The global burden of kidney cancer: a call to action

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Introduction

Kidney cancer, is the 12th most common cancer worldwide, with more than 338,000 new cases annually. Furthermore, the International Agency for Research on Cancer projects a 22% increase by 2020, to about 413,000 cases (an increase of 75,000). [1] The steady rise in incidence of kidney cancer is a global health risk. As the world's population ages, and the prevalence of known risk factors such as obesity and hypertension increases, the burden of kidney cancer *on individuals and society* is predicted to increase significantly. The most frequent type of kidney cancer is renal cell carcinoma (RCC) which represents over 90% of all renal malignancies. [2] Clear cell RCC, which is the most common histological subtype accounts for approximately 75% of the cases. The rest have a non-clear RCC subtype including papillary RCC, chromophobe RCC, collecting duct carcinoma or unclassified RCC. [3] Each RCC subtype is associated with specific genetic and clinical characteristics and sensitivity to treatment. [4,5] The aim of this report is to increase awareness of the growing global burden and the risk factors of kidney cancer, and the challenges clinicians currently face in the diagnosis and management of patients with the disease.

Global burden of kidney cancer

Limited data exist on the global burden of kidney cancer. Initially, RCC has an asymptomatic clinical course. However, 25-30% of the patients present with metastatic disease (mRCC) at the time of diagnosis with not only premature mortality but major morbidity. [6] For example, one third of those experience painful bone metastases and with the rising incidence of RCC with our ageing populations, the number who live with bone metastasis will increase. Bone metastases lead to the mobidity of skeletal-related events (SREs) including not only bone pain, but fractures and spinal cord compression requiring radiotherapy or surgery.[7] Recent data indicate that 85% of RCC patients with bone metastasis experience SREs over the course of their disease with a mean number of 2.4 per patient.[8] A study in the United States in patients with mRCC diagnosed with bone metastasis between 1998 and 2010 reported that 20.8% of their hospital visits involved at least one SRE. The inflation adjusted mean annual costs associated with these SRE visits increased by 207% in this interval. These findings emphasize the need for cost-effective treatment strategies to prevent and/or treat SREs. [9] Increasing burden is also being observed with localized disease. The estimated number of surgically removed misdiagnosed benign renal masses in the US increased by 82% from 2000 to 2009. Small renal masses (SRMs) are more likely to contain benign histology and almost 6,000 benign lesions were removed in 2009 alone. Strategies to prevent over-treatment with unnecessary costs are needed.[10] Many of these patients experienced potentially unnecessary costs and the risks of treatment by nephrectomy (partial or radical) or ablation. A recent study demonstrated that the burden of complications after surgery for clinically localized kidney cancer is associated with age and comorbidity status. High-risk patients (≥ 75 years and Charlson comorbidity index count >2) had a higher risk of experiencing a post-operative complication than the low-risk patients (odds ratio of incurring a post-operative complication: 1.9 (95% CI; 1.3-2.8)). [11]

The current RCC surveillance guidelines (EAU, AUA, NCCN and CUA) for followup of RCC patients after partial nephrectomy vary greatly in terms of frequency of assessment, diagnostic radiation exposure and therefore cost with limited evidence of overall benefit. Standardization and rationalization of these surveillance guidelines can reduce cost little risk of compromising cancer control.[16]

Other RCC-related economic studies in the US showed that the annual cost (2009) to treat RCC patients who received targeted therapies was three- to fourfold greater than the cost to treat RCC patients who received other therapies. [12] Two studies, one in mRCC patients aged ≥ 18 years and one in mRCC patients aged ≥ 65 years who received targeted therapies (sunitinib, sorafenib, bevacizumab or pazopanib) showed that the health costs (excluding the cost of the drugs themselves which is large) over a period of 30 days was considerable higher in patients who experienced adverse events.[13,14] In a Danish study, costs were measured per patient year during a 2-year follow-up from 2002-2005 (immunotherapy only) and from 2006-2009 (targeted therapy). A different pattern of health care costs (lower inpatient costs, higher outpatient costs, lower radiotherapy costs, higher radiology costs and higher separately calculated drug costs) for the period 2006 to 2009 was observed but total health care costs per patient per year (€27,856 vs. €27,676, RR 1.05, p=0.5) did not significantly differ after implementation of targeted therapy for patients with mRCC.[15]

Health-related quality of life (HRQOL) issues associated with tumour burden such as anorexia, fatigue, pain, anemia, hypercalcemia, venous thromboembolism and psychological concerns along with the impact of treatment-related side-effects on HRQOL require further study. [17]

Future research is needed to understand the impact of different factors on the burden of RCC.

