Therapeutic approaches in clear cell and non-clear cell renal cell carcinoma

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Renal cell carcinoma accounts for 2.4% of all malignancies worldwide diagnosed with 338,000 estimated new cases globally in 2012. In the last decade, the therapeutic landscape for renal cell carcinoma patients has changed tremendously. In this review, we will summarise the treatment options currently available for clear-cell localised, advanced and metastatic renal cell carcinoma; as stated in the ESMO clinical practice guidelines, the EAU guidelines and the NCCN guidelines. Furthermore we will discuss the recommended therapies in patients diagnosed with non-clear cell tumours.

(Belg J Med Oncol 2016;10(7):256-262)

Introduction

Renal cell carcinoma (RCC) accounts for 2.4% of all malignancies worldwide diagnosed with 338,000 estimated new cases globally in 2012. In Europe 114,000 patients were diagnosed with RCC in 2012 of which 1,660 in Belgium.[1-3] This malignancy is most commonly present in men, as 64% of Belgian patients diagnosed in 2012 were male.[3] With an increasing incidence and associated mortality of RCC over the past several years, clear guidelines on diagnosis and treatment are of the utmost importance.

Diagnosis and classification of renal cell carcinoma

Diagnosis of RCC is performed through combination of physical examination, laboratory examination and imaging. Due to the improved techniques available; such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI); the number of (incidental) detected renal tumours has significantly increased which has a profound effect on the treatment option.

Determining the morphology of the tumour is also an important assessment in order to choose the right therapy for each patient. A new RCC classification was reported in 2013 by *Srigley et al*. Clear-cell RCC accounts for 70-85% of the cases making it the most abundant variant of RCC. The main subtypes of non-clear cell RCC include papillary, chromophobe, collecting duct, unclassified RCC and translocation carcinomas in which papillary and chromophobe RCC are the most frequently found subtypes (7-15% and 5-10% of all cases, respectively).[4] Each morphological variant corresponds with a specific molecular pathway which could indicate which therapies are the best option for each patient.[5]

Staging and risk assessment of renal cell carcinoma

In order to stage RCC, the Union for International Cancer Control tumour-node-metastasis staging system should be used (*Table 1*).[6] Risk assessment, needed to determine prognostic information, is dependent on the localisation of the disease.

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: renal cell carcinoma, surgery, systemic therapy.

Acknowledgements: This publication is a joined publication between *Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine* and *The Belgian Journal of Medical Oncology.*

Table 1. Staging of RCC according to TNM classification.

T	Primary tumour		
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney		
T1a	Tumour ≤ 4.0 cm		
T1b	Tumour > 4.0 cm but ≤ 7.0 cm		
T2	Tumour > 7.0 cm in greatest dimension, limited to the kidney		
T2a	Tumour > 7 cm but ≤ 10 cm		
T2b	Tumour > 10 cm, limited to the kidney		
T3	Tumour extends to major veins or peri-nephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades peri-renal and/or renal sinus fat (peri-pelvic) but not beyond Gerota's fascia		
T3b	Tumour grossly extends into the vena cava below the diaphragm		
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota's 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 metastases		
cM0	Clinically no distant metastasis		
cM1	Clinically distant metastasis		
pM1	Pathologically proven distant metastasis, e.g. needle biopsy		
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1–3 T4	Any N1 Any	M0 M0 M0
Stage IV	Any	Any	M1

Table adapted from Escudier et al.[5]

In localised RCC, two models exist to determine the risk of progression: the stage, size grade and necrosis score and the University of California Los Angeles Integrated staging system.[7,8] The former works favourably for patients with localised RCC while the latter also provides prognostic information for mRCC.[5]

On the other hand, the Memorial Sloan Kettering Cancer Centre score or Motzer score is the standard prognostic model used in patients with advanced and/or metastatic disease.[9] Due to the use of targeted therapies, this prognostic model was updated and validated in 2009 and renamed the International Metastatic RCC Database Consortium criteria or Heng criteria. In this model, patients are stratified into three risk categories: favourable risk (no risk factors), intermediate risk (one or two risk factors) and poor risk (three or more risk factors). Favourable risk patients have a 2-year overall survival (OS) of 75%, intermediate risk patients have a

Table 2. The International Metastatic RCC Database Consortium criteria.

