Renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) denotes cancer originated from renal epithelium and accounts for >90% of cancers in the kidney. The disease encompasses >10 histological and molecular subtypes, of which clear cell RCC (ccRCC) is most common and accounts for most cancer-related deaths. Although somatic *VHL* mutations have been described for some time, more-recent cancer genomic studies have identified mutations in epigenetics regulatory genes and demonstrated marked intratumour heterogeneity, which could have prognostic, predictive and therapeutic relevance. Localized RCC can be successfully managed with surgery whereas metastatic RCC is refractory to conventional chemotherapy. However, over the past decade, marked advances in treatment of metastatic RCC have been made, with targeted agents including sorafenib, sunitinib, bevacizumab, pazopanib and axitini that inhibit vascular endothelial growth factor (VEGF) and its receptor(VEGFR) and everolimus and temsirolimus, which inhibit mTOR complex 1, being approved. Since 2015, agents with additional targets aside from VEGFR have been approved, such as cabozantinib and lenvatinib; immunotherapies such as nivolumab have also been added to the armamentarium for metastatic RCC. Here, we provide an overview of the molecular biology of RCC, with

a focus on ccRCC, as well as updates to complement current clinical guidelines and an outline of potential future directions for RCC research and therapy.

[H1] Introduction

Renal cell carcinoma (RCC) encompasses a heterogeneous group of cancers derived from renal tubular epithelial cells[1] and is among the 10 most common cancers worldwide. Key advances in histopathological and molecular characterization of RCC over the past two decades have led to major revisions in its classification[2-5]. Major subtypes[6] with ≥5% incidence are clear cell RCC (ccRCC)[7], papillary RCC (pRCC)[8] and chromophobe RCC (chRCC)[9] (FIG. 1). The remaining subtypes are very rare (each with ≤1% total incidence)[5] and in cases where a tumour does not fit any subtype diagnostic criteria, it is designated as unclassified RCC (uRCC, ~4% total incidence)[10]. ccRCC is the most common subtype and accounts for the majority of kidney cancer deaths and is the focus of this Primer[11]. Indeed, owing to the predominance of clear cell histology in metastatic disease (83-88%)[12,13], tumours with non-clear cell histology have been grouped as 'nccRCC' (Table 1) for feasibility in conducting clinical trials[14-16]. Furthermore, recent cancer genomic studies have revealed an overt complexity of intra-tumour[17-19] and inter-tumour[7,20] heterogeneity in ccRCC, which could contribute to the heterogeneous clinical outcomes observed[21-23].

Localized RCC can be treated with partial or radical nephrectomy (removal of the kidney)[24], ablation[25] (destruction of the malignant tissue with heat or cold) or active surveillance[26] (monitoring of tumour growth with periodic radiographic studies). Despite nephrectomy with curative intent, ~30% of patients with ccRCC with localized disease eventually develop metastases[27-30], which require systemic therapies and is associated with high mortality. Targeted therapy against vascular endothelial growth factor (VEGF) and mTOR pathways have been developed, but treatment response is varied and most patients eventually progress[31]. However, increased genomic and molecular understanding of metastatic ccRCC has contributed to an unprecedented number of drugs approvals in the United States and European Union (currently 12 approved drugs with six different effective mechanisms of action are approved). In this Primer, we discuss these new approvals and the major progress made in biology of ccRCC that led to their development. Furthermore, we present insights into genomics-based risk and treatment stratification and discuss

treatment sequencing and combinations that are paving the way for the future design of personalized clinical management plans.

[H1] Epidemiology

[H2] Incidence and mortality

Kidney cancer accounts for approximately 2% of all cancer diagnoses and cancer deaths worldwide, with incidence rates generally higher in developed countries (FIG. 2)[32]. Annually, ~295,000 new kidney cancer cases are diagnosed and ~134,000 deaths are recorded worldwide[33,34]. Kidney cancer accounts for ~63,000 new cases and ~14,000 deaths yearly in the United States[35], and for ~84,000 new cases and ~35,000 deaths in Europe[36]. Men are more affected than women (a 2:1 ratio of new diagnoses).

