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# Developing an algorithm for the management of Renal Cell Carcinoma: focus on metastatic disease

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**Abstract:** The treatment paradigm in renal cell carcinoma (RCC) is rapidly changing. The incidental finding of small renal tumours combined with the development of novel therapeutic agents targeting the vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin (mTOR) pathways or inhibiting the interaction of the programmed death 1 (PD 1) receptor with its ligand have dramatically improved the prognosis of patients suffering from this malignancy. At the same time, the availability of multiple effective options with similar indications complicates the development and applicability of guidelines in this disease. We conducted a systematic review of the existing guidelines. Our study revealed areas of agreement as well as of discrepancies amongst the published scientific papers included. By critically evaluating these areas, we developed a therapeutic algorithm for RCC. We suggest that this methodology can define the practices of wide applicability and areas of future research.

**Keywords:** *Renal cell carcinoma • Metastatic Disease • Therapeutic algorithm*



## Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all new adult malignancies (1). Incidental diagnosis because of the widespread use of abdominal imaging has led to a migration towards earlier stages at diagnosis, which are potentially curable (2). Nevertheless, the incidence of all stages of RCC has increased over the past several years, contributing to a steadily increasing mortality rate per unit population.

Our armamentarium of systemic therapy in RCC is rapidly improving. Novel agents targeting the vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin (mTOR) pathways or inhibiting the interaction of the programmed death 1 (PD 1) receptor with its ligand have been approved since 2006 and have dramatically improved the prognosis of metastatic renal cell carcinoma (mRCC). These rapid developments have resulted in continuous changes in the respective clinical practice guidelines (CPG)/experts recommendations. Several national and international urological and medical oncology societies and associations have published guidelines on the diagnosis and treatment of RCC (3-11).

In an effort to develop intergroup guidelines, the Hellenic Genito-Urinary Cancer Group has adapted a novel methodology of systematic review and critical evaluation of existing guidelines, instead of developing its own guidelines (12, 13). In order to develop a therapeutic algorithm for RCC, we conducted a systematic review of the existing guidelines in MEDLINE according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement. Our aim was to identify areas of agreement and discrepancies and, through a critical evaluation of our findings, to create an algorithm regarding the therapeutic approach of RCC based on the most recent developments in the field. Hereby, we report the resulting treatment algorithm focusing on the therapy of mRCC.

## Methods

We conducted a systematic review by a MEDLINE search of bibliographical database according to the PRISMA guidelines. All studies providing CPGs/expert recommendations regarding the treatment of RCC were considered eligible to be included in our analysis. Only

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articles in English were included. In case of multiple guidelines published by the same society, only the most recent publication was included. We also searched for articles with level of evidence (LoE) I not included in the publications retrieved by our search. Detailed description of our methodology has been published elsewhere (13). Our algorithm was based on the data regarding temporary management of RCC. Therefore, it does not include recommendations for patients treated with cytokines because of their limited application.

# Results

The search strategy retrieved 120 articles providing CPGs/expert recommendations regarding the treatment of renal carcinoma. Overall, 14 papers published between 2008 and 2015 were eligible for the systematic review.

European Association of Urology (EAU), European Society of Medical Oncology, Japanese Urological Association, African-Middle East, Sociedad Española de Oncología Médica and Slovak Oncology Society published guidelines for the whole spectrum of RCC management. The National Comprehensive Cancer Network guidelines were focused on systemic therapy, whilst the AUA, the 2011 EAU International Consultation on Urologic Diseases (EAU-ICUD) and the Japanese Society of Endourology and Extracorporeal Shockwave Lithotripsy published guidelines on localised or locoregional disease. The strength of the recommendations was mainly (but not always) based on the LoE of the available data. The definitions of LoE were similar across all papers, with the availability of phase III randomised controlled trials (RCTs; and/or meta-analyses of RCTs) universally accepted as representing the highest LoE.

## Histology

World Health Organization (WHO) in its recent edition classifies renal tumours according to histology, chromosomal aberrations and molecular pathways (14).