Trends, incidence and mortality

In 2012 there were an estimated 338,000 estimated new cases of kidney cancer (2.4% of all cancers) with 144 000 kidney cancer-related deaths worldwide. The incidence of kidney cancer varies widely among countries and among ethnic groups within countries. Reported age-standardized rates (ASRs) in men varied from approximately 1/100,000 in African countries to >15/100,000 in several Northern and Eastern European countries and among Afro-Americans. Rates for women were half of those for men. High rates were seen in northern and eastern Europe, North America and Australia but the highest incidence rates were estimated in the Czech Republic (22.0/100 000 in men and 9.9/100 000 in women), ,. Relatively low rates were estimated in much of Africa and South-East Asia.[1] The particularly high kidney incidence rate in the Czech Republic and elevated rates in surrounding regions including eastern Germany, Slovakia, Austria, the Baltic countries and northern Italy have not yet been explained.[18] Incidence rates are still rising in most countries of the world, most prominently in Latin America populations.[19] Mortality patterns follow incidence patterns, with the highest mortality rates observed in the Czech Republic (9.1/100 000 for men and 3.6/100 000 for women) and the Baltic countries. Stabilization of mortality in most countries or even decrease has been achieved in many highly developed countries in northern and most western European countries (average annual percentage change; AAPC for the last 10 years:

-1 to -3%), United States (AAPC: -0.9 to -1.3% in blacks and -1 to -1.3 % in whites) and Australia (AAPC: -0.5 to 2.0%).[19]

The increasing incidence trend of kidney cancer could at least partially be explained by the increase of incidentally detected SRMs with better prognosis due to the widespread use of imaging modalities such as ultrasound and computed tomography (CT) over the last decades.[20,21] Furthermore, the changing prevalence of known modifiable risk factors for kidney cancer such as smoking, obesity and hypertension may also be influencing the incidence trends of kidney cancer.[22] The declining mortality trend in highly developed countries can be attributed to the availability of improved treatments.[19] The explanation for the international variations in incidence and mortality of kidney cancer is probably a combination of genetic variations unique to ethnic and regional populations, differences in availability of imaging modalities and improved treatment options, lifestyle choices and well-established risk factors.

Global hotspots for kidney cancer

Biomarkers

The development of clinically useful biomarkers of risk or for earlier diagnosis of kidney cancer using germline genetics or serum/urine biomarkers has been slow. Molecular characteristics of clear cell RCC including genetic and gene expression profiles have been identified as potential novel prognostic biomarkers. For example, urine biomarkers such as aquaporin-1 and perilipin-2 need to be incorporated in composite models [23] and prospectively validated in well-designed validation studies to test their clinical utility. During the last decade, many epigenetic alterations have been found to be associated with kidney cancer, including DNA methylation, histone modifications and miRNA regulations. These epigenetic alterations may also lead to the development of innovative biomarkers and precise treatments.[24]

Genomic studies identifying the genes which are critical in carcinogenesis enable clinicians to manage patients according to their genotype.[25] Seven targeted drugs have been approved for mRCC patients in recent years. Unfortunately, their efficacy has been limited in that complete responses are extremely rare [26] and it remains unclear how to select the optimal therapy for a particular patient. There is currently a multitude of markers developed that may identify patients who are likely to benefit from a particular agent, and predict response to treatment and drug toxicity. However, individual markers have yet to be validated.[27,28] There is also increased interest in the identification of the molecular signature of the various non-clear cell RCC subtypes and development of biomarkers as there are currently no FDA-approved targeted therapies for these patients.[29,30] A topic that may present major challenges to biomarker development and personalized-medicine is the occurrence of intra-tumour heterogeneity in clear cell RCC. [31] Research in understanding and characterizing the heterogeneity of cancer cells has the potential to guide biomarker optimization and the development of more effective treatment strategies.

