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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guideline for treatment of kidney cancer (2019)

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Abstract
In this article, we review de state of the art on the management of renal cell carcinoma (RCC) and provide recommendations on diagnosis and treatment. Recent advances in molecular biology have allowed the subclassification of renal tumours into different histologic variants and may help to identify future prognostic and predictive factors. For patients with localized disease, surgery is the treatment of choice with nephron-sparing surgery recommended when feasible. No adjuvant therapy has demonstrated a clear benefit in overall survival. Considering the whole population of patients with advanced disease, the combination of axitinib with either pembrolizumab or avelumab increase response rate and progression-free survival, compared to sunitinib, but a longer overall survival has only been demonstrated so far with the pembrolizumab combo. For patients with IMDC intermediate and poor prognosis, nephrectomy should not be considered mandatory. In this subpopulation, the combination of ipilimumab and nivolumab has also demonstrated a superior response rate and overall survival vs. sunitinib. In patients progressing to one or two antiangiogenic tyrosine-kinase inhibitors, both nivolumab and cabozantinib in monotherapy have shown benefit in overall survival compared to everolimus. Although no clear sequence can be recommended, medical oncologists and patients should be aware of the recent advances and new strategies that improve survival and quality of life in patients with metastatic RCC.

Keywords Kidney · Immunotherapy · Cancer

Introduction: incidence and epidemiology

Renal cell carcinoma (RCC), which originate within the renal cortex, are responsible for 80–85% of all primary renal neoplasms. Other parenchymal epithelial tumours, such as oncocytomas, collecting-duct tumours, and renal sarcomas, occur infrequently.

According to GLOBOCAN 2018, 403,262 new kidney cancer cases were diagnosed in the world, with an age-standardized rate (ASR) of 9.1 cases per 100,000-person-year [1]. This means the 8th most frequent tumour among men and the 12th among women. In addition, a number of 174,098 deaths due to kidney cancer occurred worldwide. In Spain, the estimated incidence in 2019 was 7331 cases (5048 in men and 2286 in women) [2]. RCC is approximately 50% more common in men compared with women. RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age; it is unusual in patients under 40 years of age and exceptionally in children.

According to an analysis of over 29,000 cases from the SEER registry, there has been a steady decrease in the size of tumours at presentation [1]. In addition, the 5-year survival rate of patients with kidney cancer has doubled over the last 50 years. This improved survival and case-fatality rate has been mostly due to the earlier detection of these tumours as incidental small masses on abdominal imaging (i.e., < 4 cm), that can be treated with curative surgery.

Some epidemiologic risk factors have been established in epidemiologic studies, such as smoking, obesity, hypertension, acquired cystic disease of the kidney, occupational exposure, as well as some familial cancer syndromes [3] Analgesic use has been also associated with an increased risk of RCC. Approximately, 2–3% of kidney cancer cases are related to an autosomal dominant inheritance, the most frequent of whom is the von Hippel–Lindau syndrome associated with clear-cell RCC. Several other factors have been related, such diabetes mellitus,

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dietary factors such as the intake of nitrite from processed meat sources, reproductive factors (e.g., increasing number of pregnancies), and prior radiation therapy (RT).

Methodology

This guideline has been developed based on the consensus of ten genitourinary medical oncologists, designed by the Spanish Society of Medical Oncology (SEOM) and the Spanish Oncology Genitourinary Group (SOGUG), with the purpose of reviewing and summarizing the available evidence regarding the management of RCC, as well as generating evidence-based statements on diagnostics and therapeutic strategies. To be in accordance with previous SEOM guidelines, the rating system for quality of the evidence (I–III) and strength of the recommendation (A–E) criteria summarized in Table 1 has been followed [4]. Systematic reviews and meta-analysis of well-designed randomized clinical trials, although not included in the table, have also been considered as level of evidence I. Recommendations are based on current evidence, but the local regulatory status of drugs and procedures should be considered by the reader.

Diagnosis and staging

Diagnosis

As the use of imaging methods has become widespread, the frequency of incidental detection of RCC has increased. So that more than 50% of renal cell carcinomas (RCC) are detected incidentally and few patients (6–10%) have the classic symptoms of the triad (flank pain, macroscopic hematuria and palpable abdominal mass). Less frequently, patients present with symptoms resulting from metastatic disease including bone pain or persistent cough. RCC was often termed the 'Internist's cancer with paraneoplastic syndromes, such as hypercalcaemia, unexplained fever, or erythrocytosis seen in approximately 30% of patients.

A thorough physical examination and laboratory evaluation must be performed that includes complete blood count, lymphocyte to neutrophil ratio, lactate dehydrogenase, serum creatinine, liver function titration and serum-corrected calcium.

Diagnosis is usually suggested by abdominal ultrasound (US) but abdominal Computed Tomography scan (CT) represents the gold standard for the assessment of primary tumour extension: local invasiveness, venous involvement, locoregional lymph nodes status or adrenal metastases. The sensitivity of CT for small renal masses is higher than 90%, approaching 100% for lesions larger than 2 cm [5].

