Provisional chapter

Medical Management of Renal Cell Cancer

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Additional information is available at the end of the chapter

Abstract

In 2018, there were an estimated 400,000 new cases of renal cell carcinoma (RCC) worldwide—with 64,000 cases in the United States and 12,600 in the United Kingdom (UK). The medical management of RCC is an integral part of treatment as between one-quarter and one-third of patients will present with metastatic disease. There has been a rapid evolution of targeted and novel treatments for RCC over the last two decades. This chapter explores the biology of renal cell carcinoma and current treatment strategies.

Keywords: renal cell carcinoma, metastatic renal cell carcinoma, tyrosine kinase inhibitor, targeted treatment, risk stratification

1. Introduction

Renal cell carcinoma (RCC) is the fourteenth most common cancer internationally [1]. There were estimated to be around 400,000 new cases worldwide in 2018, with 64,000 cases in the United States of America and 12,600 in the United Kingdom (UK) [1–3]. The increasing incidence of RCC worldwide over the past three decades has been attributed to increasing obesity, increasing height, and increasing tobacco smoking [4, 5]. RCC is also noted to be twice as prevalent in men than women [4]. Overall, 25–30% of patients have locally advanced RCC or metastatic disease at presentation [6], although in the UK, the proportion is 40% [3]. Systemic therapy and, in selected cases, surgical intervention has an important role in the management of metastatic RCC. The landscape of available systemic treatment options has developed rapidly over the past 10 years with a wide variety of systemic strategies now being employed. This chapter will review current therapies in the metastatic setting, consider the evidence for adjuvant systemic treatment, as well as look at some of the promising new therapies that are likely to emerge in the coming years.

2. Histological subtypes

Renal cell carcinoma is divided into several histological subtypes, of which the most common is clear cell renal cell carcinoma (ccRCC), accounting for approximately three-quarters of all kidney cancers [7]. Clear cell RCC originates from the epithelium of the proximal convoluted tubules. Most are sporadic, but there is a strong familial connection with those with a first-degree relative more likely to be effected and around 5% are associated with hereditary conditions such as Von Hippel–Lindau disease, tuberous sclerosis, and adult polycystic disease. The next most prevalent histological subtypes are papillary (10%) and chromophobe (5%) [7]. These three histological subtypes make up 90% of renal cell carcinomas and are also most common in patients over the age of 50 years. Other rarer subtypes, such as medullary and Xp11 translocation, are typically seen in younger people. A better understanding of the genetic drivers for renal cell carcinoma has led to the development of targeted systemic agents and revolutionised the metastatic treatment landscape.

3. Staging and risk stratification in renal cell carcinoma

Staging for RCC is based on the TNM 8 classification and staging groups [8]. The staging takes into account the size and loco-regional extent of the tumour in addition to lymph node and distant metastatic spread [9]. **Table 1** illustrates this is in further detail.

In metastatic renal cell carcinoma, the decision to treat and, more importantly the choice of initial treatment, is based on risk stratification of the patients into three groups. The choice of initial systemic therapy in metastatic RCC may be informed by risk stratification using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model [10–12].

The six adverse risk factors in the IMDC model are as follows [11]:

- time from original diagnosis to initiation of targeted therapy <1 year;
- Karnofsky performance score < 80;
- haemoglobin < lower limit of normal;
- neutrophil > upper limit of normal;
- platelet > upper limit of normal; and
- serum calcium > upper limit of normal.

Patients with none of these risk factors are considered to be in the favourable-risk group, those with one or two are considered to be in the intermediate-risk group, and those with three or more risk factors are considered to be in the poor-risk group. These groups correlate with median overall survival: 43.2 months in the favourable-risk group, 22.5 months in the

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

Prognostic groups

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

Table 1. TNM staging of renal cell carcinoma [8].

intermediate-risk group, and 7.8 months in the poor-risk group [11]. Oncologists use this, or similar risk stratification, to decide upon the most appropriate treatment from the systemic options available. The advantage of the IMDC-model-based risk stratification is that it has been validated in both clear cell and non-clear cell histopathological groups and after first line and subsequent lines of treatment [11–14].