Risk factor	Limit used in the risk model
Karnofsky performance status	Lower than 80%
Haemoglobin	Lower than normal lower limit
Time from diagnosis to treatment	Less than 1 year
Corrected calcium	Higher than the normal upper limit (10 mg/dL)
Platelets	Higher than the normal upper limit
Neutrophils	Higher than the normal upper limit

2-year OS of 53%, and poor risk patients have a 2-year OS of 7%.[10] Risk factors used to assess the risk to progression are listed in *Table 2*. Risk assessment is very important since the choice of first line treatment could depend on these factors.

Management of localised renal cell carcinoma

For localised disease, treatment given to the patient depends on the staging of the renal tumour.

Localised renal cell carcinoma

In patients with T1 tumours, surgical resection by means of partial nephrectomy is the recommended treatment option. Surgeons can chose to perform the partial nephrectomy through open surgery, laparoscopic surgery or through a coelioscopic robot-assisted approach. One should also strive for partial nephrectomy if the patient has bilateral tumours, a compromised renal function, a solitary kidney or familial RCC. If for any reason partial nephrectomy would not be possible, a laparoscopic radical nephrectomy should be conducted.[11] It has however been demonstrated that treatment of early stage RCC with partial rather than radical nephrectomy was associated with improved survival.[12] Next, in case of cortical tumours, with a maximum diameter of three centimetres, radio frequency or cryoablation treatments are an option. This especially in patients with high surgical risk, bilateral tumours, a compromised renal function, or a solitary kidney. These therapeutic options have shown a significant prolongation in disease free survival and a trend towards longer OS although these techniques are associated with a higher local recurrence rate than conventional surgery.[13,14] An important remark has to be made for elderly patients and those with competing health risks. Due to comorbidities of surgical and ablative treatments and the shorter life expectancy in this population, the ESMO guidelines recommend active surveillance in these patients if only presented with small renal masses.[5,15] The EAU guidelines on the other hand also approve the use of ablative therapy in this patient population.[16,17]

In patients with T2 tumours, the only preferable treatment option is laparoscopic radical nephrectomy.[5] In contrast, the EAU guidelines report that also in T2 tumours open, laparoscopic or coelioscopic robot-assisted approaches are usable. Which surgical technique is used, should therefore depend entirely on the expertise and the skills of the surgeon.[5,18]

Locally advanced renal cell carcinoma

For patients with T3 and T4 tumours where the tumour volume extend into the inferior vena cava, open radical nephrectomy has to be performed, although a laparoscopic approach might be considered. It has been reported that radical nephrectomy can lead to an increased risk for chronic kidney disease and is associated with increased risks of cardiovascular morbidity and mortality.[19-21] In case of adrenal and/or lymph node invasion on CT or palpable/visible adenopathy at time of surgery, an adrenalectomy and/or extensive lymph node dissection is recommended.[22] The beneficial use of adjuvant therapies in patients with locally advanced RCC is currently explored.[5] However, the initial results from the ASSURE trial comparing adjuvant sunitinib and sorafenib with placebo did not show any benefit in disease free survival or OS.[23] Neo-adjuvant approach in this setting is still experimental and needs further assessment in clinical trials.

Management of advanced/metastatic renal cell carcinoma

About 30% of all RCC patients present with metastatic disease at time of diagnosis.[24] In metastatic disease, the

use of targeted therapies and immune checkpoint inhibitors are the recommended therapy. The different types of targeted agents will be discussed later on. However, surgery is still applicable in these patients, both presenting with clear-cell and non-clear cell morphology.

Surgery

Cytoreductive nephrectomy before the start of any systemic therapy is generally recommended in patients with a potentially surgically resectable primary tumour mass. It was previously demonstrated in the era of interferon immunotherapy that cytoreductive nephrectomy harboured an OS benefit in mRCC patients.[25,26] A phase III trial (CARMENA) is currently ongoing to assess the value of cytoreductive nephrectomy in the era of targeted agents. Recently, two retrospective analyses reported the same effect for cytoreductive nephrectomy in mRCC patients treated with various targeted agents already indicating that this approach is still recommended provided that patients have good performance status, good prognostic features, large primary tumours and limited number of metastases.[27,28]

Also metastasectomy can be considered. RCC frequently leads to synchronous or metachronous metastases in lung, bone, liver, and brain.[29,30] Removal of these metastases is only performed in patients with slow evolving disease and solitary or few easy accessible pulmonary or abdominal metastases, with long disease free survival after nephrectomy, or in case of a partial response of metastases to targeted therapy or immunotherapy.[5] Retrospective studies reported that patients with complete metastasectomy have better OS and quality-of-life compared to incomplete or no metastasectomy.[31-36] Another retrospective study reported that patients with low tumour burden after administration of targeted agents exhibit longer disease free survival with significant time off targeted therapy following metastasectomy.[37] These studies point out the usefulness of metastasectomy. However, longer follow up of this cohort is needed to determine the effect on OS and before any recommendation regarding this multimodality approach in patients with mRCC can be made.