Novel imaging modalities

Further research is warranted to determine the role of advanced magnetic resonance imaging (MRI) modalities (Perfusion MRI (pMRI) and diffusion weighted imaging (DWI)) and radiomics analysis which have the potential to serve as diagnostic, therapeutic, and prognostic RCC imaging biomarkers.[32,33] Other emerging imaging techniques are the iodine-124 (^{124}I)- girentuximab PET/CT [34] and 99m technetium-sestamibi single photon emission computed tomography (SPECT). [35]

Challenge of finding preventive measures

There is a strong interest in investigating the underlying biologic pathways that might be able to explain an association with kidney cancer risk for obesity and hypertension.[36] Analysis of somatic signatures (both genomic and proteomic) of kidney cancer is needed to improve the understanding of the etiologic risk factors and prognosis with potential implications for prevention and treatment.[37]

Treatment hot spots

Checkpoint inhibition is revolutionizing the treatment approach for mRCC but cancer vaccines also look promising. The most impressive new data are the prolonged survival data of the immune checkpoint inhibitor nivolumab [38] and tyrosine kinase inhibitor cabozantinib.[39] Both were recently approved for second-line treatment of advanced/mRCC patients. Nivolumab shows good quality of life data while those for cabozantinib are still awaited. Further clinical trials need to investigate novel agents and combinations/sequences of different agents including nivolumab or cabozantinib to optimize treatment outcome. Novel local treatments such as high-intensity focused ultrasound (HIFU), irreversible electroporation and microwave ablation are being studied and research is underway to further refine the most studied ablative therapies (RFA and cryoablation).[40]

Causation

The causes of kidney cancer are poorly understood. Germline mutations in specific genes, cigarette smoking, overweight/obesity and hypertension are established risk factors for RCC, worldwide. Chronic kidney disease is also a significant risk factor for RCC, specifically in dialysis patients.[41] Specific dietary habits such as meat intake and related mutagens are suspected risk factors [42] but require further investigation. There is strong evidence that moderate alcohol consumption (up to 30 grams (about 2 drinks) a day) reduces the risk of kidney cancer. There is insufficient evidence for the effect of high alcohol intake.[43] Large collaborative studies with uniform data collection are needed to make a complete list of established risk factors of kidney cancer. This is necessary to develop successful preventive measures.

Genetic predisposition

Hereditary RCC is currently estimated to be the cause of 4% of all kidney cancers. A family history of kidney cancer (kidney cancer in first-degree relatives) is associated with a two- to fourfold increased risk of RCC.[44] Familial forms of RCC develop at an earlier age and are often multiple and bilateral.[45] Several heriditary renal cancer syndromes have been described. Von Hippel-Lindau (VHL) syndrome is the most commonly inherited RCC, with up to 40% of those inheriting the mutated VHL tumour suppressor gene developing RCC.[46] This gene was first described in VHL and has proven to be critical to the development of most spontadic RCCs as well (ref). Other hereditary types of RCC occur with tuberous sclerosis, hereditary papillary RCC, Birt-Hogg-Dubé syndrome, and heriditary leiomyomatosis.

Cigarette smoking

Smoking is also associated with kidney cancer.[47] Current smokers have a 52% increase and ex-smokers a 25% increased risk of kidney cancer, compared with those who have never smoked.[48] In male smokers the increase is 54% and in females, 22%. There is a strong dose-dependent increase in risk for both.[49] This is unexplained.

Obesity

There is strong evidence that being overweight or obese increases the risk of kidney cancer.[43] A dose-response meta-analysis of obesity, assessed by body mass index (BMI; waist circumference and waist-to-hip ratio) found a 30% increased risk of kidney cancer for every 5 kg/m2 increase in BMI (RR 1.30; 95% CI 1.25-1.35), an 11% increased risk for every 10 cm increase in waist circumference (RR 1.11; 95% CI 1.05–1.19) and a 26% increase in risk for every 0.1 unit increase in waist-to-hip ratio (RR 1.26; 95% CI 1.18-1.36).[43]

Hypertension

Hypertension is also significiant risk factor for kidney cancer. In a large prospective European cohort study, both elevated systolic (≥ 160 mm Hg) and diastolic (≥ 100 mm Hg) were associated with a two- to threefold increased risk of RCC.[50] The results suggest that hypertension rather than the use of antihypertensive medication increases the risk [50] and that effective blood pressure control may lower the risk.[50,51]

Acquired cystic kidney disease

Acquired cystic kidney disease (ACKD), chronic renal failure and dialysis are strong risk factors for RCC.[52,53]

Adult attained height

There is strong evidence that being tall increases the risks of kidney cancer. The analysis of the worldwide research found a 10% increase in the risk of kidney cancer for every 5 cm of increased height (RR 1.10, 95% CI 1.08–1.12). Developmental factors leading to greater linear growth are probably linked to an increased risk of kidney cancer.[43]

Analgesics

A recent large meta-analysis found that acetaminophen and non-aspirin nonsteroidal anti-

inflammatory drugs (NSAIDs) are associated with a significant risk of developing kidney cancer.[54]

Arsenic in drinking water

The evidence suggesting that consumption of drinking water that contains arsenic increases the risk of kidney cancer is limited.[43]

