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SPECIAL ARTICLE

Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Renal cancer is the 14th most common malignancy worldwide, with >430 000 new cases diagnosed in 2020.[1] The incidence varies geographically, with higher incidence in Europe and North America. Renal cell carcinoma (RCC) accounts for ∼90% of all renal cancers.[1-3]

While incidence rates of renal cancer have been steadily increasing, including a slow rise over the past decade, mortality rates have slowly declined.[1,2] This can be explained in part by increased rates of incidental diagnoses on abdominal imaging.[1] Improvements in treatments are also contributing to the declining mortality rates.

There are several established risk factors for RCC such as smoking, obesity, hypertension and chemical exposures, which have been described previously.[3] An estimated 6%-9% of renal cancers have germline mutations in genes associated with cancer predisposition.[1] Several autosomal dominant syndromes have been described, including von Hippel—Lindau syndrome (VHL), hereditary leiomyomatosis and RCC (HLRCC) or fumarate hydratase (FH)-deficient RCC, hereditary papillary RCC, tuberous sclerosis complex, Birt—Hogg—Dubé syndrome and succinate dehydrogenase (SDH)-deficient RCC.[1]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

The initial presentation of RCC, based on the classic triad of flank pain, gross haematuria and palpable abdominal mass, has been largely replaced by incidental detection.[1] The recommended diagnostic investigations are summarised in Figure 1. Contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis is required for accurate staging of RCC for tumours of all stages. For advanced disease, neuroimaging [CT or magnetic resonance imaging (MRI)] and bone scan are desirable before starting systemic therapy. Positron emission tomography is not recommended for routine staging or assessment of RCC.

Histopathological confirmation of RCC is mandatory for all patients before starting systemic treatment. Core biopsy of the renal tumour or metastatic site, or examination of the nephrectomy sample at surgery, provides histopathological confirmation with high sensitivity and specificity, and negligible risk of tumour seeding.[4,5] Histopathology

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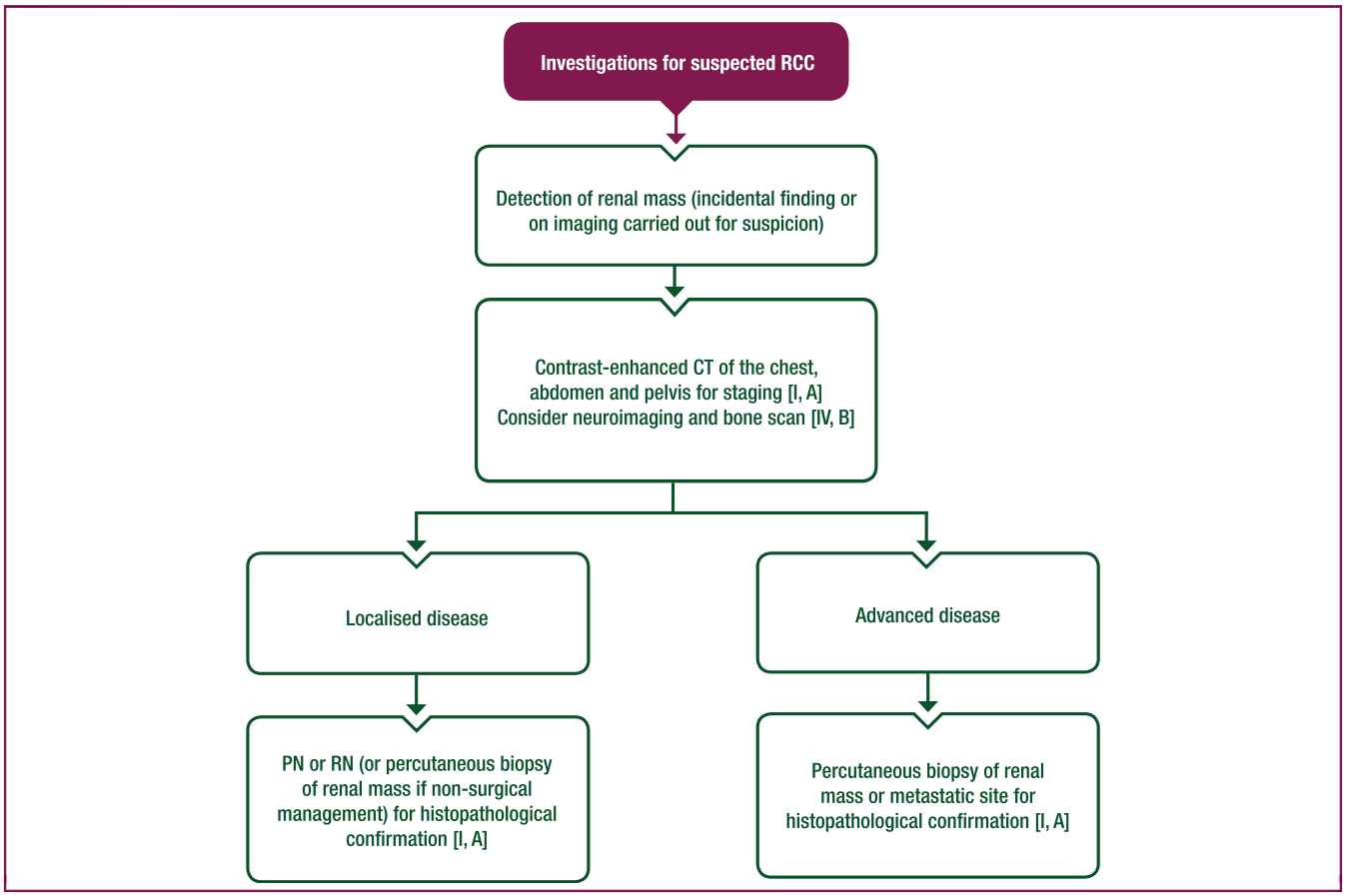

Figure 1. Algorithm for the diagnosis of RCC.
Purple: algorithm title; white: other aspects of management.
CT, computed tomography; PN, partial nephrectomy; RCC, renal cell carcinoma; RN, radical nephrectomy.

assessment to establish the underlying subtype (clear-cell versus variant histology) and presence of sarcomatoid or rhabdoid differentiation using established criteria is strongly recommended due to prognostic and therapeutic implications.[6] More recent classification based on molecular analysis techniques that are not currently widely available, while recommended, is not yet mandated. Patients with suspected metastatic relapse after nephrectomy for renal cancer do not necessarily need a repeat biopsy of the metastatic site, but the decision should be made on an individual basis, especially in the case of late relapse, which is common in RCC. The risk of relapse of the primary tumour and the interval between primary surgery and relapse are relevant in this decision.

