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What is the role of real-world data in metastatic renal cell cancer?

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“Important considerations remain over the quality of real-world data; it is important for major centers to have the resources to maintain prospective databases with accurate data entry by skilled personnel.”

First draft submitted: 21 May 2021; Accepted for publication: 21 July 2021; Published online: 11 August 2021

Keywords: immunotherapy • RCC • real-world data • TKI • VEGF

Renal cell cancer (RCC) is the seventh commonest cancer in the UK and the 14th worldwide [1,2]. The mainstay of treatment for localized disease is surgery. Recurrence rates are high, with 50% of patients presenting with distant metastatic disease within 5 years of radical treatment approaches [3]. Late diagnosis is frequent, with 25–31% having metastatic cancer at initial presentation; RCC therefore has a high burden of morbidity and mortality, and incidence rates are predicted to continue to rise.

The most common histological subtype is clear cell RCC (ccRCC) comprising ~75% of RCC [2]. ccRCC is highly a vascularized tumor, with the von Hippel Lindau (VHL) tumor suppressor gene frequently inactivated leading to the overexpression of the HIF-2 α oncoprotein and its downstream targets including VEGF, PDGF, TGF- α , erythropoietin and the c-MET proto-oncogene [4]. This intense vascularity can even be detected clinically; palpable metastases are often pulsatile. Pathological classification of non-ccRCC (nccRCC) includes more than a dozen different histopathological entities. The most frequent subtypes are papillary renal cell carcinomas (10–15%) and chromophobe renal cell carcinoma (4–5%), with medullary, translocation and collecting duct RCCs encountered more rarely.

Current management strategies

For many years, management of metastatic disease was fraught with resistance to cytotoxic chemotherapy, and there were poor responses and levels of high toxicity to immunotherapy with cytokines. Despite these setbacks, it has been recognized for decades that RCC is both a highly vascular and immunogenic tumor type (spontaneous resolution of metastatic disease may occur after nephrectomy). Novel antiangiogenic therapies and immune checkpoint blockade has shifted the paradigm. Angiogenesis-directed tyrosine kinase inhibition became the backbone of treatment from 2006 with practice changing phase III randomized control trials showing significant response rates and increased progression-free survival [5]. We now have six tyrosine kinase inhibitors (TKIs) in regular use for metastatic RCC (mRCC) in UK practice. Despite these advances in antiangiogenic therapy, survival plateaued.

Efficacy of targeting the immunogenic tumor microenvironment with PD-L1/PD-1 inhibitors in the second-line setting has been used in routine clinical practice since 2016 with further phase III randomized data showing improved response rates and overall survival compared with standard of care with the mTor inhibitor everolimus [6]. More recent data have paved the way for regulatory approval for the use of immunotherapy and immunotherapy–TKIs combinations in the first-line setting and mTOR-VEGF directed treatment in the second-line setting [7–11]. In the space of just over a decade we have gone from having no significantly life-prolonging treatments, to more than 10.

Naturally there is intense interest in the role of systemic therapy in the adjuvant setting, in an attempt to increase the cure rate of surgery. Trials with tyrosine kinase inhibitors were disappointing, and although sunitinib was approved in the USA on the basis of an improved disease-free survival, there is no evidence of an overall survival

Table 1. Outcome of prognostic groups in Memorial Sloan–Kettering Cancer Center and International Metastatic Renal Cell Cancer Database Consortium systems.

		Favorable	Intermediate	Poor
MSKCC 463 patients Six clinical trials of cytokine Immune therapy 1982–1996	Patients (%)	18	62	20
	Median survival (months)	30	14	5
	2-year survival (%)	55	31	6
IMDC 645 patients, 7 centers Nontrial Antiangiogenic therapy 2004–2008	Patients (%)	23	51	26
	Median survival (months)	Not reached	27	8.8
	2-year survival (%)	75	53	7

IMDC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan-Kettering Cancer Center

benefit, and it is not widely used [12]. There are several ongoing adjuvant trials incorporating immune checkpoint inhibitors and early results are promising [13].