Table 1 Levels of evidence and grades of recommendation

Category, grade	Criteria
Quality of evidence	
I	Evidence from at least 1 properly randomized, controlled trial[a]
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than 1 centre), or from multiple time-series or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Strength of recommendation	
A	Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered
B	Moderate evidence of efficacy—or strong evidence of efficacy but only limited clinical benefit—supports recommendation for use. Should generally be offered
C	Evidence of efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the chemoprophylaxis or alternative approaches Optional
D	Moderate evidence of lack of efficacy or of adverse outcome supports a recommendation against use Should generally not be offered
E	Good evidence of lack of efficacy or of adverse outcome supports a recommendation against use Should never be offered

[a]Although not included in the original table, systematic reviews and meta-analysis of well-designed randomized clinical trials have also been considered as level of evidence I

CT perfusion allows quantitative evaluation of tissue perfusion using scanners with contrast with greater sensitivity and specificity than for multiphase CT (100% and 66.7% vs. 93% and 50%, respectively) [6]. CT is also accurate for chest staging.

Magnetic resonance imaging (MRI) is not recommended for routine clinical practice but may provide additional information on venous involvement by tumour thrombus. However, for tumours sized ≤ 20 mm in diameter, gadolinium-enhanced sequences with fat saturation have been shown to be more sensitive than contrast-enhanced CT [7].

Renal biopsy shows high sensitivity and specificity in identifying malignancy. Severe complications are rare, occurring in less than 1%. It is especially recommended before treatment with ablative therapies as well as in patients with advanced disease before starting systemic treatment [8]. The final histopathological diagnosis, classification, grading and evaluation of prognostic factors are based on the nephrectomy specimen when available [8].

Most brain and bone metastases are symptomatic at diagnosis. Therefore, bone scan is not performed routinely and will only be requested if there is a serum alkaline phosphatase (ALP) elevation or bone pain. CT or MRI of the brain will be performed if there are clinical signs or symptoms suggestive of M1.

The use of [20] F-fluorodeoxyglucose positron emission tomography (PET)/CT is not recommended as a primary diagnostic imaging modality for RCC due not reliable for detecting primary cancer [8]. Continued research in promising molecular tracers are ongoing in metastatic disease, where uptake values have shown prognostic implications in targeted therapy with correlations in progression-free survival (PFS) and overall survival OS) [9].

Staging

The Union for International Cancer Control (UICC) tumour, node and metastasis (TNM) 8 staging system should be used [10] (Tables 2 and 3).

Recommendations

- CT scan is the gold standard for staging of RCC. Level of evidence: III. Grade of recommendation: A.
- Abdominal MRI is an alternative in several circumstances. Level of evidence: III. Grade of recommendation: C.
- The use of bone scan or brain CT (or MRI) is not recommended for routine clinical practice. Level of evidence: III. Grade of recommendation: D.

Table 2 Kidney cancer TNM-staging AJCC UICC 2017

T	Primary tumour		
	TX	Primary tumour cannot be assessed	
	T0	No evidence of primary tumour	
	T1	Tumour 7 cm or less in greatest dimension, limited to the kidney	
		T1a	Tumour 4 cm or less
		T1b	Tumour more than 4 cm but not more than 7 cm
	T2	Tumour more than 7 cm in greatest dimension, limited to the kidney	
		T2a	Tumour more than 7 cm but not more than 10 cm
		T2b	Tumour more than 10 cm, limited to the kidney
	T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
		T3a	Tumour extends into the renal vein or its segmental branches, or tumour invades the pelvicalyceal system or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia
		T3b	Tumour extends into vena cava below diaphragm
		T3c	Tumour extends into vena cava above the diaphragm or invades the wall of the vena cava
	T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	
N	Regional lymph nodes		
	NX	Regional lymph nodes cannot be assessed	
	N0	No regional lymph node metastasis	
	N1	Metastasis in regional lymph node(s)	
M	Distant metastasis		
	M0	No distant metastasis	
	M1	Distant metastasis	

Table 3 Stage grouping for RCC based on AJCC TNM 2017

Stage	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1, T2, T3 N1 M0
Stage IV	T4 Any N M0
	Any T Any N M1

- In patients without previous tumour diagnosis, a renal tumour core biopsy is recommended before treatment with ablative therapies, as well as in patients with metastatic disease before starting systemic treatment. Level of evidence: III. Grade of recommendation: A.

Pathological and molecular classification

Renal cell carcinoma (RCC) is a heterogeneous disease that encompass several different entities from histology, molecular and clinical perspective. RCCs arise from a variety of specialized cells located along the length of the nephron, giving rise to the diversity of histologic RCC types [11].

The most common type of RCC is clear-cell renal cell carcinoma (ccRCC) that represents up to 75% of RCCs. Other subtypes of RCC include Papillary (10–15%), Chromophobe (5%), Oncocytic (< 5%), Xp11 translocation (< 1%) or collecting-duct carcinomas (< 1%). A subset of RCCs remain unclassified (5%) [12]. Sarcomatoid features are present in < 10% of RCC tumours, mostly seen in patients with predominant clear cells areas.

Mutations in the gene encoding von Hippel–Lindau disease tumour suppressor (VHL) that lead to stabilization of hypoxia inducible factor (HIF) are present in most ccRCCs (sporadic and hereditary forms). Loss of VHL function results in an upregulation of angiogenesis. The Cancer Genome Atlas (TCGA) performed a comprehensive analysis in more than 400 ccRCC tumours showing 19 significantly mutated genes. In addition to VHL gene, altered in nearly 90% of patients, mutations modifying the SWI/SNF chromatin-remodeling complex (PBRM1, ARID1A, and SMARCA4) and other epigenetic regulators such as SETD2 and BAP1 are frequently found. A poor-survival subgroup was found to have a metabolic shift [13].