Diagnosis

Symptoms

Th diagnosis of RCC may be delayed since most renal tumours remain asymptomatic until at least locally advanced. The classic presentaton with the triad of flank pain, gross hematuria, and palpable abdominal mass is now rare (6-10%). These symptoms and signs were common and reflect advanced stage and often aggressive histology with low cure rates. Potentially misleading paraneoplastic syndromes including fever and night sweats are found in approximately 30 % of patients with symptomatic RCCs. A few symptomatic patients present with symptoms caused by metatstatic disease, such as bone pain or persistent cough. The presence of these symptoms as well as non-reducing varicocele and bilateral lower extremity oedema should prompt radiological investigation.[55]

Imaging

The majority of the renal masses are detected by abdominal ultrasound (US) or computed tomography (CT) performed for other medical reasons. Contrast-enhanced US can be helpful in specific cases for the further evaluation. If there are contraindications or if the CT results are indeterminate, magnetic resonance imaging (MRI) is used for further analysis. [55] Recent findings revealed that CT and MRI remain the diagnostic mainstay for RCC with almost equally high diagnostic accuracy but that different imaging modalities may be useful in specific cases requiring more information on staging or tumour spread. For the staging of RCC and small renal masses (≤ 4 cm), the diagnostic performance of MRI even surpassed that of contrast-enhanced CT. The newer contrast-enhanced ultrasound (CEUS) technique seems to be increasingly valuable but more research is needed. The value of positron-emission tomography (PET)/CT in the characterization of renal masses should also be further investigated.[56] in press??? Standardization and validation of new techniques such as perfusion MRI (pMRI), diffusion weighted imaging (DWI) and radiomics are needed prior to implementation into clinical practice.[33]

Renal mass biopsy

Percutaneous renal mass biopsies (RMB) provides histopathological confirmation of RCC. It is recommended in select SRM patients prior to treatment [57] [58] and in patients with metastatic RCC to select the most suitable form of treatment.[59] In a recent systematic review and meta-analysis percutaneous RMB appears to be safe and accurate. Needle core biopsies have better diagnostic accuracy compared with fine needle aspiration for cytology. The accuracy of

tumour grading is 87% using a simplified two-tier system (high-grade vs. low grade).[60] R RCCs are heterogeneous, and biopsy may occasionally miss components of high-grade disease or different histological subtypes with underestimation RCC risk when single biopsy procedures are used.[61] Approximately 20-30% of the surgically removed renal masses are benign and might not have been treated if this was recognized in advance.[62] If RMB could reliably identify these patients, a significant proportion could be spared of surgery, treatment-related complications and treatment costs. Future studies are needed to identify the optimal role of RMB in risk stratification of patients with renal masses.

Risk assessment and prognosis

Demographic, clinical and imaging characteristics are used to stratify the patients according to their risk. TNM stage, Fuhrman nuclear grade and RCC subtype [2] provide important prognostic information. Nomograms combine these characteristics in an attempt to predict the malignant potential of the tumours preoperatively. No specific molecular marker can currently be recommended for use in clinical practice.[63]

The Memorial Sloan-Kettering Cancer Center (MSKCC) risk model is the most widely used risk assessment model but was developed during the cytokine era. More recently, the International Metastatic Renal Cancer Database Consortium (IMDC) risk model has been validated to yield an accurate prognosis for all patients with mRCC treated with first-line [64,65] and second-line targeted therapy [66] (Table 1).

Treatment options and outcomes

Localized renal masses

Several options exist for the management of clinically localized renal masses suspicious for RCC or SRMs including active surveillance (AS), thermal ablation and surgery [partial (PN) or radical nephrectomy (RN)]. Surgery is the gold standard for the treatment of RCC which can be performed by an open or minimally invasive approach (laparoscopy and robot-assisted laparoscopy which has very limited availability on a worldwide basis). Radical nephrectomy has been the mainstay treatment for RCC for over 50 years (ref Robson 1969). Within the past decade there has been a shift towards increased use of nephron-sparing surgery (partial nephrectomy).[67] The evidence for it's superiority over RN is highly controversial but the practice is being adopted nevertheless because of the appeal of preserving renal function. Thermal ablation, which may include cryoablation or radiofrequency ablation (RFA), is usually performed percutaneously with image guidance on an outpatient basis(ref Gervais). Active surveillance has emerged as an option for elderly and/or comorbid patients with SRMs which have a low likelihood of aggressive malignancy and patients have limited life expectancy.