The median age of patients with RCC in the Surveillance, Epidemiology, and End Results (SEER) database in the United States was 64 years with a near normal distribution[37]. Accordingly, when RCC is diagnosed at younger ages (≤46 years, which represents the lowest decile of the age distribution)[37,38], the possibility of an underlying hereditary kidney cancer syndrome — which accounts for 3-5% of all RCCs[5] — should be considered (Table 2)[39,40].

The incidence of RCC highest in the Czech Republic, with age-standardized annual rates of 22.1 and 9.9 new cases per 100,000 men and women, respectively, over the period 2003-2007[41]. The incidence is also very high in the Baltic and Eastern European countries, although the reasons for this excess are not known. Overall, incidence rates have been increasing over time in most populations, but mortality rates have levelled off or are decreasing since 1990s. This divergent pattern of increasing incidence and decreasing mortality is particularly evident in developed countries. For example, analyses within the SEER database indicate that the increase in RCC incidence is confined to small and localized tumours, likely due at least in part to increasingly frequent incidental detection of small renal masses (tumours ≤4 cm in size) that are unlikely to have metastasized from increased use of abdominal imaging[42]. The global increases in the prevalence of obesity, an established RCC risk factor, might also play a part in increasing incidence, as well as influencing clinical outcome[41,43].

[H2] Risk factors

RCC incidence increases markedly with age and is higher for men than women. In the United States, incidence varies by ethnic group, with rates highest among Native American, Indigenous Alaskans and African Americans, and lowest among Asian Americans and people of Pacific Island descent[35]. The major established risk factors for RCC include excess body weight, hypertension and cigarette smoking[44], which were factors in approximately half of all diagnosed cases in one US study[45]. Other medical conditions that have been associated with RCC in epidemiological studies include chronic kidney disease, haemodialysis, kidney transplantation, acquired kidney cystic disease, a previous RCC diagnosis and, possibly, diabetes mellitus[44]. Many lifestyle, dietary, occupational and environmental factors have also been associated with RCC with varying levels of evidence[46].

For example, contradictory reports exist on the association between red meat consumption and RCC risk[47,48]. Moderate alcohol consumption (≥11g per day) seems to reduce the risk for RCC[48,49]. In a case–control study on physical activity and the risk of RCC, inverse trends in risk were found, and the authors concluded that 9% of RCC cases could be avoided by increasing physical activity[50]. However, the inverse association might have involved other confounding factors such as BMI and social class correlates. Other studies have found no such inverse association[51].

Genetic factors also contribute to RCC risk, as evidenced by individuals with a family history of renal cancer having an approximate twofold increased risk[52]. Investigations into familial RCC have uncovered mutations in at least 11 genes (namely *BAP1, FLCN, FH, MET, PTEN, SDHB, SDHC, SDHD, TSC1, TSC2,* and *VHL*), some of which have also been implicated in sporadic RCC development[39]. A notable example is *VHL*, the mutated gene underlying von Hippel-Lindau disease, which is characterized by a high risk of developing ccRCC[53]; inactivation of the VHL protein, leading to unchecked expression of oncogenic hypoxia-inducible factors (HIF-1 and HIF-2), is also a hallmark of sporadic ccRCC tumours (see Mechanisms, below)[39,54]. Genome-wide association studies (GWAS) of RCC have identified six susceptibility loci to date, on chromosome regions 2p21, 2q22.3, 8q24.21, 11q13.3, 12p11.23 and 12q24.31[55-58]. The 2p21 locus maps to *EPAS1*, a gene encoding the HIF-2α subunit [55] whereas the biological effects underlying the 11q13.3 locus seems to be attributable to changes in the regulation of

CCND1 (encoding cyclin D1, which is involved in cell cycle regulation)[59]. The locus 12p11.23 probably maps to changes in *BHLHE41* (encoding basic helix-loop-helix family member e41, which is thought to have a role in regulation of the circadian rhythm)[60]. The disease genes underlying the other GWAS susceptibility loci have yet to be identified.