Laboratory assessment of serum creatinine, haemoglobin, leukocyte and platelet counts, lymphocyte-to-neutrophil ratio and serum-corrected calcium should be carried out. These tests are used in prognostic scoring systems and treatment selection for advanced disease, including the International Metastatic RCC Database Consortium (IMDC) score (see Staging and risk assessment section).[7]

Pathology

Clear-cell RCCs (ccRCCs) represent ∼80% of malignant renal tumours in adults. The remaining 20% consist of several subtypes with different histological, molecular and cytogenetic profiles. Papillary RCC (pRCC) is the most common of these.[8]

The fifth edition of the World Health Organization (WHO) classification of urogenital tumours, published in 2022, contains significant revisions.[6] With increasing use of massive parallel sequencing to identify molecular alterations in renal tumours, the WHO has introduced a molecular-driven renal tumour classification with 11 subgroups.[6] Molecular-defined renal tumours are those which show very heterogeneous morphological aspects and can therefore not be diagnosed by morphology alone. Such tumours include previously described molecular subtypes (such as microphthalmia transcription factor family translocation carcinomas and SDH-deficient RCC), as well as new entities including *SMARCB1*-deficient medullary RCC, *TFEB*-altered RCC, *ALK*-rearranged RCC and *ELOC*-mutated RCC (Table 1).[6]

The incorporation of molecular-driven classification highlights a shift to using genome sequencing to identify actionable mutations for more personalised treatments. Testing for germline mutations is recommended for younger patients, those with multiple or bilateral lesions, those with first- or second-degree relatives who have had RCC, those with related disorders associated with known predisposing conditions and those who have exhausted standard therapeutic options. While molecular techniques

Table 1. New molecular-defined RCC entities defined by the WHO[6]

RCC subtype (WHO)	Genetic alteration	Comments
Eosinophilic solid and cystic RCC	*TSC* mutation and activation of mTOR pathway	Typically clinically indolent Responses with use of mTOR inhibitors have been reported
ELOC-mutated RCC	*ELOC* (*TCEB1*) mutation	Clear cells with abundant cytoplasm and presence of fibromuscular bands Based on limited data, seem to behave indolently and are associated with good prognosis
ALK-rearranged RCC	*ALK* rearrangements	Typically morphologically very heterogeneous Responses with use of ALK inhibitors have been reported
SMARCB1-deficient medullary RCC	*SMARCB1* loss	Highly aggressive subtype Frequently occurs in young patients with sickle cell trait (although not required for diagnosis)
TFEB-altered RCC	*TFEB* translocation and *TFEB* amplification	*TFEB*-translocated RCC is typically clinically indolent *TFEB*-amplified RCC is typically highly aggressive, tends to occur in older patients
FH-deficient RCC	*FH* loss or mutation	May be associated with HLRCC

ALK, anaplastic lymphoma kinase; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; WHO, World Health Organization.

are becoming more widely available, many laboratories still lack access to them, and most of the identified targets are not currently actionable. When genome sequencing is not available, pathologists should include comments regarding the possible molecular alterations in their diagnoses, along with a detailed morphological description.[6] Currently, the identification of ccRCC as opposed to pRCC or another established subtype (e.g. chromophobe, collecting duct, etc.) remains the priority. The identification of sarcomatoid features, which may be observed in any RCC subtype and are characterised by the presence of spindle or mesenchymal-like cells, has become increasingly important for the consideration of systemic therapy. The latest WHO classification no longer differentiates between type 1 and type 2 pRCC, reducing its importance. The clinical relevance of the new WHO subtypes remains uncertain.

Recommendations

- Patients with suspected renal cancer should have appropriate investigations with cross-sectional imaging, histopathology analysis and laboratory tests [I, A].
- Neuroimaging (CT or MRI) and a bone scan are desirable before starting systemic therapy for advanced disease [IV, B].
- Histopathology analysis should be carried out to determine tumour subtype and results should be available before starting systemic treatment [I, A].
- The recent WHO classification is not routinely required; instead, attention should be given to established subtypes with well-defined treatment algorithms, such as ccRCC and pRCC [IV, B].
- Genetic assessment is recommended for younger patients, those with multiple or bilateral lesions, those with first- or second-degree relatives who have had RCC, those with related disorders associated with known predisposing conditions and those who have exhausted standard therapeutic options [IV, A].

STAGING AND RISK ASSESSMENT

Staging

Staging should follow the eighth edition of the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) system (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2024.05.537).[9]

Risk assessment

Given the variable clinical course of RCC, the use of prognostic models is recommended in both localised and metastatic disease for the assessment of individualised risk.

Localised disease. The approval of adjuvant pembrolizumab for high-risk RCC makes the TNM prognostic classification used in KEYNOTE-564 clinically relevant; this is now the preferred risk classification for operable disease. As per the trial protocol, intermediate-high risk is defined as pathological (p)T2, grade 4 or sarcomatoid, N0, M0, or pT3, any grade, N0, M0.[10] High-risk disease is defined as pT4, any grade, N0, M0, or any pT, any grade, lymph node positive, M0. Other risk models testing pre- and post-operative scores can be used for prognostic purposes.[11,12]

Advanced disease. The IMDC score, developed in the vascular endothelial growth factor receptor (VEGFR)-targeted therapy era, is a useful tool for predicting the prognosis of patients with advanced RCC. This scoring system uses six clinical and laboratory risk factors to produce three risk categories: favourable, intermediate and poor.[7] The risk category can be used to estimate prognosis and guide treatment decisions in first-line therapy and beyond.[13] It should be noted, however, that this scoring system was validated in the era of VEGFR tyrosine kinase inhibitor (TKI) therapy and its predictive value with immune checkpoint inhibitor (ICI) therapy is less certain.

Molecular prognostication and biomarkers. The introduction of the molecular-driven classification for RCC by the

WHO highlights the prognostic implications of certain gene mutations, as discussed above. Gene expression panels can identify high-risk disease in operable cases and can potentially identify angiogenic versus immunogenic tumours in advanced disease;[14] however, these are not applicable for routine use. Programmed death-ligand 1 (PD-L1) has been unreliable as a biomarker in renal cancer, and serum and urine biomarkers are experimental.

Recommendations

- Staging should follow the eighth edition of the UICC TNM system [IV, B].
- Prognostic scoring systems should be used to assess risk in operable disease (KEYNOTE-564 classification) and advanced disease (IMDC classification) [I, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Role of surgery and local therapy

T1 tumours (≤7 cm). Partial nephrectomy (PN) is the preferred option in organ-confined tumours measuring ≤7 cm (elective indication). This recommendation is based on a systematic review of multiple retrospective studies and a prospective, randomised controlled trial comparing radical nephrectomy (RN) with PN in solitary T1a-b N0 M0 renal tumours (<5 cm) with normal contralateral kidney function, which showed that PN was associated with significantly better preservation of renal function.[15]

PN can be carried out via open, laparoscopic or robot-assisted laparoscopic approaches. Conventional or robot-assisted laparoscopic RN is recommended if PN is not technically feasible. A nephron-sparing strategy, including PN, is the standard of care (SoC) in patients with compromised renal function, solitary kidney or bilateral tumours, with no tumour size limitation (imperative indication). Renal mass biopsy before surgery for clinical T1a tumours is recommended, as up to 30% are benign and may not need an intervention; however, a clear consensus has not been reached.[16]

Radiofrequency ablation (RFA), stereotactic body radiotherapy (SBRT), microwave ablation and cryoablation (CA) are non-surgical options, particularly in patients with small cortical tumours. These may be especially appropriate for patients who are frail, present a high surgical risk, have a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours, or decline surgery. Pre-intervention biopsy is recommended to confirm malignancy and subtype in this setting.[17] Systematic reviews suggest a long-term cause-specific survival with RFA that is equal to PN, with a low metastasis rate but slightly higher local recurrence rate compared with PN and CA.[15] The quality of the available evidence prevents definitive conclusions regarding morbidity and oncological outcomes for RFA and CA. Data from meta-analyses as well as prospective and retrospective studies support the efficacy and safety of SBRT, including favourable long-term outcomes.[18] Further randomised trials are needed to define its efficacy; SBRT cannot be strongly recommended without these data.