A recent systematic review of 107 studies summarized evidence of the effectiveness and comparative effectiveness of different treatment strategies for treating patients with a renal mass suspicious for localized RCC. Strength of evidence was given for each comparison, and

was moderate or low for many outcomes and often insufficient for comparisons involving active surveillance.[68,69]

Cause specific survival (CSS) was excellent and comparable across all treatment options (median 5-year CSS of 95%). Overall survival (OS) rates were similar among treatment strategies. Differences in 5-year OS were explained by competing risks of death. OS ranged from 69 to 94% in uncontrolled studies of AS (median follow-up 12-35 months). Patients selected for AS and thermal ablation were older and had greater morbidity resulting in inferior OS outcomes. Thermal ablation showed the highest local recurrence rate but reached equivalence with other treatment modalities when secondary ablations were considered. [68,69]

Renal functional outcomes were similar between PN and thermal ablation and better than RN in the long run. RN was associated with the largest decrease in estimated glomerular filtration rate and highest incidence of chronic kidney disease. End-stage renal disease rates were low among all treatment modalities (0.4%-2.8%). Comparative data on AS were lacking.[68,69]

Thermal ablation was associated with the most favourable perioperative outcomes. When compared to RN, thermal ablation had fewer conversions to open surgery and shorter length of stay. When compared to PN, thermal ablation had less estimated blood loss, less blood transfusions, no conversions to open surgery or RN, and shorter length of stay. PN had the highest blood transfusion rate which was significantly greater than for RN and thermal ablation. PN was associated with the highest rates of urological complications but overall rates of minor and major complications were similar among all treatment options.[68,69]

The current evidence does not reveal superiority of one particular treatment strategy over another. However, PN is recommended as the preferred option for T1b tumours.[55,63] A systematic review of oncological outcomes following surgical management of solitary localized renal tumours < 5 cm with normal contralateral kidney function revealed that PN should be favoured over RN whenever technically feasible. [70] Another systematic review of the perioperative and quality-of-life outcomes showed that PN results in significantly better preservation of renal function over RN. [71]

Locally advanced RCC (Stage T3-T4,N±,M0)

Open RN remains the standard of care for locally advanced RCC when the tumour is expected to be completely resectable. There is no proven role for adrenalectomy in the absence of radiological evidence of adrenal involvement. The roles for regional lymphadenectomy and excision of enlarged nodes remains controversial(ref). Several RCTs of neo- and adjuvant targeted therapy with sunitinib, sorafenib, pazopanib, axitinib and everolimus have been of limited benefit or negative respectively or are ongoing(update with S-TRAC data, mention checkpoints?). Currently, there is no evidence for the use of adjuvant VEGF receptor or mTOR inhibitors in these patients.[55]

Advanced/metastatic RCC

Cytoreductive nephrectomy

Cytoreductive nephrectomy (CN) was an established treatment option in mRCC during the cytokine era.[72] The role of CN in the era of targeted therapies is currently being investigated

in two prospective studies (NCT0093033 and NCT01099423) but observational data suggests it may still be of benefit(re Heng). CN is not usually recommended in patients with poor performance status, CNS or bone metastases. For most patients CN is palliative and systemic therapies are necessary.[55,63] Results of a recent systematic review suggest a benefit from complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.[73] No general guidelines can currently be given on the local treatment of metastases in mRCC patients.

Systemic treatment

Immunotherapy

For many years, standard treatment of patients with mRCC consisted of cytokine-based immunotherapies (interferon-α or interleukin-2) with modest clinical benefit and significant toxicity. The prognosis was poor with a mean of approximately 10 months.[74]

Interferon-α and interleukin-2

Interferon-α (IFN-α) has been superseded by targeted therapy in patients with clear cell mRCC in the last 10 years. High-dose interleukin-2 (HD IL-2) is a treatment option for a high-selected group of mRCC patients with a higher objective response rate (25%) compared with the historical response rate (14%) demonstrated in a recent prospective study.[75] IL-2 remains a toxic treatment with significant treatment-related morbidity and mortality.

Immune checkpoint inhibitors

Monoclonal antibodies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (ipilimumab) and the programmed death 1 (PD-1) receptor (nivolumab and pembrolizumab) or its ligand PDL-1 (atezolizumab) enhance the anticancer immune response. Recently, a randomized phase III study compared nivolumab with everolimus in mRCC patients treated with one or two lines of VEGF targeted therapy. Median OS was 25 months (95% CI, 21.8 - not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The hazard ratio (HR) for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002). No PFS advantage was seen for nivolumab. The objective response rate was 25% for nivolumab vs. 5% for everolimus (P<0.001). Nivolumab was well tolerated with a grade 3 or 4 adverse event rate of 19% versus 35% for everolimus. [38] Nivolumab was associated with HRQOL improvement compared with everolimus.[76] A phase III study is currently investigating the combination of nivolumab and ipilimumab versus sunitinib in the first line (NCT02231749). Several early-phase studies combining TKIs with immune checkpoint inhibitors are ongoing.