Papillary tumours include two main subtypes (type I and type II), which differ in their molecular drivers and prognosis. Histologic subtypes may be subclassified in different molecular subgroups associated with patient survival [14]. Type I pRCC, with more favorable prognosis, is associated with mutations in the MET oncogene. Type II pRCC is associated with the activation of the NRF2-ARE pathway. Different molecular subtypes were described by the TCGA, being the most distinct the subgroup defined by the CpG Island Methylator Phenotype (CIMP), which was associated with the worst OS [15]. Type II is also found in the hereditary leiomyomatosis and RCC syndrome associated to aberrations in the Krebs cycle gene fumarate hydratase (FH). Chromophobe RCCs were also studied in the TCGA project displaying the mitochondrial function as an important player of the disease biology. Moreover, recurrent genomic structural rearrangements involving the TERT promoter region and elevated TERT expression were described [16, 17].

Although distinct histology tumour subtypes may condition different sensitivity to therapies, validated predictive biomarkers are not available for clinical use [17, 18].

Important features of RCC are the significant regional genomic heterogeneity and the tumour evolution ("branching"), which influence the aggregate molecular pattern and should be considered for future classifications and therapeutic decisions. [18].

Local and locoregional disease

Surgery is the preferred treatment for stages I, II and III. The choice of surgical procedure depends upon the extent of disease and the patient's age and comorbidities [19].

For T1 tumours (< 7 cm), an open or laparoscopic partial nephrectomy (PN), if technically feasible, is recommended as the preferred option. Partial nephrectomy has oncologic outcomes data comparable to radical nephrectomy. This approach is associated with better long-term preservation of renal function and similar oncological outcomes than radical nephrectomy. Partial nephrectomy is also the standard approach for patients with bilateral tumours, those with inherited syndromes, impaired renal function or a single functional kidney [20–22]. Laparoscopic radical nephrectomy (RN) is an alternative if partial nephrectomy is not possible. Ablative procedures (ablation, microwave ablation or cryoablation) are options in development for elderly patients or those with high surgical risk, and for multiple bilateral tumours as in hereditary RCC. Renal biopsy is recommended to confirm malignancy if surgery is not going to be performed [21]. For T2–T4 tumours (> 7 cm) a radical nephrectomy (RN) is the treatment of choice. A laparoscopic RN is preferred in T2 and selected T3a tumours, due to less surgical-related complications than open RN. For T3b and T4 tumours, open RN is the treatment of choice. Resection of venous tumour thrombus is indicated when feasible, although it is associated with a high risk of complications. Extensive lymphadenectomy and adrenalectomy have not been shown to add survival benefit and should not be routinely performed when abdominal CT shows no evidence of invasion [20].

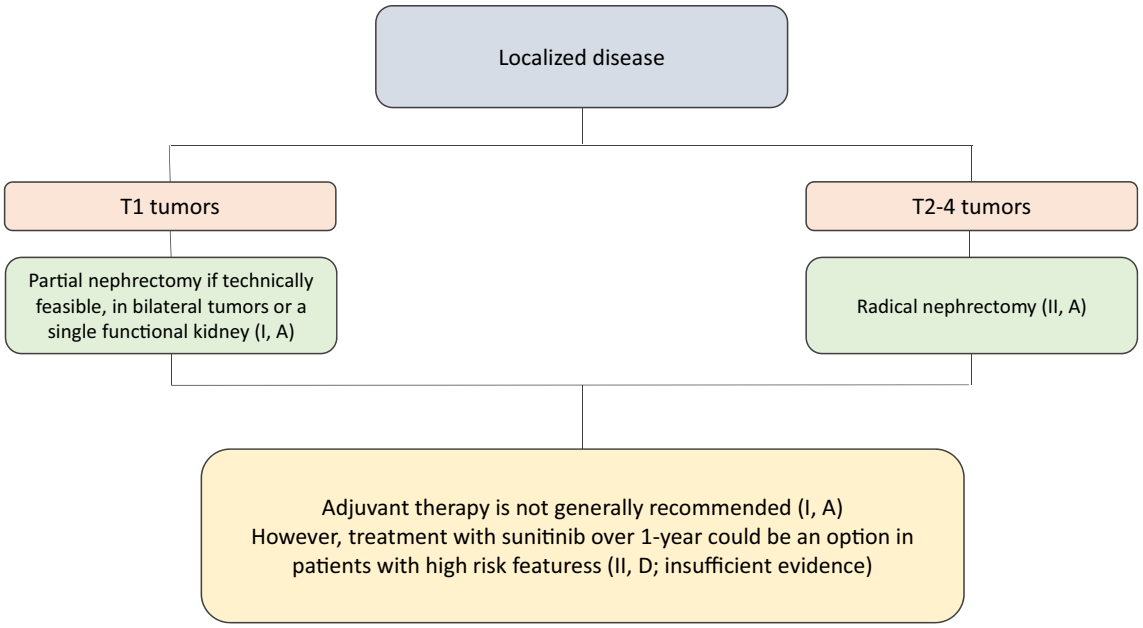

Fig. 1 Treatment algorithm in localized disease

Initial active surveillance is also an acceptable alternative in elderly or high-risk patients with small renal masses (< 3 cm) [23, 24]. Patients should be followed with repeated abdominal imaging every 3–6 months [19]. Several different classifications have been proposed to assess the risk of recurrence in patients with localized renal cell cancer treated with nephrectomy [19, 20].