4. Metastatic systemic treatment options

4.1. Overview

The treatment objective in metastatic cancer is different to the primary setting. Treatment is palliative and the benefits, in terms of progression-free and overall survival, must be carefully balanced against the quality of life of the patient and potential side effects that any treatment may cause. The evolution of therapies has led to an increase in the median overall survival in metastatic RCC to beyond 2 years, and is likely to increase further as more treatments are developed [15–17].

4.2. Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) are a mainstay of targeted treatment in renal cell carcinoma. The drugs are designed to inhibit tyrosine kinases and enzymes, which themselves activate pathways of growth within the tumour cell. There are many different targets for TKIs, and in renal cell carcinoma, agents are targeted at vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and the mammalian target of rapamycin (mTOR). Over half of patients have abnormalities in the von Hippel Lindau (VHL) gene, which leads to an increased expression of hypoxia inducible factors (HIF) [18]. In turn, accumulation of HIF switches on hypoxia-inducible genes such as VEGF and PDGF, and further downstream, mTOR. Expression of VEGF and mTOR drives tumour growth and angiogenesis [18].

The most commonly used TKIs employing VEGF are sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib, and employing mTOR everolimus and temsirolimus. The action of these agents at a cellular level is illustrated in **Image 1**. Multiple clinical trials have shown the efficacy of these agents in RCC and are summarised in **Table 2**. The most commonly observed side effects for TKI therapy are rash, diarrhoea, hypertension, fatigue, and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) [19–26].

Bevacizumab has also been used in renal cell cancer. Bevacizumab is a monoclonal antibody, which blockades the VEGF ligand, binding with VEGF-A. Initial trials of bevacizumab versus interferon alpha (IFN-**α**) showed a progression-free survival (PFS) benefit, but no OS benefit as crossover was allowed on progression [27]. When used in combination, IFN-**α** bevacizumab showed a higher response rate and PFS, but again OS was not demonstrated, and there was also significant toxicity [27]. Although it remains a first-line treatment option, in practice, due to the high toxicity of the treatment and efficacy of other first-line treatment options, it is rarely used. Trials also explored the combination of bevacizumab and mTOR inhibitors; however, no clinical benefit was determined and toxicity proved to be a limiting factor [28–31].

4.3. Immunotherapy

One of the most exciting areas of development in systemic therapy has been immunotherapy. The purpose of immunotherapy is to unmask the cancer to the body's own immune system. Historically, IFN-**α** has been used in RCC with a modest effect, and overall response rates