## TNM (staging)

The TNM staging system, approved by the American Joint Committee on Cancer and the Union for International Cancer Control, should be used (15).

## Risk assessment

For advanced disease, the International Metastatic RCC Database Consortium score has gained approval over the previously used Memorial Sloane Kettering Cancer Centre score, because it was developed and validated in patients receiving the current standards of treatment (16). The IMDC uses the following six factors in order to classify risk of death by advanced RCC:

- Karnofsky Performance status <80%
- Haemoglobin <lower limit
- Time of diagnosis to treatment < 1year
- Corrected calcium > upper normal limit
- Platelets > upper normal limit
- Neutrophils> upper normal limit

Molecular prognostication with the use of gene signatures is still under evaluation in order to become part of everyday clinical practice (17).

## Management of micrometastatic disease

### *Adjuvant systemic therapy*

Adjuvant cytokine treatment is not recommended [I, A] (4-6, 8, 9, 18). A randomised study published in 2014 showed that the combination of 5-fluorouracil, interferon-a and interleukin-2 did not produce a survival benefit, whilst toxicity was considerable (19). On the other hand, targeted therapy with tyrosine kinase inhibitors (TKIs) is a reasonable option to study in the adjuvant setting. However, the ASSURE study showed no benefit from adjuvant sunitinib or sorafenib (20). On the contrary, S-TRAC study showed a prolongation of disease-free survival (DFS; 6.8 years for adjuvant sunitinib vs. 5.6 years for placebo, p = 0.03) amongst patients with localised clear-cell RCC at high risk for tumour recurrence after nephrectomy (pT > 3 and/or pN+) (21). Adverse events were significantly higher with sunitinib treatment. The recent results from PROTECT trial, unfortunately, did not offer conclusive evidence in favour or against adjuvant treatment. Adjuvant administration of pazopanib did not meet its primary endpoint of prolonging DFS [hazard ratio: 0.862; 95% confidence interval , 0.699, 1.063; p = 0.165] in the decreased dosage of 600 mg daily, which was needed in order to control toxicity. Nevertheless, 31% risk reduction was shown in the population with a dosage of 800 mg (22). The discrepancies between these three studies are not easily explained and mature overall survival (OS) data are yet to come. According to these data sunitinib has not yet been approved as adjuvant therapy. Similarly, the updated guidelines of the European Association of Urology do not recommend sunitinib after tumour removal in these patients (23).

## Management of metastatic disease

### *Surgery*

Cytoreductive nephrectomy is universally recommended in patients with good performance status (PS) [III, A]

(24). The presence of significant symptoms owing to the primary tumour should also be taken into consideration in this respect.

## Systemic treatment

### i. First-line treatment

The optimal time to start systematic therapy is not well defined. A period of observation, especially in some patients with mRCC with no symptoms and limited tumour burden, should be considered. Furthermore, no society recommends 'pseudo-adjuvant' therapy after complete excision of metastatic disease.

#### ia. Good and intermediate prognosis

At this setting, there is a plethora of therapeutic options. This created the need for criteria to select the most appropriate treatment for every individual patient. Risk group and histological subtype are currently the two most accepted criteria.

Sunitinib, pazopanib and bevacizumab combined with interferon are the three standard treatments [I, A] (25-27). They have all shown improved efficacy (progression-free survival, PFS) over interferon or placebo in phase III trials.

Recently, cabozantinib has been reported to prolong PFS compared to sunitinib in a randomised phase II trial and its role in the first-line treatment has to be further studied (Figure 1) (28).

#### ib. Poor prognosis

Temsirolimus is the only drug [II, A] that showed improvement of OS versus interferon in this population (29). Although temsirolimus is universally recommended as the standard in this setting, vascular endothelial growth factor receptor (VEGFR)-TKIs are more commonly used (30), representing the most important deviation from guidelines in real-world (Figure 1).

ic. Duration of first-line therapy

Real-world evidence suggest that 'treatment holidays' can be safely offered in the case of successful first-line therapy, especially when complete remission (with or without surgery) is achieved. This practice is widely used in everyday clinical practice but is not supported by strong evidence and further complicates the development of guidelines in this setting (31, 32).