[H1] Mechanisms/pathophysiology

[H2] Genes and pathways

In ccRCC, the *VHL* tumour suppressor gene is the most frequently mutated gene[7,54], and its complete loss through genetic (point mutations, indels and 3p25 loss) and/or epigenetic (promoter methylation) mechanisms constitutes the earliest, truncal oncogenic driving event[61,62]. VHL is the substrate recognition component of an E3 ligase complex that ubiquitinates HIF-1α and HIF-2α for proteasome-mediated degradation[53,63,64]. Loss of VHL, therefore, leads to aberrant accumulation of HIF proteins despite an adequately oxygenated tissue microenvironment, which in turn results in uncontrolled activation of HIF target genes that regulate angiogenesis, glycolysis and apoptosis (FIG. 3). Accordingly, human ccRCC tumours are rich in lipids and glycogens, and are highly vascular[65,66] — which underlies why agents that primarily inhibit VEGF and its receptor VEGFR are effective treatments for metastatic ccRCC[14,15,67]. However, *VHL* loss alone is insufficient to induce ccRCC as evidenced by the long latency (>30 years) in individuals who harbour *VHL* germline mutations to develop ccRCC[53] and by the observation that *Vhl* loss in mice is unable to induce ccRCC[68]. These results suggest that additional genetic and/or epigenetic events are probably needed for ccRCC to develop[69].

To identify these events, large-scale cancer genomic projects have been undertaken, and have revealed several novel prevalent mutations in ccRCC, including *PBRM1* (29-41% of tumour samples), *SETD2* (8-12%), *BAP1* (6-10%), *KDM5C* (4-7%) and *MTOR* (5-6%)[7,70-73]. Interestingly, *PBRM1*, *SETD2* and *BAP1* encode chromatin and histone regulating proteins, are located at 3p21 and function as tumour suppressors[7,70-72]. As *VHL* resides at 3p25, a single copy loss of the short arm of chromosome 3 (3p) would result in haploinsufficiency of these four tumour suppressor genes, corroborating the fact that 3p loss (that is, loss of heterozygosity) is nearly a universal event in ccRCC[61] and constitutes an early genetic event[69]. By contrast, *MTOR* mutations in ccRCC are generally missense and functionally activating[73,74], which

could explain the reason mTOR pathway inhibitors, including everolimus and temsirolimus, are effective[75,76].

How individual mutations and their interactions contribute to the pathogenesis and their values as prognostic or predictive biomarkers in ccRCC are largely unknown. Nevertheless, a few studies have demonstrated interesting clinical correlations that warrant future validation. As inactivation of VHL is the founding event of ccRCC, its mutation status has no effect on clinical outcome, whereas mutations involved in disease progression such as *PBRM1*, *SETD2* and *BAP1* as well as *KDM5C* (which is also involved in chromatin modification) were shown to associate with aggressive clinical features[77-79]. Small renal masses harbouring *PBRM1* mutations were associated with stage III pathological features (that is, extrarenal growth but not extending beyond Gerota's fascia see below)[71], whereas *BAP1* mutations were associated with larger tumour sizes, higher Fuhrman nuclear grade (large nucleus with prominent nucleolus) and worse cancer-specific survival[77,78,80]. Interestingly, mutations in *BAP1* and *PBRM1*[70] or *KDM5C*[20] seem to occur mutually exclusively in ccRCC, offering a molecular subclassification of ccRCC. Furthermore, mutations of *KDM5C*, which is located at Xp.11, were predominantly detected in male patients and correlated with long-term therapeutic benefit from sunitinib[20]; and mutations of *SETD2* were associated with reduced relapse-free survival[80].

[H2] Tumour heterogeneity and cancer evolution

As Nowell first described 40 years ago[81], genetic diversity within tumours is thought to provide the substrate upon which selection can act, to enable tumours to adapt to new microenvironmental pressures and metabolic demands during the natural history of the cancer (FIG. 4A). Such genetic diversity has been studied extensively in ccRCC. For example, in a study of four patients with ccRCC who had multiple tumours were subjected to multi-region genetic analysis, *VHL* mutation and 3p loss of heterozygosity were found to be ubiquitous events across all regions sampled[17]. By contrast, common driver events such as *SETD2*, *PBRM1*, *MTOR*, *PIK3CA*, *PTEN* and *KDM5C* mutations were present heterogeneously within the primary tumour and metastatic sites — in some regions but not others. Such genetic characteristics enable the construction of tumour phylogenies, whereby the 'trunk' of the evolutionary tree depicts mutations found in the most recent common ancestor (MRCA) that are present in every tumour cell. 'Branched'

mutations are found in some subclones but not others; these mutations may be regionally distributed across the tumour, occupying distinct regional niches within the primary tumour or different niches between the primary and metastatic sites of disease.