Regarding the role of systemic therapies in localized tumours, several randomized trials failed to demonstrate a consistent reduction in progression-free survival or OS, either with 1-year adjuvant sunitinib or sorafenib (ASSURE), pazopanib (PROTECT), axitinib (ATLAS), or 3-year sorafenib (SORCE) [25–30]. Only one study (S-TRAC) has shown a significant improvement in disease-free survival (DFS) in patients who received adjuvant sunitinib for 1 year. This benefit seems to be especially apparent in the group of patients with higher risk features. Mature OS data are not available yet. Moreover, toxicity of sunitinib was considerable in this population [25]. However, differences in population prognostic features and dose intensity of therapy between both studies are remarkable [26, 27]. The European Medicines Agency has not approved adjuvant therapy due to the imbalance between risk and clinical benefit of these drugs.

The role of neoadjuvant therapy for localized renal cell cancer has been studied in several small clinical trials. Their results suggest that this approach is feasible, and might be useful in large unresectable masses, high-level venous tumour thrombus involvement, and patients with large masses and imperative indications for nephron-sparing surgery. Nevertheless, at present, this approach still remains investigational. There are several ongoing clinical trials testing novel agents and immunotherapy combinations in the perioperative setting. Eligible patients should be offered to participate in randomized clinical trials [31].

Recommendations

- Partial nephrectomy is recommended in T1 tumours, if technically feasible, as well as in bilateral tumours or a single functional kidney. Level of evidence: I. Grade of recommendation: A (Fig. 1).
- Radical nephrectomy is recommended in T2-4 tumours. Level of evidence: II. Grade of recommendation: A.
- Adjuvant therapy after nephrectomy is not generally recommended (Level of evidence: I, Grade of recommendation: A); however, treatment with 1-year sunitinib could

be individually considered in patients with high-risk features (Level of evidence I, Grade of recommendation: D).

Advanced disease

Prognostic classification

In patients with metastatic renal carcinoma (mRCC), classical anatomical and histological features have limited prognostic value. The most important clinical prognostic factor in mRCC is the ECOG performance status. Several prognostic models have been developed to date, but the most widely used are the MSKCC and the IMDC models.

The Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, derived from studies in the citokines era in 1999 [32] and updated in 2002 [33], identified five variables as risk factors for short survival: time from diagnosis to treatment of < 1 year, Karnofsky performance status < 80%, high serum lactate dehydrogenase, low serum hemoglobin, and high corrected serum calcium. These factors were combined to stratify patients into three risk groups with a favorable (0 risk factors), intermediate (1–2 risk factors), or poor (3 or more risk factors) prognosis, with median OS of 30, 14, and 5 months, respectively (Table 4).

In a retrospective study that included 645 patients treated with anti-VEGF therapies (sunitinib, sorafenib and bevacizumab), the International Metastatic Database Consortium (IMDC) [34] identified six independent predictors of poor OS: time from diagnosis to treatment of < 1 year, Karnofsky performance status < 80%, low serum hemoglobin, high-corrected serum calcium, neutrophilia and thrombocytosis. This model has been also validated with pazopanib [35]. In 2013, an external validation of his model was performed in a series of 1028 patients with mRCC who had been treated with anti-VEGF, and compared with four other prognostic models [36]. The six predefined risk factors were validated as independent predictors of survival. The median OS in the favorable, intermediate, and poor-risk groups was 43.2, 22.5, and 7.8 months, respectively (Table 5). Finally, this model has also been validated for patients in second-line therapy after progression to VEGF-targeted agents [37] and for patients with non-clear mRCC [38].

Table 4 MSKCC prognostic model

Prognostic factor (PF)	Risk category	Median OS (months)
KPS < 80 Diagnosis to therapy < 1 year Anemia Hypercalcemia Elevated lactate dehydrogenase	Favorable risk (0 PF)	30
	Intermediate risk (1–2 PF)	14
	Poor risk (≥ 3 PF)	5

Table 5 IMDC prognostic model

Prognostic factor (PF)	Risk category	Median OS (months)
KPS < 80 Diagnosis to therapy < 1 year Anemia Hypercalcemia Thrombocytosis Neutrophilia	Favorable risk (0 PF)	43
	Intermediate risk (1–2 PF)	22
	Poor risk (≥ 3 PF)	7.8

Recommendation

Prognostic classifications, such as MSKCC and IMDC (for patient treated with anti-VEGF therapies), should be used for management of mRCC patients.

Level of evidence: II, Grade of recommendation: A

Role of surgery in advanced renal cell carcinoma

Most patients with stage IV RCC have unresectable disease and require systemic therapy. However, surgery may have a role in the management of some patients. Two prospective clinical trials assessed the role of cytoreductive nephrectomy (CN) in the last 10 years. The SURTIME trial was designed to compare upfront CN followed by targeted therapy (sunitinib) vs. upfront sunitinib with delayed CN after three cycles [39]. The study, although positive for its progression-free rate primary objective, was underpowered for the OS analysis, and the advantage seen in the delayed nephrectomy arm should be taken as an exploratory analysis. The non-inferiorty CARMENA trial randomized patients with metastatic disease at diagnosis to nephrectomy followed by sunitinib or to sunitinib alone, stratified according to MSKCC prognostic group [40]. Median OS, the primary endpoint of the study, was 18.4 months for sunitinib alone vs. 13.9 months in the sunitinib plus nephrectomy group. Noninferiority was demonstrated with a HR for death and 95% confidence interval (CI) of 0.89 (95% CI 0.71–1.10; upper boundary of the 95% CI for noninferiority ≤ 1.20). However, the possible benefit of primary CN in some subgroup of patients, as well as the value of delayed nephrectomy remains controversial (36).