Prognostic factors in mRCC

Real-world data have several important uses in mRCC. It is clinically apparent that there is a huge range in survival from mRCC, with some patients dying within weeks of presentation and others living for many years with metastatic disease. Predicting prognosis is useful to inform patients, stratify patients for clinical trial entry, and for prognosis directed therapy. The initial prognostic scoring system developed by Motzer at the Memorial Sloan-Kettering Cancer Center (MSKCC) was developed from multivariate analysis of clinical trial data of 463 patients entered into clinical trials of immunotherapy from 1982 to 1996 [14]. Patients were stratified into favorable, intermediate and poor prognostic groups using the clinical factors of time from diagnosis to treatment and performance status, and the biological factors anemia and hypercalcemia and raised lactate dehydrogenase (LDH). Although extremely informative and influential, the wider population of patients with renal cancer was not represented. Heng analyzed 645 consecutively treated non-trial patients from seven North American centers in order to develop the International Metastatic RCC Database Consortium (IMDC) score. Patients were treated with sunitinib, sorafenib or bevacizumab/interferon from 2004 to 2008 [15]. In this analysis, LDH lost significance on multivariate analysis, and raised neutrophil and platelets were added. The prognostic groups and outcomes are shown in Table 1 and demonstrate that although outcomes of favorable and intermediate prognostic groups improved in the TKI era, patients with poor prognosis continued to have extremely short survival. Thankfully the advent of immunotherapy has brought some hope for these patients, who appear to benefit proportionally greater than favorable prognosis patients [16].

The IMDC real-world data has, in turn, been used to stratify patients in contemporary clinical trials, and this has led to prognostic stratification of patients in drug licenses (e.g., ipilimumab/nivolumab is licensed in intermediate and poor prognosis patients) to further provide risk-directed treatment selection in the clinic. With the advent of checkpoint inhibition, the pendulum may need to swing again with statistical analysis of immunotherapy trials showing that the IMDC baseline risk factors were no longer prognostic of OS with ipilimumab and nivolumab. Performance status, LDH, tumor burden and raised neutrophil:lymphocyte ratio were predictive of overall survival in the ipilimumab/nivolumab arm of CheckMate 214 [17]. With novel treatment approaches, prognostic models need to adapt and evolving real-world data can facilitate this and, in turn, guide trials of the future.

Real-world data in mRCC

We know that clinical trials do not fully represent the whole population of mRCC patients. At best, ~30% of patients with mRCC enter clinical trials of systemic therapy [18]. To assess a drug's efficacy, randomized clinical trials can only include patients who meet certain criteria and therefore do not fully represent those patients we see. Real-world data can give us valuable insights into unusual presentations, uncertainties and help guide our advice to patients. There are several areas in which real-world data are important in the management of mRCC, such as treatment on non-ccRCC; management of specific metastatic sites such as brain, glandular and head and neck; patients with oligometastatic disease for whom active surveillance is appropriate management; elderly patients; patients with Karnofsky Performance Status <70; and patients with comorbidities excluding them from trials, such as those with cardiac disease, autoimmune disease or transplant recipients. All of these patients are well represented in the real-world population but not in clinical trials.

Non-clear-cell histology is frequently excluded from phase III trials in mRCC. There are currently eight recruiting phase II/III trials on clinicaltrials.gov open for non-clear-cell cancer; there are 58 for those with clear-cell histology. Despite representing up to one in five patients, they represent an unmet need in terms of data. Cooperative real-world studies can provide valuable information in the management of such patients [19].

Pancreatic metastases have an incidence of 5% in mRCC, with large retrospective studies showing that the presence of at least one glandular metastasis site in mRCC is associated with a significantly longer overall survival [20]. Ten percent of mRCC patients present with brain metastases, and approximately 65% of these are symptomatic [21]. Javelin 101 and Checkmate 214 excluded patients with CNS metastases; Keynote 426 and Checkmate 9ER excluded those with active CNS metastases. Therefore, much of the information on the management of brain metastases in RCC is based on real-world studies. Patients with mRCC seen in everyday clinical practice are more likely to have poor-risk disease and impaired performance status compared with phase III trial participants; this may have an impact on the variation in post-trial reported survival outcomes [18]. Reassuringly, meta-analyses have shown that overall and progression-free survival with TKI therapy in real-world datasets and clinical trials are remarkably similar [22,23].