Active surveillance is an option for those with a short life expectancy and for patients with small renal masses (≤4 cm); indeed, the growth rate of renal tumours is low in most cases (mean 3 mm/year) and progression to metastatic disease is reported in 1%-2% of patients.[17,19] In all cases, a risk—benefit discussion should occur with the patient.

T2 tumours (>7 cm). Minimally invasive RN is the preferred option. Other approaches are likely to have similar oncological outcomes.

Locally advanced RCC (T3 and T4). Open RN remains the SoC for complex T3 and T4 tumours, although robotic and laparoscopic approaches can be considered. Routine adrenalectomy or lymph node dissection is not recommended when abdominal CT and intraoperative exploration show no evidence of adrenal or lymph node invasion.[20]

The evidence regarding management of venous tumour thrombus is based on retrospective studies.[21] Resection of venous thrombi is challenging and associated with a high risk of complications. Surgical intervention should be considered, but the most effective approach remains uncertain and outcomes depend on tumour thrombus level.

There is no established role for neoadjuvant therapies.

Unique considerations for VHL-associated RCC. VHL is a rare, autosomal dominant, hereditary disorder caused by germline pathogenic variants in the *VHL* gene. Approximately 70% of patients with VHL will develop RCC during their lifetime.[22] Historic approaches to the management of RCC in this population have mostly relied on surgical or ablative approaches; however, given the propensity of patients with VHL to develop multiple RCCs, this often requires multiple procedures.

Belzutifan is a novel hypoxia-inducible factor 2α transcription factor inhibitor. A recent phase II, open-label, single-group trial of 61 patients investigated belzutifan in VHL-associated RCC.[23] The overall response rate (ORR) was 64% and there was a reduction in the need for subsequent intervention. Belzutifan appears to be well tolerated and should be recommended for patients who do not require immediate surgery.

Adjuvant therapy in ccRCC

The phase III KEYNOTE-564 trial evaluated pembrolizumab (17 cycles of 200 mg three times weekly) versus placebo as adjuvant therapy in 994 patients with ccRCC with intermediate-high- or high-risk disease (as defined by the trial protocol), or M1 and no evidence of disease (NED).[10] After a median follow-up of 57.2 months, pembrolizumab was associated with improved overall survival (OS) [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.44-0.87, $P = 0.005$] and disease-free survival (DFS) (HR 0.72, 95% CI 0.59-0.87) versus placebo.[24] This is the first adjuvant therapy with proven survival benefit in operable RCC and is

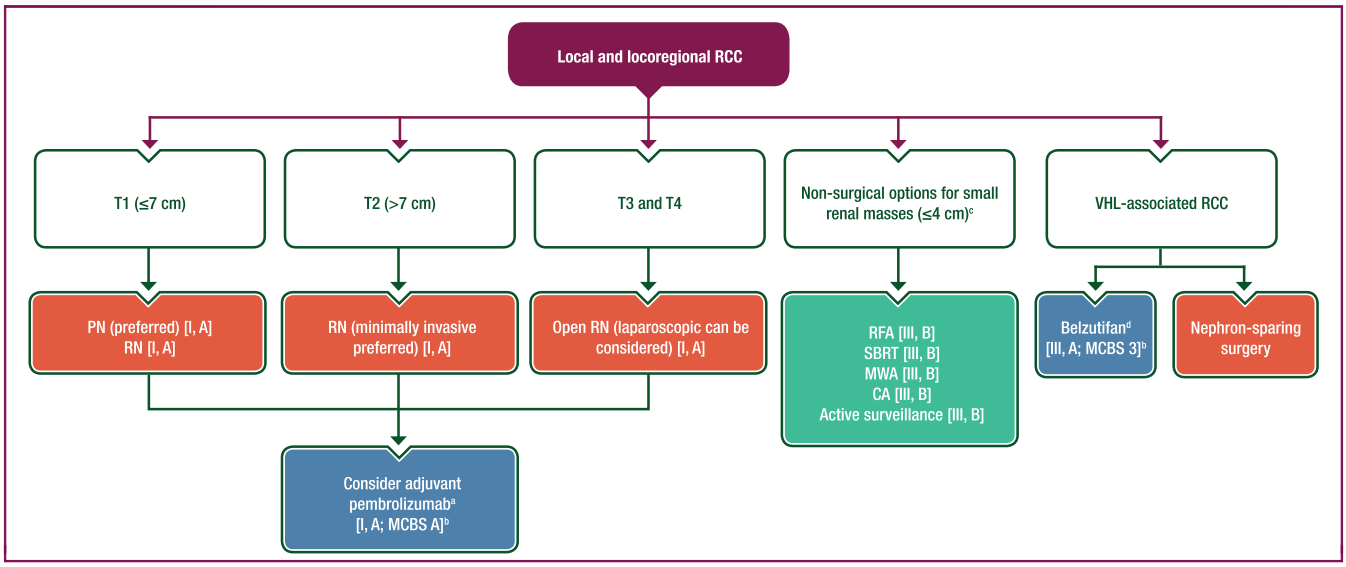

Figure 2. Management of local and locoregional RCC.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
CA, cryoablation; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Score; MWA, microwave ablation; PN, partial nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RN, radical nephrectomy; SBRT, stereotactic body radiotherapy; T, tumour; VHL, von Hippel—Lindau syndrome.
[a]If appropriate at final histology (e.g. T2 with nuclear grade 4 or sarcomatoid differentiation, ≥T3 or regional lymph node metastasis).
[b]ESMO-MCBS v1.1[75] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]For example, in cases of high surgical risk, patient frailty, solitary kidney, compromised renal function, hereditary RCC or bilateral tumours.
[d]FDA approved, not EMA approved.

recommended in patients with intermediate-high- and high-risk (KEYNOTE-564 criteria) ccRCC, after careful patient selection and counselling regarding potential acute and long-term adverse events (AEs). If used, treatment should start within 12 weeks of surgery and continue for up to 1 year.