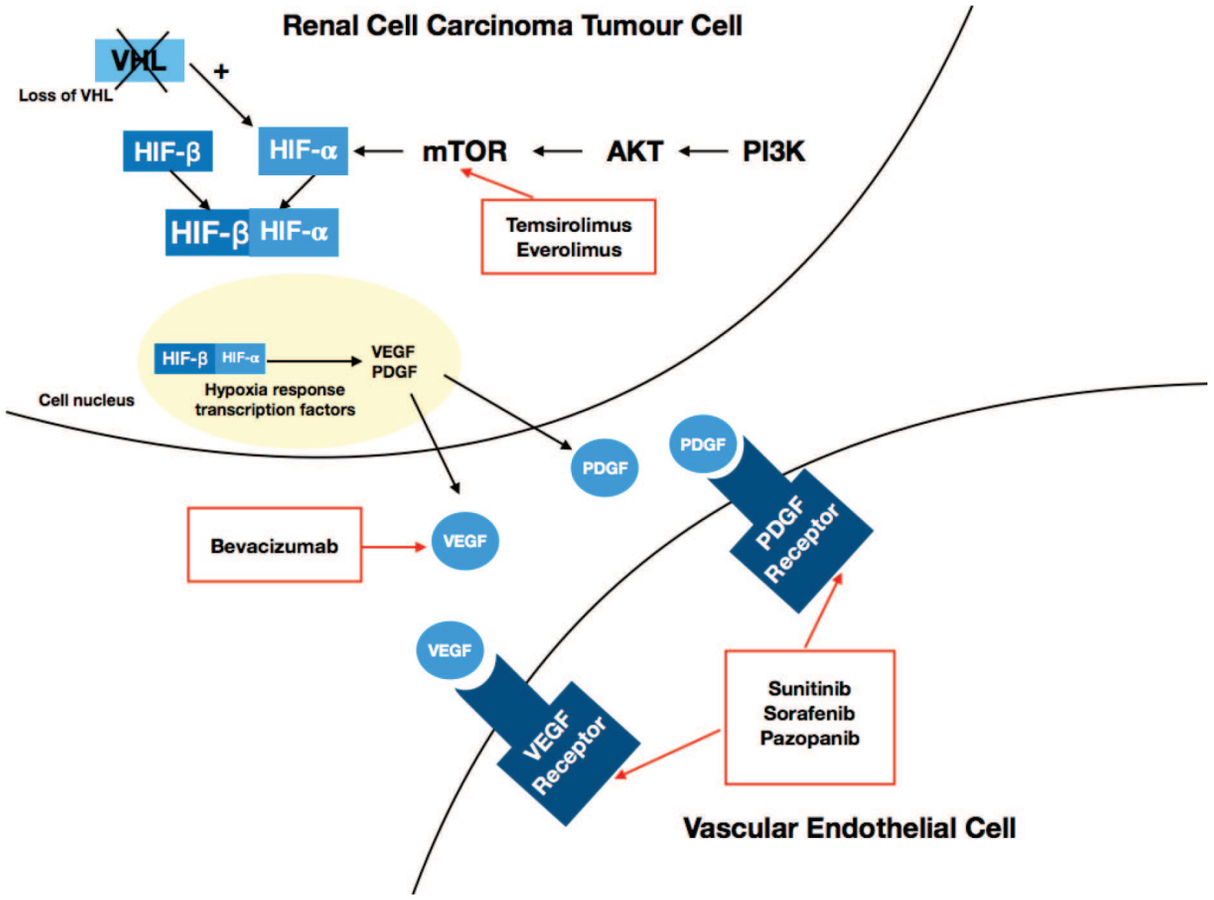

Image 1. A graphic showing how loss of the von Hippel Lindau (VHL) protein results in up regulation of hypoxia induced factors (HIF) and in turn vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) and the actions of targeted therapies.

(ORR) were around 10–15% [17]. More recently, studies have investigated Nivolumab, a fully human IgG4 anti-programmed cell death-1 antibody (anti-PD-1) that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2 and RCC [17, 32]. In the CheckMate 025 study, patients were randomised to receive either nivolumab or everolimus, OS was 25 vs. 19 months in favour of nivolumab, and less grade 3 or 4 toxicity was seen in the nivolumab arm [33]. This trial led to the FDA approval of nivolumab for RCC in 2015 with European approval quickly following.

After the success of single agent immunotherapy, attention turned to the investigation of combination immunotherapy in metastatic RCC. Here, nivolumab was used in combination with a second agent ipilimumab, a monoclonal antibody, which targets cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). CheckMate 214 trial randomised nivolumab and ipilimumab against sunitinib. Median OS was not reached in the combination immunotherapy arm compared to the immunotherapy used for 26 months with sunitinib, and PFS was 11.6 vs. 8.4 months in favour of combination immunotherapy [16].

The mechanism of action of the various immunotherapy agents can be complex. In short, they upregulate the body's own immune response against the 'foreign' tumour cells. For those