Lastly, palliative nephrectomy in metastatic disease is only considered when the patient has symptoms related to the primary tumour site and if the patient is fit enough to undergo surgery.[38]

Systemic therapies

Systemic treatment is strongly dependent on the risk stratification according to the Heng criteria (*Table 2*) and previously administered therapies. The therapeutic landscape for patients presenting with clear-cell mRCC is well documented, while this is scarce for patients with non clear-cell mRCC. An overview of the current therapeutic regimens for mRCC is given in *Table 3*.

First-line treatment of clear-cell mRCC patients

To select the appropriate first-line therapy, a distinction has to be made between good/intermediate and poor prognosis patients.

Patients presenting with good/intermediate risk to progression have multiple options that are possible in first-line treatment of their illness. Firstly, a period of active observation has to be considered without substantial risk for poorer outcome after crossing over to an active agent. This is especially true in patients with limited tumour burden.[5] Once patients require targeted therapy, three targeted agents are available which have proven efficacy in treatment-naïve mRCC patients: the humanised anti-VEGF monoclonal antibody bevacizumab (in combination with interferon-α), or the tyrosine kinase inhibitors (TKI) sunitinib and pazopanib. All three targeted agents were tested in phase III trials and have shown a comparable improvement in objective response rate and progression-free survival (PFS) versus interferon-α or placebo (median PFS ranging from 8.5 to 11.1 months) but only sunitinib showed almost negligible benefit in OS while bevacizumab and pazopanib did not.[39-46] Furthermore, the COMPARZ study demonstrated non-inferiority of pazopanib versus sunitinib based on PFS (8.4 versus 9.5 months) and OS (28.4 versus 29.3 months).[47,48] Both therapies demonstrated class-specific toxicities, such as fatigue and hand-foot syndrome, that have to be monitored when patients are treated with one of these agents in first-line.[47,49] The same caution holds true for bevacizumab as the American CALGB90206 study reported more toxicity than was observed in the European AVOREN trial.[39,44] Next, also sorafenib and high-dose interleukin-2 remain therapeutic options in these patients while interferon-α in monotherapy is no longer recommended.[5]

In poor prognosis mRCC patients with relapsed or medically unresectable RCC, the inhibitor of mammalian target of rapamycin (mTOR) temsirolimus was the only drug with level I evidence of efficacy with improved PFS and OS compared to interferon-α. Note that the six risk factors to determine poor prognosis patients in this clinical trial were different from the current Heng criteria: less than one year between diagnosis and treatment, Karnofsky performance status lower than 70%,

haemoglobin lower than normal limit, corrected calcium higher than 10 mg/dL, lactate dehydrogenase greater than 1.5 times the normal upper limit, and metastasis to one or more organ sites.[50] Further analysis have also demonstrated that the TKIs are viable options in this patient population. Although the consideration has to be made that, depending on the patient, only best supportive care is suitable.[5]

Second-line treatment of clear-cell mRCC patients

Second-line therapy is dependent on the targeted agent administered as first-line treatment.

Patients that received prior cytokine therapy (in ever decreasing numbers), can be treated with a TKI, namely sunitinib, sorafenib or pazopanib. Phase III studies demonstrated PFS of respectively 8.3 months, 5.5 months and 7.4 months while no benefit in OS was seen.[42,46,51-53]

More recent, the second-generation TKI axitinib was proven to be useful as second-line therapy in mRCC patients. Axitinib achieved longer PFS (12.1 months) versus sorafenib but not OS with comparable safety profile to other first-generation TKIs.[54,55]

For patients that progressed after a first-line TKI, the therapeutic landscape has changed drastically in the last months. Before September 2015, these patients were treated with either axitinib (AXIS trial) or the mTOR inhibitor everolimus (RECORD-1 trial). Both exhibited superior PFS (4.8 and 4.9 months) over sorafenib and placebo, respectively, but again failed to have a significant impact on OS.[54-56] Also, despite its PFS inferiority to axitinib, sorafenib was able to demonstrate longer OS in this patient cohort progressing on sunitinib compared to the mTOR inhibitor temsirolimus and might therefore still remain a treatment option in these patients although use of axitinib is preferred.[54,57] Note hereby is that in multiple studies OS is dependent on the risk stratification according to the Heng prognostic model and on other parameters such as which prior TKI was administered.