The DFS and reported OS benefits observed in KEYNOTE-564 contrast with other trials of immunotherapy in the adjuvant setting (e.g. atezolizumab[25] and ipilimumab—nivolumab[26]). Differences in trial design, duration of treatment, ICI activity or increased toxicity associated with the use of ipilimumab may offer explanations for the contrasting results. Biomarker data from these trials are also required.

Adjuvant VEGFR-targeted therapies have demonstrated inconsistent benefit in phase III randomised trials.[27,28]

An algorithm for the treatment of local and locoregional RCC is shown in Figure 2.

Recommendations

- Surgical resection remains the SoC for localised renal cancer [I, A] with either minimally invasive or open approaches preferred depending on tumour size and complexity.
- Several nephron-sparing options, ranging from surveillance to PN, are recommended for small renal masses (T1 ≤4 cm) [III, B].
- Belzutifan may avoid surgeries and can be considered for patients with germline *VHL* variants and localised renal cancer [III, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3; Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved].
- Adjuvant pembrolizumab should be considered for patients with intermediate-high- or high-risk operable ccRCC (as defined by the KEYNOTE-564 criteria) after careful patient counselling regarding potential long-term AEs [I, A; ESMO-MCBS v1.1 score: A]. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
- Adjuvant VEGFR-targeted therapies are not recommended [I, D].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Role of surgery and local therapy in advanced and metastatic ccRCC

Upfront cytoreductive nephrectomy (CN) is no longer considered the SoC in unselected patients with intermediate-risk asymptomatic primary ccRCC and all patients with poor-risk asymptomatic primary ccRCC in the advanced and metastatic setting.[29] Due to the inclusion criteria and subset analysis from the CARMENA trial, CN may still be considered for patients with low-volume single-organ metastatic disease with a large primary tumour, or for patients who have had a near complete response (CR) to upfront systemic therapy.[29] These patients may be candidates for observation rather than systemic therapy after CN, although data are limited regarding long-term outcomes in this setting.

Metastasectomy, thermal ablation, stereotactic radiosurgery, SBRT, CyberKnife radiotherapy (RT) and hypofractionated RT can be considered for selected patients with low metastatic burden after multidisciplinary team (MDT) review, although randomised or robust prospective data to support their use are lacking.[30] Typically, these treatments focus on a single site of disease.

A DFS and OS advantage was demonstrated with pembrolizumab in patients with M1 and NED after metastasectomy in the KEYNOTE-564 study.[24] Systemic therapy rather than surgery is the optimal approach for early relapse (<1 year) after nephrectomy, making surgery in this population controversial. A multidisciplinary approach is required for these patients and surgery is usually avoided. Surveillance is also an option for patients who relapse after nephrectomy with indolent, low-burden, IMDC favourable-risk disease.[31]

Systemic treatment for advanced and metastatic ccRCC

An algorithm for the systemic treatment of advanced and metastatic ccRCC is shown in Figure 3.

First-line treatment. First-line treatment with programmed cell death protein 1 (PD-1) inhibitors in combination with either VEGFR-targeted therapy or cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibition has improved OS for patients

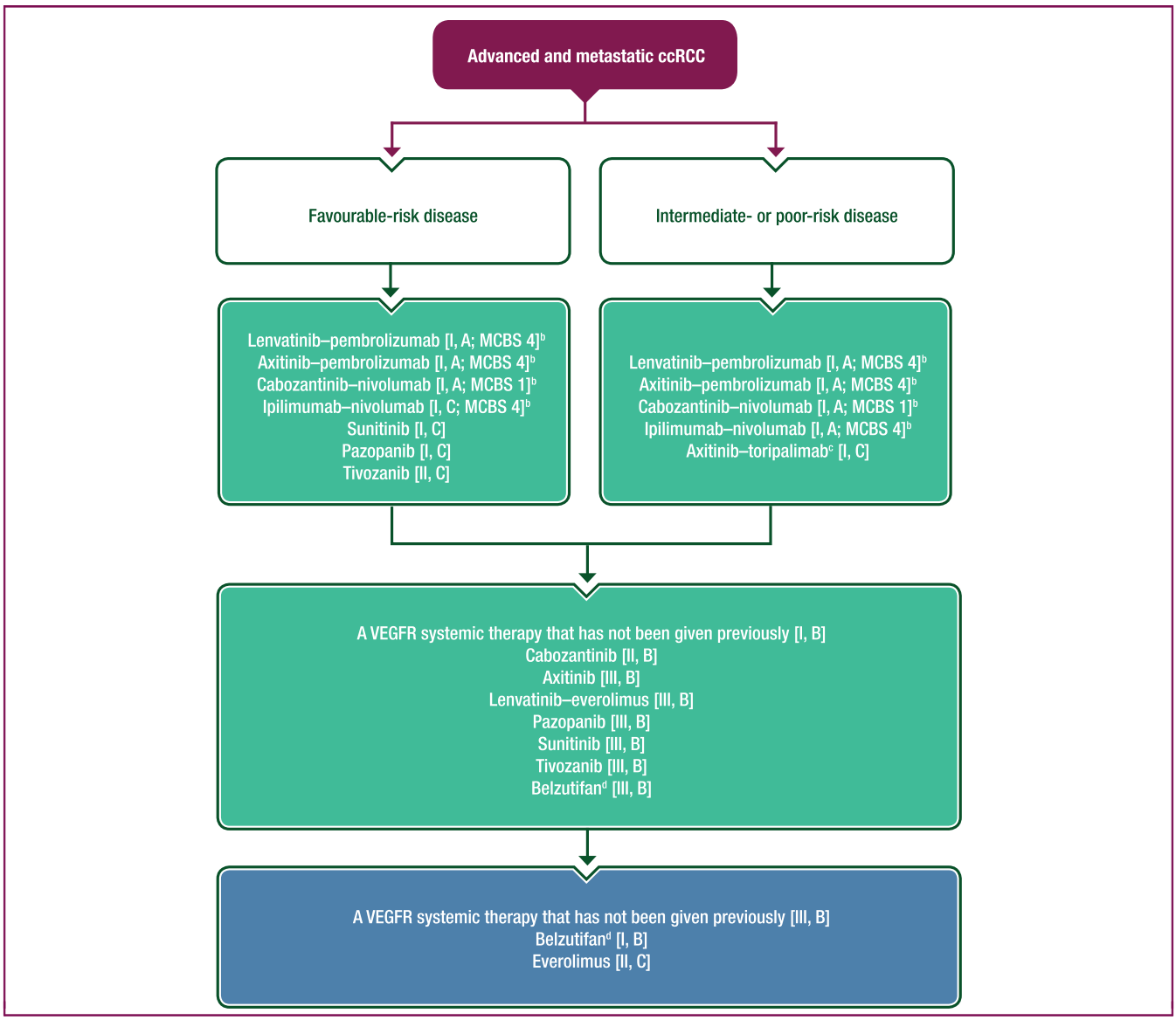

Figure 3. Systemic treatment for advanced and metastatic ccRCC.[a]
Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
ccRCC, clear-cell renal cell carcinoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; VEGFR, vascular endothelial growth factor receptor.
[a]See Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.05.537, for treatment options when ICIs are contraindicated or not available.
[b]ESMO-MCBS v1.1[75] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]Not EMA or FDA approved.
[d]FDA approved, not EMA approved.