Metastasectomy and other local treatment strategies (stereotactic radiosurgery. sterotactic body radiotherapy or hypofractionated RT) can be considered for selected patients. A systematic review including 2350 patients point towards a benefit of complete metastasectomy in terms of OS and cancer-specific survival [41]. With the exception

of brain and possibly bone metastases, metastasectomy remains the most appropriate local treatment for most sites. There is also some evidence for local control benefits such as pain relief for bone metastases. No general guidelines can be given to identify cases to refer for local treatment of metastases. Patient selection should be discussed in a multidisciplinary team. Good PS, solitary or oligometastases, metachronous disease with disease-free interval > 2 years, the absence of progression on systemic therapy, low or intermediate Fuhrman grade and complete resection have been associated with favorable outcome after local treatment of metastases from RCC.

Recommendations

- Debulking or cytoreductive nephrectomy (CN) should not be considered mandatory in patients with intermediate–poor IMDC/MSKCC risk who require systemic therapy. Level of evidence: I. Grade of recommendation: A.
- CN may have a role in the management of mRCC in patients with limited metastatic burden amenable to surveillance or metastasectomy, in patients requiring palliation, and potentially delayed CN in patients with a favorable response or stable disease after initial systemic therapy. Level of evidence: II. Grade of recommendation: B.
- Metastasectomy can be considered in selected patients with limited number of metastases with long metachronous disease-free interval. Level of evidence: II. Grade of recommendation: C.

First-line systemic therapy

Active surveillance could be a viable therapeutic option for selected patients with stable or indolent, asymptomatic and good-prognosis mRCC patients [42], and should be discussed extensively with the patient. Early palliative care is strongly recommended.

Four vascular endothelial growth factor (VEGF)-targeted agents have demonstrated efficacy in phase III trials that included mainly good and intermediate risk patients with clear-cell histology [43–47]. Sunitinib, pazopanib and bevacizumab plus IFNα significantly improved PFS compared with IFNα or placebo, with median PFS of 8.5-11 months communicated in pivotal trials [43–45]. Furthermore, pazopanib demonstrated not to be inferior to sunitinib in the phase III COMPARZ trial [48]. Tivozanib, a selective VEGFR tyrosine-kinase inhibitor (TKI), showed superiority when compared with sorafenib in a phase III trial, with a median PFS of 11.9 months [47]. Based on these results, these four oral VEGFR-TKIs have become standard of care in these patients. In addition, a fifth VEGFR-TKI, cabozantinib, showed to improve PFS and response rate compared with sunitinib in a randomized phase II study in intermediate and poor IMDC risk patients [49]. Finally, temsirolimus, a mTOR inhibitor, was tested in a phase III study vs. IFNα in poor-risk patients only, and demonstrated evidence of improved OS in this patient population [50]. In the absence of predictive factors of response to targeted therapy, the choice of TKI is based on drug efficacy and toxicity profiles, as well as patient and physician preference and experience.

Immunotherapy has emerged as a new strategy for first-line metastatic RCC. For patients with intermediate and poor IMDC risk, a large phase III trial demonstrated that the combination of nivolumab and ipilimumab was superior to sunitinib in terms of OS (HR for death, 0.63; $P < 0.001$) and response rate, with a high complete response rate (9%) [51]. On the other hand, the combinations of pembrolizumab and axitinib and avelumab–axitinib in patients with previously untreated advanced RCC, resulted in higher objective response rate and progression-free survival than sunitinib. So far, only the combination of pembrolizumab–axitinib has demonstrated a longer OS (HR for death 0.53; $P < 0.0001$), whereas the final OS results of avelumab–axitinib, as well as the results of other phase III trials combining VEGFR-TKI and immune checkpoints inhibitors are awaited [52, 53]. Finally, high-dose interleukin-2 (HD-IL2) remains a viable option in centers with experience for high-selected good-risk patients [54].

Recommendations

- Considering a decision based on the whole population of patients with metastatic clear-cell RCC, the combination of pembrolizumab–axitinib should be considered the first option, based on the benefit observed in OS over sunitinib (Level of evidence: I, grade of recommendation A). Until mature results of OS are available, the combination of avelumab–axitinib is recommended as an alternative that increase PFS over antiangiogenic TKI (Level of evidence: I, grade of recommendation B). Sunitinib, pazopanib and tivozanib are reasonable options when the above-mentioned combinations are not available, particularly in patients with good and intermediate IMDC prognosis, based on the longer PFS observed compared to interferon placebo, or sorafenib, respectively (Level of evidence: I, grade of recommendation B). HD-IL2 could be still considered as an option for high-selected patients in centres with experience (Level of evidence: III, grade of recommendation: C) (Fig. 2).
- Considering a decision based on IMDC subgroups, the combination of Ipilimumab–nivolumab should be considered the first option for patients with metastatic clear-cell RCC and IMDC intermediate or poor prognosis,