Trial	Drug	Number of patients (n)	Line of treatment	Disease-free survival (DFS) (months)	Overall survival (OS) (months)
Motzer et al.: sunitinib versus interferon alpha in metastatic renal cell carcinoma [19]	Sunitinib versus interferon alpha	750	First line	Sunitinib 11 interferon alpha 5 HR 0.42 p < 0.001	Sunitinib 28.7 Interferon alpha 23.7 HR 0.8209 p = 0.051
Sternberg et al.: pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomised phase III trial [20]	Pazopanib versus placebo	435	Treatment naive or cytokine pretreated	Pazopanib 9.2 placebo 4.2 HR 0.46 P < 0.001	Not available
Motzer et al.: pazopanib versus sunitinib in metastatic renal cell carcinoma [21]	Sunitinib versus pazopanib	1110	First line	Sunitinib 9.5 Pazopanib 8.8 HR 1.05	Sunitinib 29.3 Pazopanib 28.4
Hudes et al.: temsirolimus, interferon alpha, or both for advanced renal cell carcinoma [22]	Interferon alpha versus temsirolimus versus temsirolimus plus interferon alpha	626 (poor prognosis)	First line	Interferon alpha 3.1 temsirolimus 5.5 temsirolimus plus interferon alpha 4.7	Interferon alpha 7.3 temsirolimus 10.9 temsirolimus plus interferon alpha 8.4
Escudier et al.: sorafenib in advanced clear cell renal cell carcinoma [23]	Sorafenib versus placebo	903	First line	Sorafenib 5.5 placebo 2.8 HR 0.44 P < 0.01	Sorafenib not reached placebo not reached HR 0.72 P < 0.001
Rini et al.: comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial [24]	Axitinib versus sorafenib	723	Second line	Axitinib 6.7 Sorafenib 4.7	Not available
Choueiri et al.: cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial [25]	Cabozantinib versus everolimus	658	Second line or subsequent	Cabozantinib 7.4 everolimus 3.9 HR 0.051 p < 0.0001	Cabozantinib 18.8 everolimus 16.5 HR 0.66 p = 0.00026

Trial	Drug	Number of patients (n)	Line of treatment	Disease-free survival (DFS) (months)	Overall survival (OS) (months)
Armstrong et al.: everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial [26]	Everolimus versus sunitinib	108 (non-clear cell histology)	First line	Everolimus 5.6 Sunitinib 8.3 HR 1.41 p = 0.16	Everolimus 13.2 Sunitinib 31.5 HR1.12 p = 0.60

Table 2. Trials of tyrosine kinase inhibitors in the metastatic renal cancer setting.

who wish for a fuller explanation, the cellular mechanism of the immunotherapy agents is now outlined. In the tumour microenvironment, tumour neoantigens are released by cancer cells. These are captured by antigen presenting cells (APCs). These neoantigens cause the expression of major histocompatibility complexes (MHC) and T-cell receptors (TCRs) on the surface of CD8+ cytotoxic T cells. PD-1 expression is induced. Tumour cells can highly express PD-L1 and PD-L2, which can bind with PD-1 on the T cell and ultimately lead to T-cell exhaustion. Drugs such as nivolumab and pembrolizumab inhibit the interaction of PD-1 with PD-L1 and PD-L2, which results in enhanced T-cell cytotoxicity, increased cytokine, and tumour-associated macrophage activity. Anti-PD-L1 antibody therapies such as atezolizumab, durvalumab and avelumab, specifically target the interaction between PD-L1 and PD-1. Tumour neoantigens also cause peptides bound to MHC II molecules to be presented to CD4+ T helper cells. Through a series of co-stimulatory signals transmitted via CD28 T cells, CTLA-4 is upregulated. The upregulated CTLA-4 competes with CD28 to bind with CD80 and/or CD86 on the APC. The interaction of CTLA-4 with CD80 or CD86 results in inhibitory signalling, which in turn promotes tumour growth. Ipilimumab is an anti-CTLA-4 antibody; thus, it blocks CTLA-4, allowing an enhanced immune response [34]. A pictorial explanation of the mechanism of both CTLA-4 and PD-1 immunotherapy targeted agents is available in **Image 2**.

Immunotherapy has a different safety profile from targeted TKI therapies or standard chemotherapies. Typically, autoimmune reactions are seen that can be varying and at times severe. The most common is diarrhoea and colitis, but pneumonitis and endocrine problems are also observed.

There has also been some investigation in using the combinations of immunotherapy with targeted agents. Nivolumab was paired with pazopanib or sunitinib in the CheckMate 014 trial; however, toxicity was very high with 70% of patients experiencing a grade 3 or 4 toxicity and 25% discontinuing the treatment due to toxicity. This trial has led to caution in combining immunotherapy and TKIs [35] (**Table 3**).