### ii. Second-line treatment

Targeting the VEGF pathway is the main therapeutic target for the most untreated patients with mRCC. However, most patients will experience progression after a median time of 9–11 months. Until now, disease progression can neither be satisfactorily defined by the existing RECIST criteria nor be accurately predicted. A percentage of patients with (ill-defined) 'slow progression' according to RECIST criteria may continue on the same regimen, especially in the absence of symptomatic disease.

Most patients who progress will require change of therapy. The treatment of relapsed disease represents the area of the most significant progress in mRCC management in the recent years. Three randomised trials established new standards for therapy after VEGFR-TKI failure: the immune checkpoint inhibitor, nivolumab, and the two multiple TKIs, cabozantinib and lenvatinib (the latter in combination with everolimus), have improved OS over everolimus in this setting (33-35). Consequently, everolimus is not recommended as second-line standard anymore, whilst the role of the other (until recently) second-line standard, axitinib, remains undefined (Figure 1).

### iii. Third-line treatment

Beyond second-line treatment, enrolment in clinical trials should be offered. However, with the emergence of the new standards in second line, several effective options exist.

In patients already treated with two TKIs, nivolumab, cabozantinib or lenvatinib + everolimus can be used [II, A]. If these drugs are not available, everolimus remains the standard option [II, B].

In patients previously treated with one TKI and nivolumab, the recommendation is cabozantinib, if available [V, A]. In the absence of cabozantinib, either everolimus or axitinib can be used [IV, C] (9, 36).

In patients previously treated with VEGF-targeted therapy and an mTOR inhibitor, sorafenib [II, B], has shown activity (37). Finally, a TKI not previously used or re-challenged with a previously effective TKI can be considered as an option in fit patients who have been exposed to multiple lines of therapy [IV, B] (Figure 1) (9).

### iv. Treatment of metastatic non-clear cell RCC

Data focused specifically on these tumours are scarce. In addition, the diverse molecular profile of the different histological subtypes makes treatment choice even more complicated. For these patients, enrolment in clinical trials should be offered, if possible. In the only available randomised (phase II) studies, sunitinib showed a trend for superiority over everolimus and it is considered by most guidelines as the treatment of choice. Non-comparative studies have also suggested that patients with non-clear-cell histology may benefit from treatment with everolimus [III, B], sorafenib, pazopanib or temsirolimus [III, B] (Figure 1) (38-40).