However, recently two new drugs became available for treatment of mRCC, namely nivolumab and cabozantinib. Both were assessed in a phase III trial and efficacy was compared to everolimus.

Nivolumab, an immune check-point inhibitor used in second- or third-line, showed comparable PFS (4.6 versus 4.4 months) but increased OS (25.0 versus 21.8 months) to everolimus with less treatment-related grade 3/4 adverse events reported after nivolumab administration. Further subgroup analyses showed no difference between nivolumab administered in patients with less than 1% PD-L1 expression compared to patients with ≥1% PD-L1 expression. Although survival was slightly longer in patients with increased PD-L1 expression, these data do not support the use of PD-L1 expression as a marker for treatment benefit in mRCC which highlights the need for better treatment response biomarkers.[58] Next in the METEOR trial; the third-generation TKI cabozantinib, administered in second- or further-line, proved superior PFS compared to everolimus (7.4 versus 3.8 months). Also a trend towards longer OS in the cabozantinib arm was found, although it did not yet reach the boundary for significance. Investigators also reported 60% dose reduction in patients that received cabozantinib, compared to 25% for everolimus, pointing out the necessity for careful adverse event monitoring in patients treated with cabozantinib.[59]

The question whether to give axitinib, cabozantinib or nivolumab as second-line targeted agents raises the needed for a phase III trial comparing the efficacy of these three drugs in a second-line setting.

Third-line treatment of clear-cell mRCC patients

Recommendations for third-line therapy of clear-cell mRCC patients depend greatly on regimens received in prior treatments. Three possible treatment scenarios exist for these patients.

Firstly, in patients whom progressed after two lines of TKIs (or bevacizumab in first-line and a TKI in second-line), the mTOR inhibitor everolimus seems to be the best treatment option.[5] However due to the recent findings concerning nivolumab and cabozantinib, these two new drugs are also a therapeutic option in these patients.[58,59]

Secondly, in patients whom progressed after one line of VEGF-targeted therapy and an mTOR inhibitor, treatment with VEGF-targeted therapy is possible. Clinical trials involving sorafenib have shown some efficacy in this patient population with a median PFS of 3.6 months.[60] Further research is also ongoing in TKI-rechallenge in this patient cohort. One study demonstrated that TKI-rechallenge was a viable option with better response to first TKI and time to rechallenge as predictive prognostic factors for PFS and OS.[61] Further research is however required before TKI-rechallenge can be recommended as therapeutic option in third-line treatment of mRCC patients. Also due to the upcoming use of nivolumab, the number of patients in this particular cohort will only decrease.

Therefore, the third patient population are those whom progressed following initial VEGF-targeted agent regi-

Table 3. Systemic treatment options.

Patient population		Treatment recommendation	
		Standard	Optional
Clear-cell First-line	Good and intermediate risk	Bevacizumab + interferon α Sunitinib Pazopanib	High dose interleukin 2 Sorafenib
	Poor risk	Temsirolimus	Sunitinib Sorafenib
Clear-cell Second-line	Post cytokines	Sunitinib Sorafenib Pazopanib Axitinib	
	Post TKI	Nivolumab Cabozantinib	Axitinib Everolimus Sorafenib
Clear-cell Third-line	Post 2 TKIs	Nivolumab Cabozantinib	Everolimus
	Post TKI and mTOR	Sorafenib	TKI rechallenge
	Post TKI and nivolumab	Axitinib Cabozantinib Everolimus	
Non clear-cell		Sunitinib Sorafenib Temsirolimus	

mens and consequent immunotherapy with nivolumab administration. These patients may benefit from treatment with an alternative targeted agent such as axitinib or cabozantinib, which are best choice as third-line therapy.[54,55,59] Everolimus, previously given as second-line therapies, also remains a viable third-line option. Additionally, referral to clinical trial centres in which these patients can participate in clinical trials to further enhance our knowledge of RCC remains important.