4.4. Sequencing of agents

The natural history of targeted agents in all cancers, and reflected here in RCC, is developing ultimate resistance. Therefore, a patient may undertake several lines of treatment. Both the European Society of Medical Oncology (ESMO) and National Comprehensive Cancer

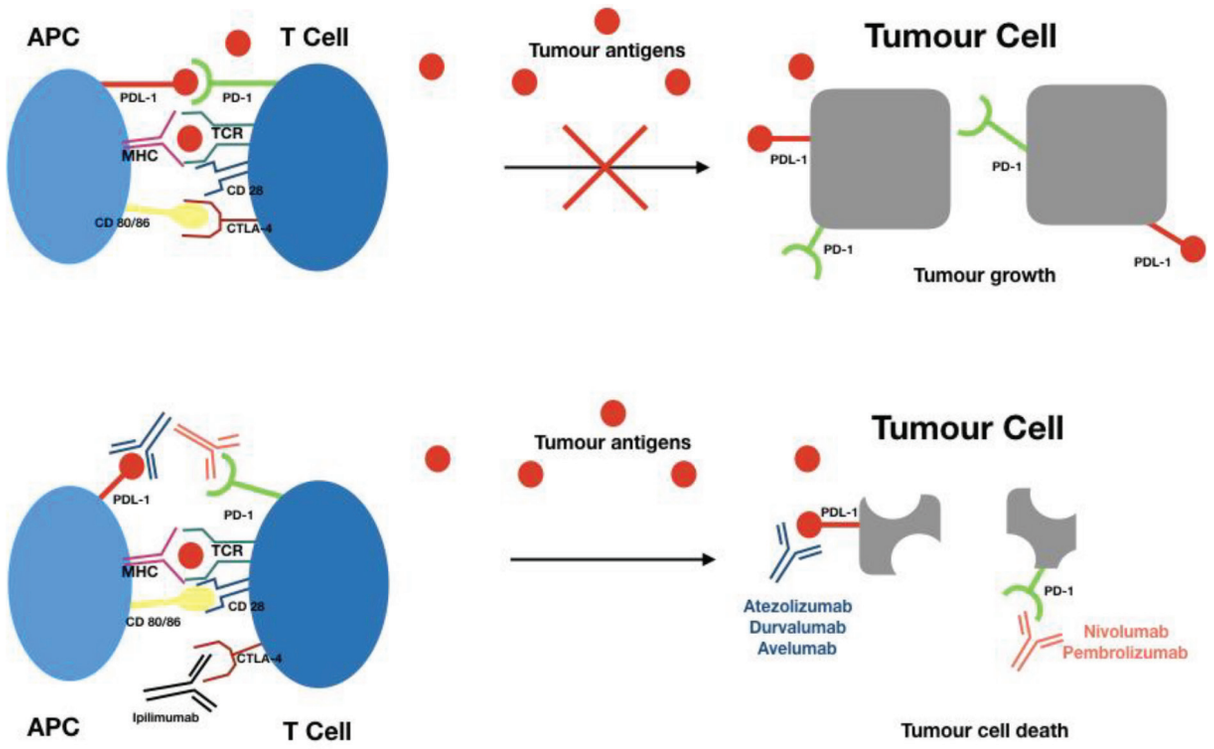

Image 2. Pictorial representation of the mechanism of action of immunotherapy agents.

Trial	Drug	Number of patients (n)	Line of treatment	Progression-free survival (PFS) (months)	Overall survival (OS) (months)
CheckMate 025 Motzer et al. [33]	Nivolumab versus everolimus	823	Second or subsequent	Nivolumab 4.6 Everolimus 4.4 HR 0.88 p = 0.11	Nivolumab 25.0 Everolimus 19.6 HR 0.73 p = 0.002
CheckMate 214 Motzer et al. [16]	Nivolumab plus ipilimumab (nivo+ipi) versus sunitinib	1096	First line	Nivo+ipi 11.6 Sunitinib 8.4	Nivo+ipi-not reached Sunitinib 26.0 18 months of OS rate Nivo+ipi 75% sunitinib 60%
CheckMate 016 Amin et al. [35]	Nivolumab in combination with sunitinib or pazopanib	55	First line	Nivolumab plus sunitinib 12.7 Nivolumab plus pazopanib 7.2	Nivolumab plus sunitinib not reached Nivolumab plus pazopanib 27.9

Table 3. Immunotherapy trials in metastatic renal cell carcinoma.