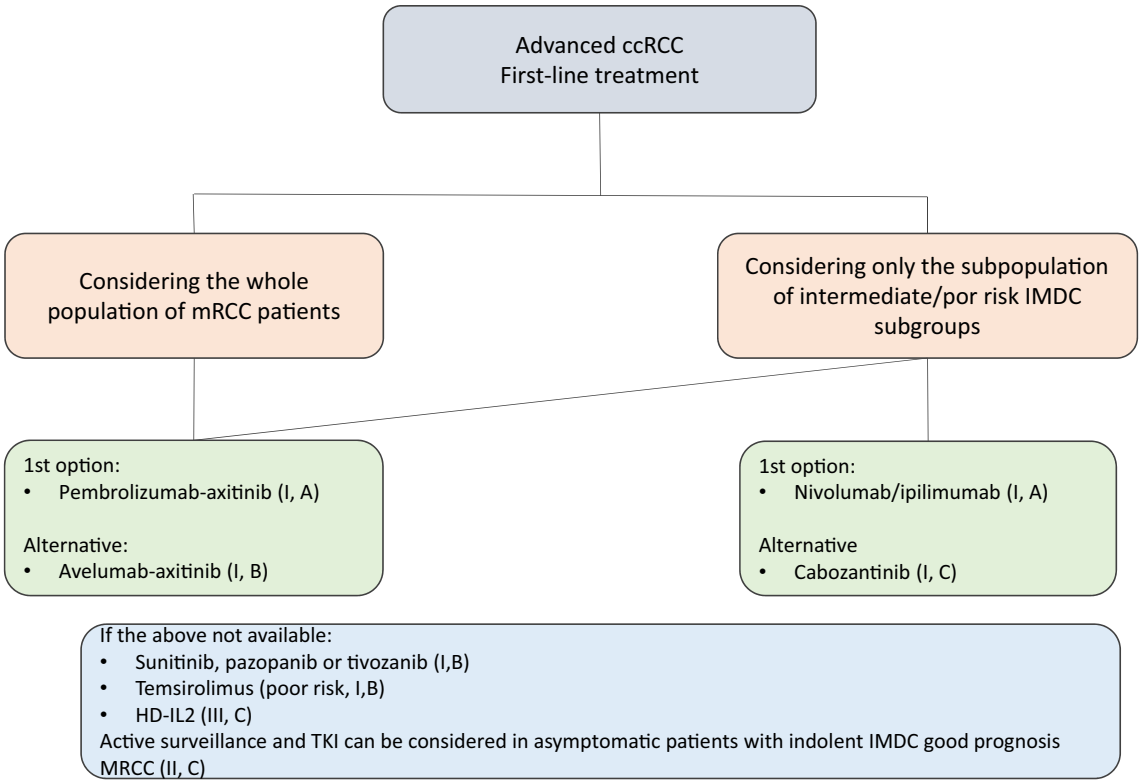

Fig. 2 Treatment algorithm in advanced disease

based on the benefit observed in OS over sunitinib (Level of evidence: I, grade of recommendation A). In this subpopulation, cabozantinib could be preferable to sunitinib based on the longer PFS obtained in a randomized phase II study (Level of evidence: I, grade of recommendation: C). Although not very used, temsirolimus remains still an option for poor- risk IMDC patients (Level of evidence I, grade of recommendation C).

- No definitive evidence is available on the benefit of the anti PD1/PDL1 plus either ipilimumab or TKI over TKI alone in patients with IMDC favorable subgroup. For asymptomatic patients with indolent and good-prognosis disease, active surveillance can be considered (Level of evidence II; grade of recommendation: C).

Second-line treatment and sequences

Until recently, either the VEGFR-TKI axitinib [55], or the mTOR inhibitor Everolimus [56] were the standard treatment for patients progressing to a previous anti-VEGF treatment, based on the results of two-phase III trials of Axitinib vs. sorafenib, and everolimus, vs. placebo. Both trials demonstrated a PFS benefit without improvement in OS.

The second-line treatment of metastatic RCC dramatically changed since 2015 after the report of two different randomized phase III trials showing improvement in OS with nivolumab [57], an antibody against PD-1, and cabozantinib, an oral TKI targeting VEGFR, MET and AXL [58]. Both drugs were compared with everolimus, included patients previously treated with at least one prior antiangiogenic, and both showed a significant improvement in OS (median 25 months, HR: 0.73; $P=0.002$, and median 21.4 months, HR: 0.58, $P<0.001$, respectively) and response rate, whereas PFS was significantly better only with cabozantinib. Nevertheless, toxicity profiles were different, grade 3–4 adverse events and treatment discontinuations for nivolumab were low compared to everolimus. On the other hand, more than 50% of patients treated with cabozantinib required dose reductions due to toxicity. Based on this data nivolumab and cabozantinib were approved by regulatory agencies. In addition, in the randomized phase III trial TIVO-3, Tivozanib was superior to Sorafenib in terms of PFS in a population of heavily pretreated patients (25% exposed to prior checkpoint inhibitors) [59]. Furthermore, the combination of lenvatinib, another oral TKI of VEGFR1-3, FGFR and PDGFR, and everolimus, improved PFS, over everolimus in a randomized phase II study of mRCC patients treated with one previous VEGF-targeted therapy, with high rate of dose reductions due to toxicity [60].

Subsequent therapy for patients with disease refractory after initial checkpoint inhibitor therapy in first-line RCC has not been well defined. VEGF-targeted therapies seem

to have the most robust efficacy. Cabozantinib is the only agent in VEGF-refractory disease with a survival advantage in a randomized phase III trial that allowed previous use of nivolumab. In absence of clear prospective data, decisions should be guided by clinical features, efficacy parameters and safety profile. Unfortunately, no valid biomarkers exist to select the most appropriate treatment for each patient.