with advanced ccRCC.[32-35] Median OS for unselected patients receiving PD-1-targeted combinations is >4 years. Lenvatinib—pembrolizumab, axitinib—pembrolizumab or cabozantinib—nivolumab is recommended for first-line treatment of advanced ccRCC, irrespective of IMDC risk group. Recent data also support the use of axitinib—toripalimab in intermediate- and poor-risk disease, although OS data are immature.[36] There is no preferred combination and indirect cross-trial comparisons are not recommended. The combination of axitinib—avelumab was not associated with an OS benefit compared with sunitinib.[37]

Ipilimumab—nivolumab is also recommended as an equal therapeutic option for first-line treatment of IMDC intermediate- and poor-risk disease and can be considered with a weaker recommendation in favourable-risk disease. The justification for now including the favourable-risk indication is based on improved efficacy observed in more recent data cuts and an existing statistical justification for the inclusion. The statistical justification is that primary endpoints of the phase III CheckMate 214 trial included analysis of IMDC intermediate- and poor-risk disease, but also the intention-to-treat (ITT) population (including favourable-risk disease). Improved OS was observed in the ITT population (HR 0.72, 95% CI 0.62-0.85).[38] Subset analysis of the favourable-risk group was not a primary endpoint; however, initial results were not favourable for this population, resulting in recommendations restricted to intermediate- and poor-risk disease.[39] Updated results are more promising, with the reported OS for ipilimumab—nivolumab in favourable-risk disease within the range observed with the VEGFR—PD-1-targeted combinations. After a median follow-up of 67.7 months, ipilimumab—nivolumab was associated with an OS HR of 0.94 (95% CI 0.65-1.37).[38] While ORR (30% versus 52%) and progression-free survival (PFS) favoured sunitinib (HR 1.60, 95% CI 1.13-2.26), improved CR rates (13% versus 6%) and durability of response (59% versus 52% with ongoing response at 5 years) were observed with ipilimumab—nivolumab.[38] Longer-term results are awaited to see if this improving trend continues.

The authors discussed the recommendation of ipilimumab—nivolumab in favourable-risk disease extensively but were unable to reach a unanimous position. The recommendation reflects a majority (70%) of authors in favour of ipilimumab—nivolumab as an option in favourable-risk disease. Those in favour of this recommendation felt that the improved OS in the ITT population of CheckMate 214, which included favourable-risk disease, justified this recommendation. The potential for durable CRs with ipilimumab—nivolumab, which are infrequently observed with sunitinib, was also discussed in favour of this recommendation. Those against the inclusion of this recommendation felt that the lack of a clear OS benefit in this subgroup, worse PFS and ORR compared with sunitinib, and the current inability to select patients with favourable-risk disease who are more likely to derive benefit from the combination, did not justify use in this population. Toxicity was also discussed, and there was consensus that the potential for life-threatening acute toxicity, as well as the potential for lifelong toxicity, must be carefully discussed with patients if ipilimumab—nivolumab is considered. Across authors both in favour of and against the inclusion of the recommendation, it was felt that IMDC risk categories may not be reflective of the biology of this disease, nor responses to ICI-based therapy, and reliable biomarkers are needed for treatment selection.

A summary of the trials establishing OS benefit with PD-1—VEGFR-, PD-1—CTLA-4- and PD-1—CTLA-4—VEGFR-targeted therapy is shown in Table 2.

In patients with a contraindication to ICIs, or where ICIs are not available, sunitinib, pazopanib or tivozanib may be used.[40-42] An algorithm for the systemic treatment of advanced and metastatic ccRCC when ICIs are unsuitable is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.05.537. Cabozantinib is an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1-targeted therapy.[43] Surveillance may be appropriate for selected patients with IMDC favourable-risk disease with low tumour burden.[31]

OS data for patients with IMDC favourable-risk disease treated with VEGFR—PD-1-targeted combinations remain immature, but these regimens do not appear clearly superior to sunitinib. Nevertheless, better response and PFS data support the use of combinations in this exploratory and

Table 2. Summary of clinical trials evaluating first-line ICI- and VEGFR-based therapy in advanced and metastatic ccRCC

Study	Comparator	OS HR	PFS HR	ORR, %	CR rate, %	Median follow-up, months
CheckMate 214[35] Ipilimumab—nivolumab	Sunitinib	ITT: 0.72 I/P risk: 0.68	ITT: 0.86 I/P risk: 0.73	ITT: 39 I/P risk: 42	ITT: 12 I/P risk: 11	67.7
KEYNOTE-426[77] Axitinib—pembrolizumab	Sunitinib	0.73	0.68	60	10	42.8
CheckMate 9ER[78] Cabozantinib—nivolumab	Sunitinib	0.70	0.56	56	12	32.9
CLEAR[79] Lenvatinib—pembrolizumab	Sunitinib	0.72	0.42	69	17	33.7
RENOTORCH[36] Axitinib—toripalimab (I/P risk)	Sunitinib	0.61 (immature)	0.65	57	5	14.6
COSMIC-313[47] Ipilimumab—nivolumab—cabozantinib	Ipilimumab—nivolumab	NR	0.73	43	3	20.2

ccRCC, clear-cell renal cell carcinoma; CR, complete response; HR, hazard ratio; ICI, immune checkpoint inhibitor; I/P, intermediate or poor; ITT, intention to treat; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor.

underpowered subset.[34-36] Sunitinib, pazopanib and tivozanib should be considered as alternatives to VEGFR—PD-1-targeted combinations in IMDC favourable-risk disease, with weaker levels of evidence.

PD-1-targeted combination therapy appears particularly active in tumours with sarcomatoid features and is strongly recommended.[44-46]

Evaluation of ipilimumab—nivolumab—cabozantinib versus ipilimumab—nivolumab in treatment-naive metastatic intermediate- or poor-risk RCC demonstrated a significant PFS benefit with the triplet combination, but with increased toxicity.[47] This combination is not currently recommended as OS data are awaited.

The optimal duration of therapy in the first-line setting remains uncertain. In CheckMate 214, nivolumab was continued to progression, whereas in ICI plus VEGFR TKI combination therapy, PD-1 inhibitors were stopped after 2 years. Treatment breaks for VEGFR-targeted monotherapy do not appear to have any detrimental effect on efficacy.[48] The benefit of continuing PD-1-targeted therapy beyond 2 years is uncertain.