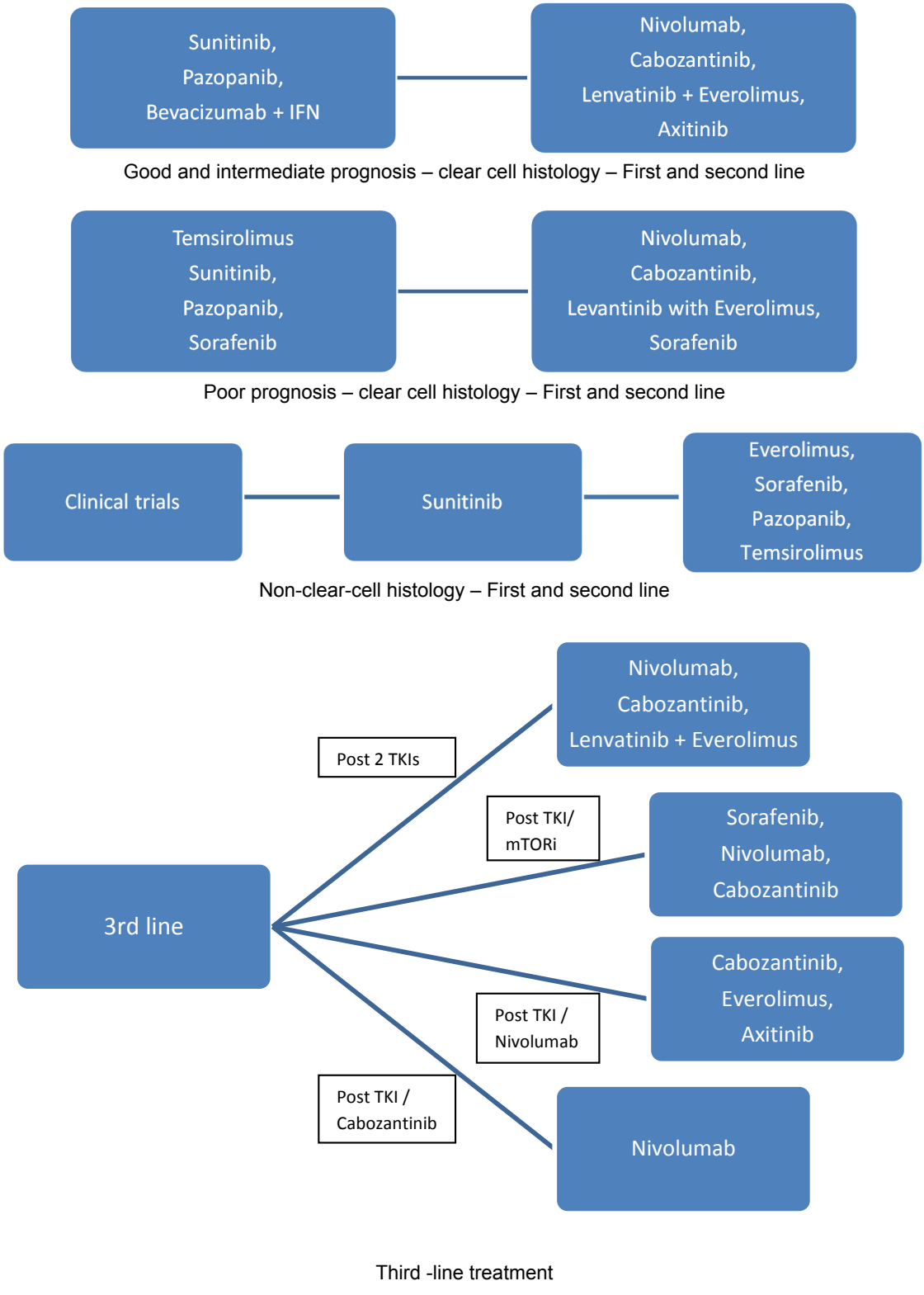


**Figure 1.** Therapeutic algorithm of renal cell carcinoma.

## Conclusions

RCC systemic treatment has changed dramatically in the recent years. New agents targeting several pathways such as the VEGF or the mTOR pathways or inhibiting the interaction of the PD 1 receptor with its ligand have offered new efficient options in our therapeutic armamentarium. However, the respective CPGs/experts recommendations change continuously, thus making the selection of the appropriate therapy somewhat problematic, especially for community oncologists (9, 11).

Our review identified differences amongst the selected papers. Cultural and economic differences and differences in the availability of active agents, which exist amongst different societies publishing guidelines, complicate therapeutic decisions. Homogenisation of existing guidelines remains, therefore, an important unmet need. Every effort trying to uniform clinical practice in medical oncology represents an essential effort towards the optimisation of cancer care. This is an effort that should be continued both at national as well as at international level. In addition, areas of discrepancies depict areas of research and translational work that demands the collaboration of clinical oncologists and basic scientists.

Our review underlined that multimodality approach and treatment at specialising centres (taking into consideration the low incidence of RCC) can ensure that patients with mRCC will get maximum benefit from the available treatment options. In addition, several effective agents are now available. The number of these options far exceeds the lines of therapy, for which guidelines are available. Therefore, individualisation of treatment remains an important element of every practice. In addition, the diversity of the classes of these changes results in a wide spectrum of side effects, distinctly different from those of cytotoxic chemotherapy and covering many fields of internal medicine. Adequate experience of treating physicians with novel agents will ensure optimal use without unnecessary treatment delays or dose modifications. Data regarding certain issues, such as optimal duration of therapy in responding patients, re-challenge with already used agents and optimal sequence of available agents, are unlikely to be fully answered by clinical trials. This underlines the importance of generating real-world evidence to guide therapeutic decisions.

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