Recommendations

- In patients with advanced RCC previously treated with one or two antiangiogenic tyrosine-kinase inhibitors, nivolumab and cabozantinib are the recommended options. Level of evidence: I. Grade of recommendation: A. Decisions to use either agent may be based on the expected toxicity and on contraindications for each drug, as randomized data is lacking.
- Axitinib, everolimus, lenvatinib plus everolimus, and tivozanib are alternatives for second-line, providing that they are available, and patients cannot receive nivolumab or cabozantinib (level of evidence I. Grade of recommendation B). In addition, they may be also acceptable options following Nivolumab and Cabozantinib. Level of evidence: III. Grade of recommendation: C.
- For patients who progress after initial immunotherapy-based treatment, we suggest treatment with a TKI-VEGFR. Options include cabozantinib, axitinib, tivozanib, sunitinib, and pazopanib. Further research is required in this context. Level of evidence: III. Grade of recommendation: C.
- Patients should be encouraged to participate in clinical trials whenever possible.

Non-clear-cell renal carcinoma

Approximately 15–25% of them shows different histology than the majority "clear cells". Most of this group (10–15%) corresponds to the papillary subtype. The treatment of localized forms (stages I, II and III) of non-clear-cell renal carcinoma (nccRCC) is comparable to the cases of CCRC. There is no evidence of the efficacy of adjuvant treatment. The S-TRAC [61] trial did not include patients with nccRCC. The negative ASSURE and PROTECT trials did include them in 21% and 7%, respectively.

Regarding the role of cytoreduction in advanced disease, positive trials of the interferon era do not refer which histologies included. The CARMENA and SURTIME trials did not include nccRCC patients. In contrast, two retrospective series, the International Metastatic Database Consortium [62] including 1700 patients, and the National Cancer Database [63] with 15,390 patients, respectively, included 30% and 20.8% of nccRCC histologies. Both showed a significant impact on OS in favor of the arm that included surgery (20.6 vs. 9.6 and 17.1 vs. 7.7 months, respectively). Therefore, and with evidence from retrospective series, cytoreductive nephrectomy would find support to be carried out in these patients. In reference to metastasectomy, the representation of the nccRCC patients is very limited, and analysis by subgroups is not available, so that the decision in each case must be individualized.

Although there is no phase III trials addressing the systemic treatment in stages IV, the use of targeted treatment is generally recommended based in non-randomized or randomized phase II trials [63]. However, there is no clear evidence to support the use of one treatment over another or one sequence over another, and the classical strategy begins with a vascular endothelial growth factor (VEFR) inhibitor (mainly sunitinib) and continues with an mTOR inhibitor (everolimus). This recommendation is sustained on extrapolation of the evidence from clear-cell tumours, and on the studies, as shown in Table 6.

With the development of the most recent TKI, new therapeutic alternatives have been added to this spectrum. There are two retrospective studies with pazopanib. The

Table 6 Main results of studies that support the use of targeted treatments in nccRRC

Study	Arms	*n* patients NCCRC	% NCCRC	Median OS	Median PFS	G3–4 toxicity
ESPN	Everolimus vs. Sunitinib	35/33	100	14.9 (95% CI 8–23.4) vs. 16.2 (95% CI 14.2–NA)	4.1 (95% CI 2.7–10.5) vs. 6.1(95% CI 4.2–9.4)	54 vs. 88%
ASPEN	Everolimus vs. Sunitinib	57/51	100	13.2 (95% CI 8–23.4) vs. 31.5 (95% CI 14.8–NA)	5.6 (80% CI 5.5–60) vs. 8.3 (80% CI 5.8–11.4)	60 vs. 78%
RECORD3	Everolimus vs. Sunitinib	31/35	13/15%	–	5.1 (range 2.6–7.9) vs. 7.2 (range 5.4–13.8	–
ARCC	IFN vs. temsirolimus	36/37	17/18%	4.3 (95% CI 3.2–7.3) vs. 11.6 (95% CI 8.9–13)	1.8 (95% CI 1.6–2.1)vs. 7(95% CI 3.9–8.9)	–
SWOG 1107	Tivantinib vs. tivantinib–erlotinib	25/25	100	–	2 vs. 5.4	32 vs. 56%

Adapted from Fernández-Pello et al. [75]

first study included 29 patients with papillary, chromophobe and non-classifiable/other histologies in first and successive lines [64]. The median PFS in the first-line subgroup was 8.1 months and the OS was 31 months. The PANORAMA study [65], included 37 patients treated in the first line. Of these, 51% had papillary histology, 24% were chromophobe, 22% unclassified and 3% Xp11.2 translocated. The PFS and OS were, respectively, 15.9 and 17.3 months. In a retrospective study with Cabozantinib [66] that included 112 patients (20% in first line), median PFS was 7.0 months and median OS 12 months. In the first-line subgroup, 23% achieved response, and 82% obtained clinical benefit. Another retrospective study focused on the second and subsequent lines, and showed a median PFS of 8.6, and a median OS of 25.4 months [67]. Finally, real-world data from the Italian Expanded Access Program [68] showed a median SLP of 7.83 months and a 1-year OS of 60%.