Second-line treatment. Prospective data in the second-line setting after first-line PD-1-targeted therapy exist for a number of agents (axitinib, pazopanib, cabozantinib, sunitinib) but these results are often contaminated by trial heterogeneity.[49-52] Retrospective and exploratory subset analyses have also been reported from studies of cabozantinib, tivozanib, lenvatinib—everolimus and lenvatinib—pembrolizumab.[53-56] Response rates of ∼20%-40% were reported across all of these studies and outcomes were in line with the expectations for sequencing therapy. These agents are all cautiously recommended due to the imperfections of the datasets. Nevertheless, despite the shortcomings of retrospective, indirect comparisons, these agents appear to be as effective as second-line VEGFR-targeted therapy in the pre-immunotherapy era. Therefore, sequencing VEGFR-targeted therapy is still strongly recommended.

Further ICI therapy after first-line PD-1-targeted combination therapy is not recommended and is potentially harmful. The phase III CONTACT-03 study evaluated atezolizumab (1200 mg intravenously every 3 weeks) plus cabozantinib (60 mg orally once daily) versus cabozantinib alone in patients who had disease progression with ICI therapy.[57] With a median follow-up of 15.2 months, the study failed to demonstrate improvements in either OS (HR 0.94, 95% CI 0.70-1.27, $P = 0.69$) or PFS (HR 1.03, 95% CI 0.83-1.28, $P = 0.78$) with ICI rechallenge. Increased toxicity was reported with second-line ICI therapy, with serious AEs occurring in 48% of patients receiving atezolizumab—cabozantinib and 33% of patients receiving cabozantinib alone. Notably, however, the usefulness of sequencing two ICIs in the case of a long disease-free interval remains unexplored. Other trials exploring these issues are ongoing.

The impressive ORR (40.9%) and median PFS (10.8 months) observed in the control arm of CONTACT-03 make second-line cabozantinib monotherapy an attractive approach.[57] Similarly impressive ORR (28%) and median PFS (9.3 months) were observed in the cabozantinib control arm of CANTATA, a phase III study investigating telaglenastat—cabozantinib versus cabozantinib alone.[58] It is worth noting that 100% of patients in CONTACT-03 and 62% of patients in CANTATA had received prior ICI therapy. These results make cabozantinib the preferred second-line VEGFR TKI therapy, if not received in the first-line setting.

The phase III LITESPARK-005 study of belzutifan versus everolimus in previously treated ccRCC included patients who had received one previous line of therapy (13% of the study population).[59] Based on its observed PFS advantage over everolimus in the overall study population, belzutifan is an option for second-line therapy after progression on VEGFR—PD-1-targeted combination therapy, but with a weaker level of recommendation than in third-line treatment, and with the consideration that alternatives such as cabozantinib may be preferable.

Third-line treatment. Belzutifan has a PFS advantage over everolimus in heavily pretreated (with ICI and VEGFR-targeted therapy) ccRCC (HR 0.75, 95% CI 0.63-0.90).[59] A higher ORR was also observed with belzutifan (23% versus 4%), while interim OS analysis showed no benefit (HR 0.88, 95% CI 0.73-1.07). Toxicity and quality-of-life data also favoured belzutifan. Belzutifan should therefore be used instead of everolimus in this setting. Sequencing VEGFR-targeted therapy is an alternative to belzutifan.

It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as in the pre-ICI era. Rechallenge with ICIs is unproven and should not be regarded as a standard option.

Treatment for advanced and metastatic pRCC

Surgery. The role of CN and other surgical techniques is not clearly defined in metastatic pRCC. While surgery may be appropriate for intermediate-risk disease, patients with poor-risk disease are unlikely to derive benefit and surgery should be avoided in this setting. There is no consensus on the definition of patients who should be considered for surgery.

First-line treatment. Despite advances in the treatment of ccRCC, there are limited high-quality studies to guide the management of non-clear-cell histologies. An algorithm for the systemic treatment of advanced and metastatic pRCC is shown in Figure 4.

Cabozantinib is the preferred first-line monotherapy for advanced pRCC, having demonstrated a PFS (but not OS) advantage compared with sunitinib.[60] Other monotherapy options include sunitinib[61,62] and pembrolizumab.[63] Data from small, randomised studies suggest that savolitinib (a MET inhibitor) is also active in the first-line treatment of *MET*-altered pRCC.[64]

Prospective single-arm trials of lenvatinib—pembrolizumab ($n = 147$) and cabozantinib—nivolumab ($n = 47$) have reported ORRs of 49% and 48%, respectively.[65,66] The toxicity profiles of these combinations were in line with expectations.

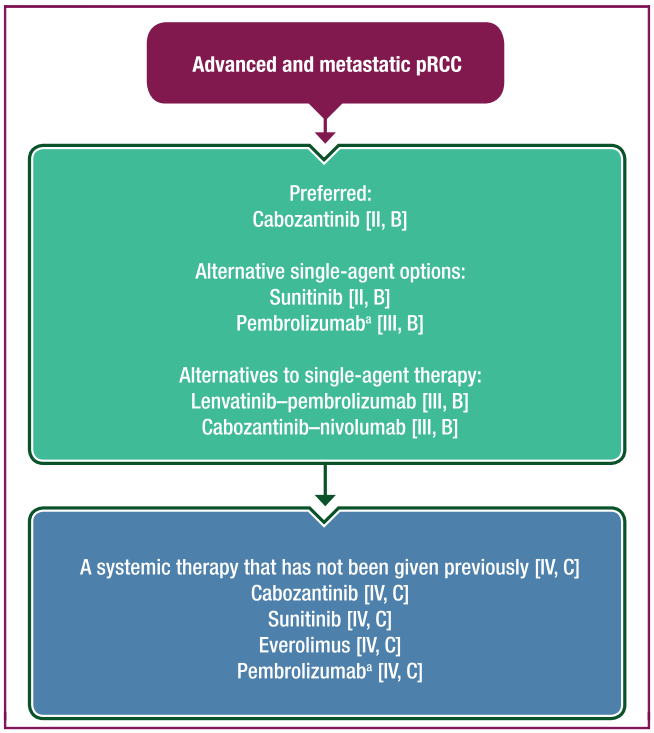

Figure 4. Systemic treatment of advanced and metastatic pRCC.
Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities.
EMA, European Medicines Agency; FDA, Food and Drug Administration; pRCC, papillary renal cell carcinoma.
[a]Not EMA or FDA approved.

Further-line treatment. Robust data are also lacking for second-line treatment of pRCC. Any targeted therapy or immunotherapy recommended in the first-line setting that has not previously been given is cautiously recommended. An OS advantage for any second-line therapy and the principle of sequencing therapy have not been proven in randomised trials. Best supportive care (BSC) alone may be considered in selected individuals.

Treatment for advanced and metastatic non-clear-cell and non-papillary histologies

There is a paucity of robust data to guide management of non-clear-cell, non-papillary RCC histologies; therefore, enrolment into clinical trials is strongly recommended. The available data are largely derived from small prospective studies and subgroup analyses from larger trials.

Surgery is used in patients with intermediate-risk advanced disease; however, there is no available evidence to support this approach as a recommendation.

