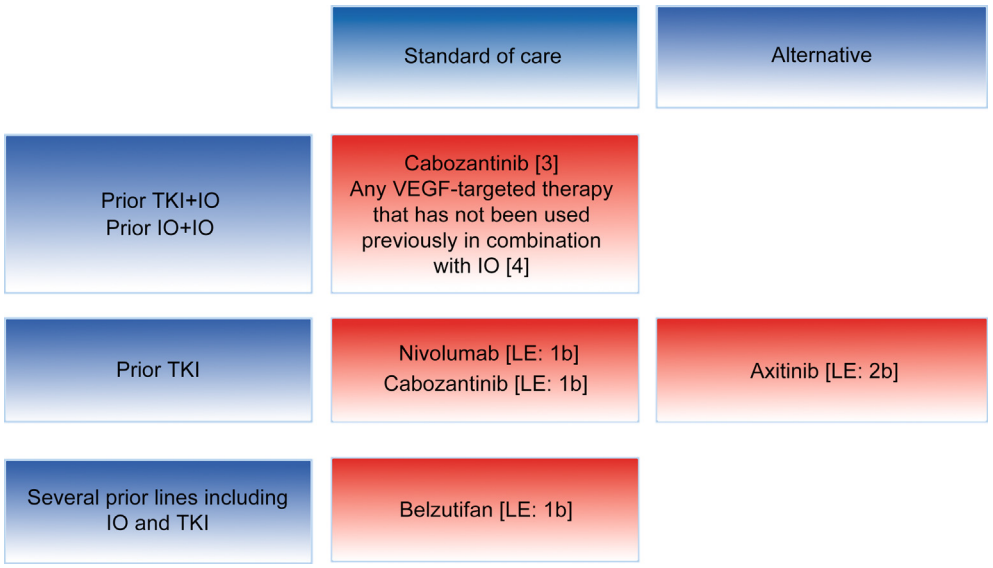

Fig. 2 – Guideline recommendations for later-line therapy. IO = immunotherapy; LE = level of evidence; TKI = tyrosine kinase inhibitor; [LE: 1b] = evidence from one randomised controlled phase 3 trial; [LE: 2b] = evidence from subgroup analysis of a randomised controlled phase 3 trial; [LE: 3] = evidence from well-designed non-experimental studies, such as comparative studies, correlation studies, and case reports; [LE: 4] = expert opinion.

where possible. Metastatic non-ccRCC is a heterogeneous group that includes pRCC, chromophobe RCC, and other rare tumours. While there have been no reports of phase 3 trials in patients with metastatic non-ccRCC, the need to study specific subtypes that have higher incidence than other non-ccRCC types is increasingly recognised.

The randomised phase 2 PAPMET trial compared sunitinib to cabozantinib, crizotinib, and savolitinib in 152 patients with metastatic pRCC [125]. PFS was significantly longer for cabozantinib than for sunitinib (HR 0.60, 95% CI 0.37–0.97), so cabozantinib as an option for patients with papillary mRCC if compared to sunitinib.

Evidence for ICI + TKI combinations is from phase 2 studies of lenvatinib + pembrolizumab and cabozantinib + nivolumab. The KEYNOTE-B61 phase 2 trial investigated lenvatinib + pembrolizumab in patients with non-ccRCC, of whom 93 (59%) has pRCC [126,127]. The primary endpoint was the ORR, which was 54% for the pRCC group at median follow-up of 14.9 mo. In a study of cabozantinib + nivolumab that enrolled 40 patients with pRCC or unclassified RCC, the ORR was 47% in the pRCC group and median PFS was 13 mo (95% CI 7–16) [128]. Indirect comparisons suggest that TKI + ICI combinations have greater efficacy than VEGFR-targeted TKI monotherapy alone. Taking these findings together with results from the academic randomised SUNNIFORECAST trial [129] investigating nivolumab + ipilimumab in therapy-naïve metastatic non-ccRCC, the updated guidelines include new recommendations for

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ICI combination therapy in metastatic non-ccRCC (LE: 1b–2a).