Network (NCCN) provide up-to-date guidelines advising oncologists of the latest evidence to help determine the most advantageous sequence of agents [36, 37]. At the time of publication, we would suggest a suitable sequence of therapies to be followed: first-line sunitinib or pazopanib (in poor-risk patients temsirolimus), second-line axitinib or nivolumab, with a preference to nivolumab in poor-risk patients, and third-line cabozantinib [36]. In non-cell histology, sunitinib is recommended first line, although few trials have specifically recruited non-clear cell histological subtypes for investigation [26, 36].

We recognise that as new agents are developed and further research is conducted in this field, the advice may change. Another strategy that has been investigated is active surveillance. Patients with indolent metastatic disease may safely remain on surveillance until their disease begins to progress. A cohort study of patients with metastatic RCC on surveillance demonstrated a median time to starting systemic therapy of 14.9 months [38].

5. Cytoreductive nephrectomy in the age of TKI

Historically, cytoreductive nephrectomy has been used in metastatic disease in a selected number of patients. It has been especially used in fit patients with asymptomatic, low burden of metastatic disease and troublesome local symptoms such as bleeding and pain [39]. However, publication of the CARMENA trial in 2018, where sunitinib versus cytoreductive nephrectomy plus sunitinib was evaluated, demonstrated non-inferiority of sunitinib alone [40]. The trial was designed to demonstrate non-inferiority and non-superiority of one investigational arm; however, it was noted that the median OS of sunitinib alone was 18.4 months versus 13.9 months as compared to sunitinib with nephrectomy [40]. Although further evaluation is required, and for symptomatic management, cytoreductive nephrectomy may still be beneficial in the metastatic setting, this new evidence has called into question the validity of this approach routinely used for patients in the contemporary systemic treatment setting.

6. Oligometastatic disease in kidney cancer

An interesting development across oncology in all tumour groups has been the change in approach to the management of oligometastatic disease [41]. Oligometastatic disease is a term used to describe a patient with a small number of metastatic lesions; in most studies, this is defined as 1–3 or 1–5 lesions [41]. Aggressive resection of the metastasis can be attempted surgically or an increasing number of patients can be treated with high doses of radiotherapy using stereotactic ablative body radiotherapy (SABR) [41, 42]. Traditionally, RCC has been thought to be a radio-resistant disease; however, large ablative doses of radiotherapy used in an SABR technique induce different pathways of apoptosis and as such good long-term control can be achieved in certain patients. Metastasis in bone, lungs, brain, lymph nodes, and adrenal glands are all potentially treatable with SABR [43–45].

Metastasectomy can be employed for metastatic disease in a number of sites including bone, lungs and brain. Good long-term outcomes have been observed, especially with careful patient selection [46, 47].

A combination of metastasectomy and post-operative SABR for brain metastasis has been employed with excellent results and has been shown to have less side effects than post-operative treatment with whole brain radiotherapy [48].

7. Adjuvant treatment

Adjuvant therapy in oncology describes the use of additional treatment alongside the primary, definitive, usually surgical, treatment, in an attempt to achieve higher rates of progression-free and overall survival. In RCC, this has not been widely employed as many trials have shown adjuvant treatment in early stage renal cancer not to translate into an overall survival benefit [49, 50]. However, it is also recognised that many patients with early stage disease will also go on to relapse, and therefore, interest in this area has remained high and guidelines recommend that for intermediate- and high-risk patients, adjuvant treatment, as part of a clinical trial, should be considered [36, 49]. In ASSURE trial, sunitinib or sorafenib failed to demonstrate an improvement in disease-free survival (DFS) compared to placebo [51]. In S-TRAC trial, sunitinib did increase 5-year DFS, but not overall survival data, although the overall survival data have not yet improved [52]. In the PROTECT trial, pazopanib failed to