An algorithm for the systemic treatment of advanced and metastatic non-clear-cell, non-papillary RCC is shown in Figure 5. Sunitinib has been shown to have activity in non-clear histologies (improved PFS compared with everolimus), supporting the use of TKI-based therapy in these rare subtypes.[61] PD-1-targeted combinations are the SoC in patients with sarcomatoid differentiation.[44-46,67] Some patients with chromophobe RCC may benefit from mammalian target of rapamycin (mTOR) inhibitors since mutation on chromosome 17 has been shown to lead to loss of the *FLCN* gene and up-regulation of mTOR.[68]

Collecting duct carcinomas and *SMARCB1*-deficient RCC are treated with platinum-based chemotherapy (ChT). Cabozantinib monotherapy is an alternative treatment for collecting duct carcinomas, having demonstrated efficacy as first-line therapy in a trial of 25 patients with advanced disease.[69] The prognosis of this rare tumour, however, remains generally poor.[70]

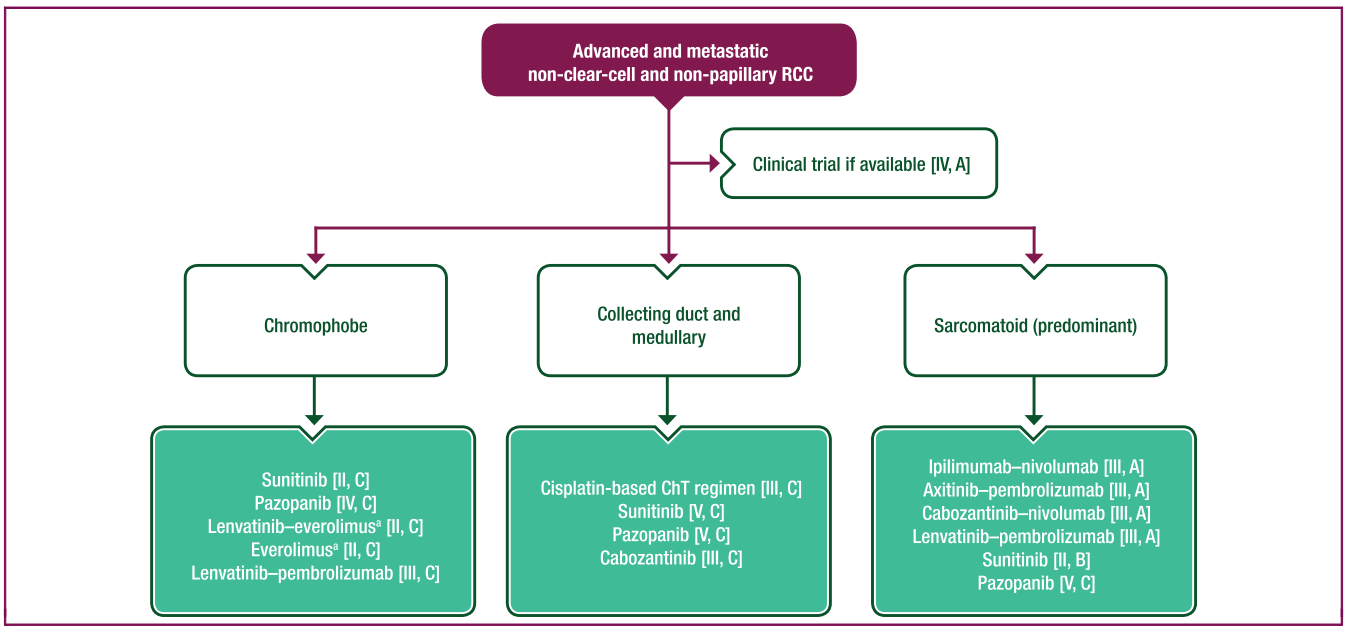

Figure 5. Systemic treatment of advanced and metastatic non-clear-cell and non-papillary RCC.
Purple: algorithm title; turquoise: combination of treatments or treatment modalities.
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; RCC, renal cell carcinoma.
[a]Not EMA or FDA approved for first-line treatment.

FH-deficient RCC is rare, aggressive and may be associated with HLRCC. Data from a phase II study investigating bevacizumab—erlotinib in HLRCC-associated RCC support the use of this combination in advanced FH-deficient disease.[71] Bevacizumab—erlotinib may be considered in this population without an accepted SoC.

After first-line therapy, no recommendations are possible for subsequent lines of therapy based on available data.

Role of RT and bisphosphonates

RT may provide symptom palliation and local control of disease, including in cases of oligometastatic disease or mixed response to ICIs and/or targeted therapies. RT is also an effective treatment for palliation and prevention of disease progression in critical sites such as the bones or brain. In malignant spinal cord compression, initial surgery followed by post-operative RT has been shown to improve survival and maintenance of ambulation compared with RT alone.[72] Low burden of metastatic disease and good ambulatory status at diagnosis are favourable prognostic factors in patients who are able to undergo neurosurgery. In the management of brain metastasis, stereotactic RT is recommended instead of whole-brain RT (WBRT). WBRT is associated with cognitive dysfunction and should be avoided. The benefits of these approaches on survival are uncertain.

Bisphosphonate therapy with zoledronic acid, as well as the receptor activator of nuclear factor kappa B ligand inhibitor denosumab, has been shown to reduce skeletal-related events (SREs) and increase time to the first SRE in patients with widespread bone metastases across a broad spectrum of cancers, but not specifically in renal cancer.[73,74] Denosumab was non-inferior to zoledronic acid in a randomised trial[73] and has the convenience of subcutaneous administration with no requirement for renal monitoring or dose adjustment, although the risk of hypocalcaemia is greater in patients with renal dysfunction. Therefore, either zoledronic acid or denosumab should be considered in patients with widespread bone metastases and reasonable life expectancy, taking into account the individualised risk, including the possibility of osteonecrosis of the jaw. It is important to note that these studies were not carried out in the era of contemporary treatments for RCC, and as such, the true benefit is uncertain.

Recommendations

Role of surgery and local therapy.

- CN should usually be avoided in advanced RCC. It should only be considered for selected patients with favourable- or intermediate-risk disease after MDT review [I, B].
- Deferred CN is an option for patients with durable and near CR at metastatic sites following systemic therapy after MDT review [II, B].
- Patient selection for local therapies or surveillance in the metastatic setting should be discussed by an MDT [III, B]. While no data exist to describe an exact population, both strategies should be avoided in patients with a high burden of metastases, short interval to recurrence or aggressive disease.
- Metastasectomy is not routinely recommended within 1 year of nephrectomy [I, D]; however, in patients with oligometastatic disease who have undergone complete resection (M1 and NED), adjuvant pembrolizumab can be offered [II, B; ESMO-MCBS v1.1 score: A].

First-line treatment for advanced and metastatic ccRCC.