3.4.4. Hereditary and syndrome-specific RCC

The updated guidelines include a new chapter specifically addressing management of the 5–8% of RCCs that are hereditary or syndrome-related. This proportion could be an underestimation because of the limitations of the studies available. To date, more than ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and extrarenal manifestations have been identified. Hereditary RCC syndromes are often suggested by a positive family history, early age of onset, and the presence of other lesions typical for the respective syndromes. The median age at diagnosis of hereditary RCC is 37 yr; 70% of hereditary RCC tumours are found in the lowest age decile (age ≤46 yr) for all RCC tumours [130] (LE: 3).

Hereditary kidney tumours are found as different entities and can also be associated with rare syndromes (Table 3).

Tumours associated with *MITF* translocation, which are somatic fusion translocations of *TFE3* and *TFEB*, may affect 15% of patients with RCC who are younger than 45 yr, and 20–45% of children and young adults diagnosed with RCC [131]. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [132–136].

To establish whether gene variants identified in a tumour are germline in origin, germline genetic testing must be performed (LE: 3). In von Hippel-Lindau (VHL) RCC and non–fumarate hydratase–deficient RCC, tumours can be observed until they reach a diameter of 3 cm, and nephron-sparing approaches are recommended for active treatment if required (LE: 3).

In VHL disease, belzutifan has been approved in Europe and the USA for the treatment of VHL-associated ccRCC that does not require immediate surgery (LE: 2). Approval was based on results from a single-arm phase 2 trial involving 61 patients with tumours ≤3 cm [137]. Belzutifan induced partial responses, with an ORR of 49% and a disease control rate of 98.4% after 21.8 mo of treatment. Over longer observation, the ORR increased to 64% at 37.8 mo. The updated guidelines recommend belzutifan for patients with VHL-related renal and other tumours who are not surgical candidates.

There is currently no approved standard first-line treatment for non-VHL hereditary or syndrome-specific RCC (LE: 3).

Table 3 – Hereditary and syndrome-specific RCC

Hereditary RCC
von Hippel-Lindau syndrome
Hereditary papillary RCC
Birt-Hogg-Dubé syndrome
Fumarate hydratase–deficient RCC, previously called hereditary leiomyomatosis and RCC
Tuberous sclerosis complex
Hereditary SDH-deficient paraganglioma/pheochromocytoma syndrome
PTEN hamartoma syndrome
BAP1 tumour predisposition syndrome
Syndrome-specific RCC
Hyperparathyroidism-jaw tumour syndrome
Chromosome 3 translocation syndrome
MITF-related melanoma and renal cell carcinoma predisposition syndrome

RCC = renal cell carcinoma.

3.5. Follow-up surveillance following nephrectomy or ablative therapies

There is no consensus on follow-up strategies after RCC treatment, with limited evidence suggesting that frequent postoperative imaging does not provide any improvement in early detection of recurrence that leads to better survival [138]. Thus, intensive radiological surveillance may not be necessary for all patients, and the use of subtype-specific risk models for follow-up stratification is recommended (LE: 3). Follow-up is also important for assessing functional outcomes and limiting long-term sequelae such as renal function impairment, end-stage renal disease, and cardiovascular events [139] (LE: 4). Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable (LE: 4).

On the basis of low-level evidence, a risk-adapted follow-up surveillance schedule following treatment for RCC is recommended.

4. Conclusions

The 2025 RCC guidelines provide the most contemporary multidisciplinary evidence base for the management of RCC according to a comprehensive, structured literature assessment to ensure new and relevant data are included. Following transparent, robust, and reproducible methods, new guideline recommendations were developed and are summarised in this update.

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Study concept and design: Bedke, Bex.
Acquisition of data: Bedke, Bex.
Analysis and interpretation of data: Bex, Abu Ghanem, Albiges, Bonn, Campi, Capitanio, Dabestani, Hora, Klatte, Kuusk, Lund, Marconi, Palumbo, Pignot, Powles, Schouten, Tran, Volpe, Bedke
Drafting of the manuscript: Bedke, Bex.
Critical revision of the manuscript for important intellectual content: Bex, Abu Ghanem, Albiges, Bonn, Campi, Capitanio, Dabestani, Hora, Klatte, Kuusk, Lund, Marconi, Palumbo, Pignot, Powles, Schouten, Tran, Volpe, Bedke.
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