Cancer vaccines

Several vaccination studies are ongoing. The multipeptide cancer vaccine IMA901 added to sunitinib failed to improve OS versus sunitinib alone as first-line treatment for advanced/metastatic RCC patients in a randomized phase III study. [77] A randomized phase III study of the autologous dendritic cell-based vaccine AGS-003 plus sunitinib versus sunitinib alone is currently ongoing (NCT01582672).

Targeted therapy

The introduction a decade ago of therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has resulted in significant improvements in PFS and/or OS, higher overall response rate and a more favourable safety profile for patients with mRCC, compared with cytokine-based therapy. Several targeted agents are currently approved in the US and Europe for the treatment of mRCC, including tyrosine kinase inhibitors (TKIs) of the VEGF receptor (VEGFR) (sunitinib, axitinib, pazopanib and sorafenib, cabozantinib), anti-VEGF antibodies (bevacizumab in combination with INF-α) and inhibitors of the mTOR pathway (temsirolimus and everolimus). The median OS in mRCC patients in clinical trials has increased beyond two years (Table 2).
Recently published real-world UK data from March 2009 to November 2012 inclusive (RECCORD registry) on the use of targeted therapy in mRCC patients show a median OS of 23.9 months for first-line treatment, which is similar to those reported in clinical trials. The majority of the patients in the first-line setting received sunitinib (78.6%).[78]
In addition to efficacy, treatment choices should also take into account HRQOL aspects of therapy. First-line treatment with sunitinib and with temsirolimus in poor-risk patients provided improved HRQOL levels versus IFN-α. First- and second-line therapy with pazopanib, everolimus and sorafenib maintained HRQOL levels similar to placebo.[17]

First-line treatment
Today, the most commonly used first-line treatments for mRCC patients are sunitinib[79,80], and pazopanib[81]and to a lesser extent bevacizumab plus IFN-α.[82,83] Temsirolimus is recommended as first-line therapy in poor-risk mRCC patients.[84] Currently, only two phase III randomized studies have directly compared TKIs (pazopanib vs. sunitinib and axitinib vs. sorafenib) as first-line treatment in mRCC patients.[85,86]

Second-line treatment
Until recently, patients who progress on first-line VEGFR-TKI therapy had the option of either a second-line alternative VEGFR-TKI (axitinib) [87,88] or an mTOR inhibitor (everolimus).[89,90] Sorafenib is also an option.[91-93] Currently, only one phase III randomized study has directly compared two TKIs (axitinib vs. sorafenib) as second-line treatment in VEGF-refractory advanced RCC. Axitinib, regardless of first-line treatment, has a PFS advantage (6.7 vs 4.7 months) but not an OS advantage over sorafenib.[87,88]
Despite the improved prognosis with first- and second line therapies complete and durable responses are rare and drug resistance will eventually develop in the majority of the patients.[94,95] Consequently, the search for novel agents has continued. Promising results suggest a future role for cabozantinib and nivolumab as part of the management of RCC. The choice of second-line agents will change based on recent studies of these recently approved agents.[39,96] Cabozantinib and nivolumab were shown to be superior as compared to everolimus, and are recommended as a new standard of care treatment option for patients with advanced RCC who failed on one or more lines of VEGF targeted therapy.[97]
Cabozantinib is a TKI inhibiting the VEGFR, MET and AXL pathway. It showed a significant PFS advantage with a median PFS of 7.4 months vs. 3.8 months for everolimus.

Median OS was 21.4 months (95% CI, 18.7- not estimable) with cabozantinib and 16.5 months (95% CI, 14.7-18.8) with everolimus. The HR for death was 0.66 (95% CI 0.53-0.83; *P*=0.00026). The objective response rate was 21% with cabozantinib vs. 5% with everolimus (*P*<0.001). [39,96] Median OS was 25 months with nivolumab and 19.6 months with everolimus. No progression-free survival (PFS) advantage was seen for nivolumab. [38]
Despite the growing evidence that the sequential use of targeted agents in mRCC can overcome transient resistance of the tumour, the choice of drugs and the optimal administration sequence have yet to be determined. A recent retrospective multicenter study (n=241) demonstrated that clear cell mRCC patients who remained on first-line TKI between 11 and 22 months, benefited from a TKI rechallenge rather than from second-line mTOR inhibitors (HR=0.5; median PFS: 9.4 (5.9-12.2) vs. 3.9 (3.0-5.5) months, *P*=0.003; time-to-treatment failure: 8.00 (5.5-110) vs 3.6 (3.0-4.6) months, *P*=0.009).[98] There is increasing evidence to suggest rechallenge either with an alternative agent from the same class or with the same targeted agent used for previous line treatment.[99]