Systemic treatment of non clear-cell mRCC patients

Most phase III trials limit the accrual to clear-cell mRCC patients and therefore no prospective randomised phase III clinical trials are performed in patients with non clear-cell mRCC. Therefore, the only available data for drug efficacy in these patients is derived from subgroup analyses of other studies or retrospective analyses. One review retrospectively analysed that objective response rate to target therapy, PFS and OS were significant lesser in non-clear cell RCC compared with clear cell RCC.[62] Recently two phase II trials assessed the efficacy of sunitinib and everolimus in this patient cohort (ASPEN and ESPN trial) reporting that sunitinib is favoured over everolimus due to prolonged OS 8.3 versus 5.6 months and not reached versus 10.5 months, respectively.[63,64] Furthermore, the RECORD-3 trial indicated that patients with non-clear cell RCC benefit more from initial treatment with sunitinib followed by everolimus as second-line targeted agent and not vice versa as proven by the increased PFS (25.8 versus 21.1 months).[65] Due to the limited data available to date on the treatment of non clear-cell RCC; sunitinib, sorafenib and temsirolimus are the recommended treatment options for this patient cohort. Larger prospective trails are of the utmost importance to assess which therapy is effective in these patients. An important consideration is to determine which molecular pathway (e.g. mTOR or cMet-RAF-MEK-ERK pathway) is altered and consequently which targeted agent could have efficacy in this cohort.[66]

Radiotherapy

RCC is considered to be a radioresistant tumour. However, if a patient should present with unresectable local or recurrent disease high fraction dose stereotactic body radiotherapy might also be an alternative therapeutic approach. Further research on the matter is however needed.[67] Next, it has already been proven that radiotherapy knows no role as adjuvant or neo-ad-

Key messages for clinical practice

1. Morphology of the tumour predicts which therapy is best treatment option.
2. Surgery remains the preferred therapeutic option in localised renal cell carcinoma patients.
3. Risk assessment according to Heng criteria indicated best first-line therapy in mRCC patients.
4. Tremendous changes in targeted agents allow for new therapeutic options in second-line therapy, such as administration of the TKI cabozantinib and PD-1 inhibitor nivolumab.
5. No clear treatment regimen exists for non clear-cell mRCC patients which highlights the need for further research in this patient cohort.

juvant therapy in local management of RCC based on negative results and high morbidity.[5]

Radiotherapy can also be used in the management of metastatic disease where it can provide a valid local treatment alternative to surgery. Depending on the site of the metastasis, conventional radiotherapy or stereotactic body radiotherapy should be applied. In case of brain metastasis, radiotherapy modalities include whole-brain radiotherapy or stereotactic radiosurgery.[68,69]

Finally, radiotherapy can be effective in a palliative setting and to prevent progression of metastases in critical sites such as bone and brain. In the latter, whole brain radiotherapy (20-30 Gy in 4-10 fractions) proved effective in local control of brain metastatic disease.[5]

Follow-up of patients

No unilateral follow-up regimen exists for either local or advanced/metastatic RCC. Follow-up is mostly depended on the type of therapy administered, risk factors and possibility of late relapse.

In case of local RCC, it is advised to perform regular CT/MRI scans to determine recurrence of the disease. The rates of local recurrence for smaller versus larger volume tumours after partial nephrectomy are 1.4-2% versus 10%.[70-72] Observation in these patients is therefore vital. A possible follow-up regimen could be imaging within six months for two years, with subsequent imaging performed annually thereafter.

On the other hand, in mRCC it is recommended to perform CT/MRI follow-up scans every two to four months to determine response and resistance on the targeted agent administered. Bi-weekly biochemical evaluations are also usable to evaluate adverse events, especially at treatment initiation.

Conclusions

The therapeutic landscape for RCC has shifted during the last decade. For local RCC the recommended treatment remains partial or radical nephrectomy by means of open surgery, laparoscopic surgery or through a coelioscopic robot-assisted approach; depending on the patient's tumour volume and risk factors. For advanced and metastatic RCC a whole variety of targeted agents is manufactured such as anti-VEGF antibodies, TKIs targeting different pathways, mTOR pathway inhibitors and immune check-point inhibitors. Comparative studies have illustrated which drugs are usable for first-, second- or further-line treatment. Most importantly are the recently reported drugs cabozantinib and nivolumab, which have shown a profound effect on PFS and OS in pretreated patients with clear cell RCC. Further comparative research is however warranted to determine which of these drugs is best suited as second-line targeted agent and if immunotherapy regimen can play a role in first-line disease. Finally, data on effective therapies in patients with non clear-cell RCC are scanty. There is an urgent need for phase II and III trials in this patient cohort to determine the best treatment option for these patients.

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For the complete list of references we refer to the electronic version of this article which can be downloaded from www.ariez.com.

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