Trial	Drug	Number of patients (n)	Disease-free survival (DFS)	Overall survival (OS)
ASSURE Haas et al. [50]	Sorafenib/Sunitinib versus placebo	1943	Sorafenib 6.1 years (HR 0.97 P = 0.718) Sunitinib 5.8 years (HR 1.02 P = 0.804) Placebo 6.6 years	At 5 years Sorafenib 80.5% Sunitinib 77.9% Placebo 80.3% *No significant difference between groups*
S-TRAC Ravaud et al. [51]	Sunitinib versus placebo	615	Sunitinib 6.8 years Placebo 5.6 years (HR 0.76 P = 0.03)	Mature data not available.
PROTECT Motzer et al. [52]	Pazopanib versus placebo	1538	HR 0.86 P = 0.165	Not available
ATLAS Gross-Goupil et al. [53]	Axitinib versus placebo	724	HR 0.870 P = 0.3211	Not available

Table 4. Trials of tyrosine kinase inhibitors in the adjuvant renal cancer setting post-nephrectomy.

show a statistically significant improvement in DFS [53]. In the ATLAS trial, using axitinib in the adjuvant setting, the primary end point was not reached and the study was abandoned due to futility at the interim assessment point [54]. It is also worth noting that the majority of patients in these adjuvant trials had ccRCC histology. A summary of the reported trials is shown in **Table 4**.

Several trials are still ongoing using targeted therapies in high-risk patients post-nephrectomy including: SORCE trial (NCT00492258) assessing sorafenib and EVEREST trial (NCT01120249) investigating everolimus [50]. Further trials are underway to assess the use of immunotherapy in the adjuvant setting using a variety of checkpoint inhibitors. These include the IMmotion101 trial (NCT03024996) with atezolizumab, PROSPER trial (NCT03055013) comparing neoadjuvant and adjuvant nivolumab versus observation, KEYNOTE-564 trial (NCT03142334) evaluating pembrolizumab versus placebo and CheckMate 914 trial (NCT03138512) comparing nivolumab with ipilimumab versus placebo [50]. The results of these trials are likely to be reported in the coming years; however, the standard of care at present is not to prescribe adjuvant therapy, of any kind, post-nephrectomy in renal cell carcinoma.

8. Emerging treatments and trends

An area of particular interest for oncologist is the search for reliable biomarkers, which will guide us into targeting our treatments to the patients who will benefit from them the most. Renal cell carcinoma is no exception and the hunt for a biomarker is of high interest to academics and drug companies alike. Biomarkers are being investigated in the areas of imaging serum, histology, and urine, both to determine treatment strategies and to differentiate between benign and malignant processes [55]. One biomarker of particular interest is carbonic anhydrase IX, which has demonstrated excellent specificity and ability to predict treatment response [56]. Researchers are also keen to identify reliable biomarkers for use with immune checkpoint inhibitors in the treatment of RCC, especially to help differentiate between the progression and pseudoprogression on treatment [57].

Research has been conducted on the use of vaccine therapy in RCC. Vaccines are designed to induce a specific immune response in the patient; however, this is yet to translate into an overall survival benefit [58, 59]. In the new era of targeted medicine and next-generation immunotherapy, the role of vaccines remains uncertain and only further research in this area, with associated success in randomised trials, will confirm vaccine therapy as a viable treatment strategy for the future.

Interesting evidence has been published on the use of SABR in patients who are not fit for partial nephrectomy. High doses of highly targeted radiotherapy are given to the tumour patients with the hope of ablation of the tumour. The treatment was well tolerated with low toxicity and good local control rates in 2 years [60]. Further ongoing evaluation of this technique is needed, but it is likely that use of SABR in this format will increase in the future.

9. Summary

The take-home points are as follows:

- prognostic risk stratification is used to guide treatment decisions in metastatic renal cell carcinoma patients;
- the mainstay of treatment for metastatic renal cell carcinoma is TKI therapy;
- immunotherapy has been shown to be effective in metastatic renal cell carcinoma and is now routinely used;
- cytoreductive nephrectomy should not be used routinely in metastatic renal cell carcinoma patients;
- adjuvant systemic treatment lacks robust evidence for routine use in renal cell carcinoma patients outside of the clinical trial setting.

The medical treatment of renal cell carcinoma is rapidly evolving with the introduction of new treatments entering the market on a regular basis. Whilst this is challenging for the physician treating renal cell carcinoma, it is excellent news for our patients who will benefit from the greater arsenal of treatments available.

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