Third-line treatment
Results of two phase III studies suggest everolimus (after two or more lines of VEGF-targeted therapy) [90] and sorafenib (after VEGF-and mTOR targeted therapies) [100] in the third-line setting. The recent ESMO guidelines describe different situations for third-line targeted treatment including cabozantinib and nivolumab. In patients treated with two TKIs, either nivolumab or cabozantinib is recommended if available. Enrolment into clinical studies is recommended.[63] Sunitinib rechallenge in the third-line or more lines setting (RESUME) is also considered as an option. Median PFS with first line sunitinib was 18.4 months (95% CI 12.5-23.7) and 7.0 months (95% CI 5.4-13.2) with sunitinib rechallenge. Objective response rate was 54% and 15%. Prospective studies are needed to confirm the clinical benefit of sunitinib rechallenge.[101] Third-line targeted therapy is highly heterogeneous. Third-line therapy in patients with favourable and intermediate risk disease based on IMDC prognostic criteria resulted in a longer OS (29.9 and 15.5 months) compared with those with poor risk disease (5.5 months) in a large international population.[102]

Treatment of metastatic RCC of non-clear histology
There is currently limited evidence regarding choice of first and subsequent lines of treatment for non-clear cell RCC. Targeted therapy of metastatic non-clear cell RCC has focused on temsirolimus, everolimus, sorafenib and sunitinib. [103-105] Novel agents targeting the c-MET receptor are currently under investigation.[63]

Treatment challenges

Optimal treatment

Future clinical studies that aim to compare different treatment strategies should be prospectively designed, have similar selection criteria, standardized treatment protocols (e.g. routinely report both clinical and pathological stage of tumour, standardized survival and renal functional outcomes) and consistent follow-up strategies using predictive markers of

response. These studies should ideally be performed in a randomized fashion. Patients most likely to benefit from nephron-sparing approaches need to be identified. A comparative study between PN and thermal ablation would give more information. Quality of life outcomes should be evaluated for the different treatment options. New prognostic markers for the various subtypes of RCC are needed which may lead to the refinement of the existing prognostic models. Prospective studies of AS with long-term follow-up are needed and AS should be studied in comparison to other treatment modalities.

Treatment challenges for patients with mRCC include investigating optimal sequential and combination therapies with existing and novel targeted (e.g. carbozantinib) and immunotherapy agents (e.g. nivolumab) to optimize treatment outcome. A greater understanding of the mechanisms underlying resistance of RCC tumours to the different targeted agents would be helpful when deciding on the optimal treatment sequence. The optimal treatment for patients with non-clear RCC needs to be identified. Novel immunotherapy strategies including immune checkpoint inhibitors, T-cell agonists, regulatory T-cell inhibitors, and tumour vaccines, and combinations with FDA-approved therapies need to be further explored. Finally, the role and optimal timing of cytoreductive nephrectomy in mRCC patients should be investigated.

Clinical trial accrual and patient engagement in trial design

Clinical trials have been largely responsible for significant advances in the treatment of kidney cancer in recent years. By participating in a clinical trial, people can obtain access to promising new treatments before they are generally available. The websites www.kidneycancer.org and www.cancer.gov give information about participating in a clinical trial. Clinical trials for kidney cancer are available at http://clinicaltrials.gov. The key to the success of clinical trials is finding suitable volunteers. Access to clinical trials primarily depends on the availability of a dedicated multidisciplinary team at the hospital. More efforts should be made to enhance patient's understanding of issues relevant to clinical trials in order to increase their willingness to participate in a clinical trial. A good relationship between patients and their physician/oncologist, transparent communication, discussion of the potential benefits and side effects, and addressing patient concerns are all associated with patients' decisions to accrue to a trial. Patient engagement may be important to refine the study design of cancer clinical trials. For example, patients may suggest additional clinical trial endpoints of health related quality of life (HRQOL) to better address their needs and concerns. Patient-reported outcomes are becoming increasingly important especially those of mRCC targeted therapy. Because each class of targeted drugs has a unique adverse event (AE) profile, it is important to determine the effect of these AEs on the HRQOL outcomes. The potentially increased impact of therapy on global functioning and quality of life is critical in the ageing population where cancer is most prevalent.