Besides these data, it has traditionally been considered that sarcomatoid histologies, tumours of the collecting ducts and medullary renal carcinoma can benefit from chemotherapy. Two series show its role in sarcomatoid histology: The Eastern Cooperative Oncology Group (ECOG) 8802 included 38 patients treated with adriamycin and gemcitabine, obtaining an objective response rate of 16%, median PFS of 3.5 months and median OS of 8.8 months [69]. A second series of 25 patients treated with adriamycin and ifosfamide obtained an SLP of 2.2 months and OS of 3.9 months [70]. There is no evidence to support the use of bevacizumab in this population, although phase II EC data would support the use of bevacizumab–erlotinib in the hereditary subgroup of patients with papillary renal cancer (CRP). MET inhibitors could be also an option in patients with this mutation. Although collecting-duct tumours are usually resistant to systemic therapy, cisplatin-based chemotherapy is usually recommended.

Pivotal studies of immunotherapy did not assess the efficacy in nccRRR histologies. In a retrospective series of 41 patients treated with nivolumab, which included 8 patients in first line [71], papillary, unclassified tumours, chromophobes, tumours of the collecting ducts, an Xp11 translocation tumour and a tubular mucinous were included. There were 20% responses in patients with papillary, collecting and unclassified ducts among 35 evaluable patients, and an additional 29% obtained stabilization. The median PFS was 3.5 months and the OS was not reached. Regarding real-world data, the expanded Italian access program [72] included a 6.7% minority histology of the total of 389 patients analyzed in 2015 and 2016. The median PFS was 4.5 months (95% CI 3.7-6.2) and the 12-month survival rate of the 60%. Data from prospective studies are also available. In the CALYPSO phase I/II trial utilizing the combination of savolitinib and durvalumab a response rate of 27% was achieved in patients with papillary renal cell carcinoma (pRCC) [73]. Finally, in the cohort B of the KEYNOTE 427B trial, 165 patients with recurrent, or metastatic papillary (71%), chromophobe (13%), or unclassified (16%). nccRCC and no prior systemic therapy, the overall response rate with pembrolizumab was 24.8% [74].

Recommendations

- First line: The current evidence is mainly based on small prospective studies and subgroup analyses from larger trials, which mainly focus on TKI or mTOR inhibitor testing. Overall, the most robust data exist for the use of sunitinib.
    - Papilar: Standard: Sunitinib [I, B] Pazopanib [II, B] Option: Everolimus [II, C] Cabozantinib [II, C].
    - Cromophobe: Option: Sunitinib [II, C] Pazopanib, [II, C] Everolimus [II, C].
    - Collecting duct/Medulary: Option: Cisplatin-based regimen [II, C] Sunitinib [II, C] Pazopanib, [II, C].
    - Sarcomatoid: Option: Nivolumab + ipilimumab [II, B] Sunitinib [II, B] Pazopanib, [II, C].
- 'Genetic' recommendations can´t be graded, as data are limited and no clear treatment recommendation can be made for these subgroups with distinct biology.
- After first-line: There is no recommendation possible based on available data.

Authors' contribution All authors have contributed equally in the drafting of the manuscript.

Compliance with ethical standards

Conflict of interest M. Lázaro AB: Janssen, Sanofi, Novartis, Astellas, BMS, Ipsen, MSD, Roche, Eusa, Takeda Travel/acommodation: Roche, MSD, Ipsen, Lilly. B. P. Valderrama Honoraria: Pierre-Fabre, Astellas, Novartis, BMS, Roche, Bayer, Ipsen. AB: Pierre-Fabre, Bayer, BMS, Sanofi, Astellas, BMS, Ipsen, Roche, MSD Travel, accomodation: Janssen, BMS, Pfizer. C. Suárez Personal financial interests: Astellas, AstraZeneca, Bayer, BMS, Eusa, Ipsen, Novartis, Pfizer, Sanofi-Aventis, Roche, MSD. G. de Velasco Honoraria: Pfizer, Ipsen. AB: Janssen, Pfizer, Novartis, Bayer, Astellas, BMS, Ipsen, MSD. Research funding: Ipsen. Other: Janssen. C. Beato Advisory board, consultancy and speaker, honoraria/travel support from BMS, Pfizer, Janssen, Astellas, EUSA pharma, Ipsen and Roche. I. Chirivella. Consultant or advisory board to Pzifer, Bristol-Myers Squibb, Ipsen, Roche and EusaPharma; has served as speaker to Pfizer, Bristol-Myers Squibb, EusaPharma and Ipsen; has received travel and/or accommodation grants from Pfizer. Aranzazu González-del-Alba reports Advisory Board, consultancy and speaker honoraria/travel support from Pierre Fabre, Roche, Bristol-Myers Squibb, MSD, Pfizer, Novartis, Bayer, Janssen, Sanofi, Astellas, EUSA pharma, Ipsen, EISAI and Astra-Zeneca, outside the submitted work. N. Laínez Ad. Boards: Pfizer, Sanofi, Ipsen, BMS,

Roche, Astra Zéneca. M. J. Méndez Advisory Board, consultancy and speaker honoraria/travel support from: Roche, Bristol-Myers Squibb, MSD, Pfizer, Novartis, Bayer, Janssen, Sanofi, Astra Zeneca, Astellas, EUSA pharma, Ipsen, and EISAI outside submitted work. J. A. Arranz No regular salary, royalties, stocks, stock options, or intellectual property rights from pharmaceutical companies. Ocasional speaking or consulting fee from MSD, BMS, Roche, Astellas, Jansen, Pfizer, Merck and Bayer. Travel expenses from MSD, BMS, Astellas, Jansen. Research funding (SOGUG) from BMS, Pierre-Fabre, Novartis.

Ethical approval (research involving human participants and/or animals) The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent For this type of study formal consent is not required.

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