Many patients with mRCC have 'oligometastatic disease,' can live for many years without systemic therapy and are managed by active surveillance. There are no randomized trials of active surveillance, although a phase II study has validated this approach [24]. There is also a large body of retrospective data on the management of oligometastatic disease with surgery and, more recently, ablative radiotherapy. By the very nature of the disease, it is impossible to truly know whether the active management of the individual lesions in oligometastatic disease leads to improved overall survival. These patients may survive for decades with metastases, and a randomized study in this setting would clearly be impossible [25]. However, metastasis-directed therapy is frequently used in this setting. It is yet to be ascertained whether patients with very low volume metastatic disease are likely to benefit from the new treatment paradigm of immunotherapy in terms of long-term survival when balanced against potential immunotherapy toxicities.

Sequencing of systemic therapy

There is a trend toward more rapid drug development and approval than in previous eras; between 2018 and 2020, the UK's NICE approved eight drugs and drug combinations in the first- and second-line settings for mRCC; some of these are for use in intermediate- and poor-risk IMDC/MSKCC scores, some are for all. In intermediate-/poor-risk mRCC, trials have shown that nivolumab plus cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib and pembrolizumab plus lenvatinib are associated with significantly higher improvement in overall survival compared with sunitinib, in the first-line setting, and cabozantinib and avelumab plus axitinib with a higher PFS [7–9,11,26,27]. Using these drugs and drug combinations in the first-line setting has led to questions about what to do as a second-line strategy with little in the way of data from controlled trials to support decision-making in the postimmunotherapy or immuno-TKI combination arena. Overall survival may well be affected by subsequent treatment lines, which may not be captured by randomized controlled trials (RCTs). There is uncertainty over the role of immunotherapy, after progression on previous immunotherapy [28]. This new arsenal of riches can cause uncertainties when trying to make recommendations to patients on the basis of both immature and simultaneously arriving data.

In mRCC, questions should focus not just on novel therapeutic agents but on sequencing, the best combination and toxicity of treatments. Outcomes from tightly controlled clinical trials may not help with this and can miss those important questions of sequencing and combinations; there is a need to generate evidence on the real-world effectiveness of scheduling of treatments for patients with mRCC. The availability of various efficacious agents has led to the possibility of sequentially using them in later treatment lines, rather than those in which they were specifically tested but these decisions are not always supported by specific data coming from prospective RCTs. The waters are going to continue to muddy with additional immunotherapy-TKI studies ongoing, the advent of the use of HIF2 α inhibitors, trials of DNA damage repair gene (PARP) inhibitors and the role of radiotherapy-drug combinations. Pooling of real-world data can help answer these important questions and is particularly useful as new drugs are introduced into mainstream treatment pathways. Cooperative groups such as the IMDC are a valuable source of information in these evidence poor areas.

Future perspective

Our focus on real-world data needs to answer the questions of who can benefit from treatment, what treatment, when to offer it and why. Approximately 50% of patients receive second-line therapy; 20% of patients get to third-line treatment, and so choosing the sequence that maximizes overall survival and quality of life can currently only be answered by real-world data [29]. Technological advances in electronic paper records and the ease with which databases can now be collated provides promise; data from cancer registries and linked patient records can provide insights into patient characteristics, therapies used and outcomes in routine oncology practice. Only RCTs can detect true differences between treatments, and we rely on these for licensing. The strict eligibility criteria of RCTs are a crucial feature to ensure high internal validity; however, this may limit external validity, as RCT populations may not reflect the diverse population seen in the clinic. Important considerations remain over the quality of real-world data; it is important for major centers to have the resources to maintain prospective databases with accurate data entry by skilled personnel. This will facilitate timely and accurate reporting of real-world data. National registry data are also important to reflect overall outcomes, and not just that of patients treated at major centers because variation in the uptake of new treatment approaches may lead to inequity of care. Real-world data will continue to have an important role in the management of all our patients with mRCC and aid decision-making in 'nonstandard' patients with mRCC, who comprise the majority of our patients.

Financial & competing interests disclosure

K Fife is affiliated with the Urological Malignancies Programme, CRUK Cambridge Centre. She has received advisory, consultancy or speaker fees from ESAI, Ipsen, Roche, Novartis, Merck, Pfizer, Eusa, BMS and Sanofi; conference support from Novartis, Ipsen and EUSA; and Institutional research funding from Roche, Merck and Exelixis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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