Future directions

This call to action aims to increase awareness of the growing burden of kidney cancer among healthcare professionals, health policy makers, advocacy groups, industry, ……

- A more focused education of general practitioners (GPs) is necessary to raise awareness of the risk factors of kidney cancer.
  - Healthy lifestyles to maintain healthy weight and blood pressure should be promoted along with continued efforts to reduce tobacco consumption.
  - Screening for hypertension and increased BMI and follow-up of smoking cessation is required
- Additional investments in clinical research and new technologies are necessary
  - The mechanisms underlying the association with kidney cancer risk for obesity and hypertension should be further investigated
  - Newer techniques that make biopsies and imaging more accurate and development of markers which may lead to individualized risk assessment should be encouraged
  - There is a need to support new developments in immunotherapy
  - Several new drugs, sequences with existing drugs and combinations for administering these drugs are under investigation
  - Development of predictive biomarkers may result in a better personalized management of kidney cancer
  - Prospective studies of active surveillance with long-term follow-up are needed and active surveillance should be studied in comparison to other treatment modalities
- A patient-centred multidisciplinary approach is required to improve patient's care
- Further research is required to determine the most appropriate follow-up strategies of treatments
- Cost-effectiveness of treatments and follow-up strategies should be addressed
- There is a need for increased understanding of and access to clinical trials

Table 1. Median overall survival (OS) estimates in mRCC patients treated with first- and second-line targeted therapy according to IMDC risk groups

Number of risk factors	Risk category	First-line targeted therapy Median OS (months)	Second-line targeted therapy Median OS (months)
0	Favourable	43.2	35.3
1-2	Intermediate	22.5	16.6
3-6	Unfavourable	7.8	5.4

Table 2. Key phase III studies of targeted therapies and nivolumab in mRCC

Therapy	Number	Median PFS (months)	Median OS (months)	Author
First-line treatment				
Sunitinib vs IFN-α	750	11.0 vs 5.0 (*P*<0.001)	26.4 vs 21.8 (*P*=0.049)	Motzer *et al*[79,80]

Pazopanib vs placebo	435	9.2 vs 4.2 (*P*=0.0001)	NA	Sternberg *et al*[81]
Bevacizumab plus IFN-α vs IFN-α	732	8.5 vs 5.2 (*P*=0.0001)	18.3 vs 17.4 (*P*=0.069)	Rini *et al*[83]
Bevacizumab plus IFN-α vs IFN-α	649	10.2 vs 5.4 (*P*=0.0001)	23.3 vs 21.3 (*P*=0.1291)	Escudier *et al*[82]
IFN-α vs temsirolimus vs temsirolimus plus IFN-α	626	1.9 vs 3.8 vs 3.7 (*P*<0.001)	7.3 vs 10.9 vs 8.4 (*P*=0.008)	Hudes *et al*[84]
Pazopanib vs sunitinib	1110	8.4 vs 9.5	28.3 vs 29.3 (*P*=0.28)	Motzer *et al*[85]
Axitinib vs sorafenib	288	10.1 vs 6.5	NA	Hutson *et al*[86]
Second-line treatment				
Sorafenib vs placebo	903	5.5 vs 2.8 (*P*<0.01)	17.8 vs 14.3 (*P*=0.029)	Escudier *et al*[91,92]
Axitinib vs sorafenib	723	6.7 vs 4.7 (*P*<0.0001)	20.1 vs 19.2 (*P*=0.3744)	Rini *et al*[87] Motzer *et al*[88]
Temsirolimus vs sorafenib	512	4.3 vs 3.9 (*P*=0.19)	12.3 vs 16.6 (*P*=0.01)	Hutson *et al*[93]
Second- and third-line treatment				
Everolimus vs placebo	410	4.1 vs 1.9 (*P*<0.0001)	NA	Motzer *et al*[90]
Cabozantinib vs everolimus	658	7.4 vs 3.8 (*P*<0.001)	21.4 vs 16.5 (*P*=0.00026)	Choueiri *et al*[39,96]
Nivolumab vs everolimus	821	4.6 vs 4.4 (*P*=0.11)	25.0 vs 19.6 (*P*=0.002)	Motzer *et al*[38]
Third-line treatment				
Dovitinib vs Sorafenib	248	3.7 vs 3.6 (*P*=0.063)	NA	Motzer *et al*[100]

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