- Lenvatinib—pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4], axitinib—pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4] or cabozantinib—nivolumab [I, A; ESMO-MCBS v1.1 score: 1] is recommended for first-line treatment of advanced ccRCC, irrespective of IMDC risk group. There is no preferred PD-1 inhibitor—VEGFR TKI combination and indirect comparisons across trials are not recommended.
- Ipilimumab—nivolumab is recommended as first-line treatment for IMDC intermediate- and poor-risk disease [I, A; ESMO-MCBS v1.1 score: 4] and is an option for favourable-risk disease [I, C].
- Axitinib—toripalimab is an option for patients with intermediate- or poor-risk disease [I, C; not EMA or FDA approved].
- Sunitinib [I, C], pazopanib [I, C] and tivozanib [II, C] are potential alternatives to PD-1-targeted combination therapy in IMDC favourable-risk disease due to a lack of clear superiority for PD-1-targeted combinations over sunitinib.
- Sunitinib [I, A], pazopanib [I, A] and tivozanib [II, B] are alternatives to first-line PD-1-targeted combinations when ICI therapy is contraindicated or not available. Cabozantinib is also an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1-targeted therapy [II, A].
- Axitinib—avelumab is not associated with OS benefit compared with sunitinib and is therefore not recommended over single-agent VEGFR TKI therapy [I, D; ESMO-MCBS v1.1 score: 3].
- Surveillance is an alternative approach in a small, undefined subset of patients with favourable-risk disease [III, C]. This approach requires careful consideration.
- Cessation of ICIs should be considered after 2 years [IV, B]. Treatment breaks from VEGFR TKI therapy do not appear to have any detrimental effect on efficacy [I, C].

Second-line treatment for advanced and metastatic ccRCC.

- Sequencing VEGFR TKI therapy after PD-1-targeted first-line therapy is the SoC [I, B]. VEGFR-targeted agents that have not been previously used should be considered [I, B]. Cabozantinib is the preferred agent for second-line treatment [II, B]. Axitinib [III, B], lenvatinib—everolimus [III, B], pazopanib [III, B], sunitinib [III, B] and tivozanib [III, B] are also options.
- For patients who received first-line VEGFR TKI therapy, nivolumab (if available and not contraindicated) [I, A; ESMO-MCBS v1.1 score: 5] and cabozantinib [I, A] are

both associated with an OS benefit. Axitinib [II, B], everolimus [II, B] and lenvatinib—everolimus [II, B] are also options.
- Belzutifan is an alternative option for patients who have progressed on VEGFR—PD-1-targeted combination therapy [III, B; FDA approved, not EMA approved].

Further-line treatment for advanced and metastatic ccRCC.
- Sequencing VEGFR TKI therapy [III, B] or belzutifan [I, B; FDA approved, not EMA approved] can be recommended.
- Belzutifan should be considered instead of everolimus in heavily pretreated patients (after PD-1- and VEGFR-targeted therapy) [I, B; FDA approved, not EMA approved].
- Everolimus remains an option for patients who have received PD-1- and VEGFR-targeted therapy [II, C], but other approaches are preferable. Everolimus should be considered when other approaches (belzutifan, other VEGFR TKIs) are not available.
- The use of further PD-(L)1-targeted therapy after progression on first-line PD-1-targeted therapy is not recommended [I, D].

Systemic treatment for advanced and metastatic pRCC.
- Cabozantinib is the preferred first-line monotherapy for advanced pRCC without additional molecular testing [II, B].
- Lenvatinib—pembrolizumab and cabozantinib—nivolumab have impressive response rates but are not proven to be superior to single-agent therapy. They may be considered as alternatives to single-agent therapy [III, B].
- Alternative single-agent options include sunitinib [II, B] and pembrolizumab [III, B; not EMA or FDA approved]. Savolitinib cannot currently be recommended in *MET*-altered tumours [II, D; not EMA or FDA approved]; randomised data are needed.
- Second-line therapy may focus on agents that have not been used previously [IV, C]. Options include cabozantinib [IV, C], sunitinib [IV, C], everolimus [IV, C] and pembrolizumab [IV, C; not EMA or FDA approved]. BSC can be considered in selected patients due to the lack of data on systemic therapy [IV, C].

Systemic treatment of advanced and metastatic non-clear-cell, non-papillary RCC.
- Enrolment into clinical trials is recommended [IV, A].
- Sunitinib [II, C], pazopanib [IV, C], lenvatinib—everolimus [II, C; not EMA or FDA approved for first-line treatment], everolimus [II, C; not EMA or FDA approved for first-line treatment] and lenvatinib—pembrolizumab [III, C] may be used for advanced chromophobe RCC.
- Cisplatin-based ChT is recommended for collecting duct carcinomas and *SMARCB1*-deficient RCC [III, C]. Sunitinib [V, C], pazopanib [V, C] and cabozantinib [III, C] are alternative options.
- ICI-based therapies including ipilimumab—nivolumab [III, A], axitinib—pembrolizumab [III, A], cabozantinib—nivolumab [III, A] and lenvatinib—pembrolizumab [III, A] are preferred for advanced RCC with sarcomatoid (predominant) histology. Sunitinib [II, B] and pazopanib [V, C] are alternative options for patients with contraindications to ICI-based therapy.
- Bevacizumab—erlotinib may be used in advanced FH-deficient RCC [III, B; not EMA or FDA approved].

Role of RT and bisphosphonates.
- Stereotactic RT is recommended for patients with brain metastases [III, B]. WBRT is associated with cognitive dysfunction and should be avoided [III, D].
- Zoledronic acid or denosumab can be considered in patients with bone metastases after consideration of individualised risk [IV, C].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

There is no robust evidence to guide recommendations regarding the frequency of follow-up imaging in early- or advanced-stage RCC.

Resectable disease

It is reasonable to use follow-up imaging based on the risk factors for recurrence and available treatment options upon diagnosis of recurrence. For patients with high-risk disease, CT scans of the thorax and abdomen should be carried out every 3-6 months for the first 2 years, regardless of whether adjuvant pembrolizumab is used. For patients with low-risk disease, annual CT scans are likely sufficient. Radiological examination after 2 years is less strongly recommended, although continuation for up to 5 years after surgery can be considered. The possibility of long-term relapses should be taken into account when planning follow-up.

Advanced and metastatic disease

During systemic therapy for advanced disease, CT scans should be carried out every ∼2-4 months to assess response to therapy. Response Evaluation Criteria in Solid Tumours (RECIST) remains the most frequently used method to assess drug efficacy; however, there is no evidence that RECIST-defined disease progression is a clinically valid endpoint that should dictate treatment interruption or modification. Therefore, clinical judgement continues to be required in addition to radiological assessment.

Recommendations

- A risk-based follow-up approach should be considered, with imaging for ≥2 years after nephrectomy [IV, B]. Continuation for up to 5 years can be considered, although the benefits of imaging after 2 years are unclear [IV, C].

- In advanced disease, CT scans should be considered every 2-4 months to assess response to therapy [IV, B]. Radiological response may be evaluated in conjunction with clinical assessment [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores is included in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.05.537. ESMO-MCBS v1.1[75] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated and verified by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.05.537.[76] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-genitourinary-cancers/renal-cell-carcinoma.

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