Furthermore, parallel evolution has also been observed, whereby recurrent branch alterations in subclones affect the same gene, signal transduction pathway or protein complex (FIG. 4B). In some cases — such as *BAP1*, *PBRM1* and *SETD*2 mutations — such recurrent but distinct alterations can be readily explained as the 'second hit' event in the evolution of the tumour. In other cases, parallel evolution suggests considerable selection pressures for disruption of the same signalling pathway or protein complex. Additionally, convergence of genetic characteristics has been noted in several studies of ccRCC[19,23,82], whereby mutations in genes occur at different time points but result in similar overall genomic and phenotypic profiles; a 'braided river' model has been conceived to illustrate this phenomenon (FIG. 4C)[69]. Regardless of the modality, a follow up study of ccRCC samples for eight patients demonstrated evidence for branched evolution in which 73-75% of driver alterations were found to be subclonal[18].

Multi-region tumour analyses suggest the intriguing possibility that evolutionary trajectories are remarkably constrained in ccRCC, which — as our knowledge of microenvironmental, therapeutic and host selection pressures grows — could render the evolutionary routes predictable and, therefore, therapeutically tractable. For example, it has been shown that patients who responded well to mTOR inhibition harbour recurrent regionally separated aberrations in components of the mTOR pathway[75]. Furthermore, some subclonal alterations might be involved in the initiation and maintenance of cell-to-cell variation necessary for clonal selection. For example, *SETD2* loss of function has been shown to impair nucleosome compaction, minichromosome maintenance complex component 7 (MCM7) function and DNA polymerase delta loading to chromatin, resulting in impaired DNA replication fork progression. Additionally, failure to load lens epithelium-derived growth factor p75 splice variant (LEDGF) and DNA repair protein RAD51 homolog 1 (RAD51) — which are involved in DNA break repair — has also been observed upon *SETD2* loss, resulting in homologous recombination repair deficiency[83]. These events are, accordingly, plausible genomic biomarkers in ccRCC dispersed within distinct regional niches within each tumour[19,84].

[H2] Immune infiltration and the tumour microenvironment

In addition to genetic alterations, gene expression, metabolic and immunological analyses of ccRCC have also yielded important mechanistic and clinical insights [20,85-87]. Of these, perhaps the immune infiltration characteristics of ccRCC is of increasing interest, given the rise of immune checkpoint-blocking therapies in this disease (see below, Management). Notably, among 19 cancer types examined by The Cancer Genome Atlas research programme, ccRCC has the highest T cell infiltration score [87]. Furthermore, higher nuclear grade and stage in ccRCC was correlated with an increase in T helper 2 and T regulatory cell infiltration[87,88].

[H2] Disease models

Although RCC cell lines have been used for mechanistic studies, [89] ccRCC tumours in patients are highly vascular — a feature that cannot be recapitulated with *in vitro* cell studies. Furthermore, such cell lines can acquire additional genetic and/or epigenetic changes during passages such that *in vitro* drug screens do not yield specific, translatable insights[90]. Nevertheless, when these cell lines were injected subcutaneously into laboratory animals, xenografted tumours largely respond to anti-VEGF therapy[91] and can be used to investigate resistance mechanisms[92,93].

More recently, patient-derived xenograft (PDX) models have been established and have been shown to recapitulate the patient's documented clinical response to targeted therapies, which could be used in pre-clinical drug trials[94]. At the same time, efforts to develop mouse models that truly reflect human ccRCC genomics and morphology have been hampered by the fact that homozygous inactivation of the *Vhl* gene in mice does not result in ccRCC[68]. However, the identification of additional recurrent, prevalent mutations in human ccRCC have rekindled efforts to generate such models. For example, homozygous deletion of *Vhl* and *Pbrm1* in a mouse model resulted in multifocal, lipid-rich, glycogen-rich, transplantable ccRCC (J.J.H., unpublished data). Interestingly, homozygous deletion of *Vhl* and *Bap1* in a mouse model resulted in early lethality (<1 month), and some mice (within a cohort of 7) carrying homozygous deletion of *Vhl* and heterozygous deletion of *Bap1* developed tumour micronodules (0.25-1.8mm) with unknown tumour incidence and molecular characteristics [95]. Overall, animal models of RCC are currently limited but being eagerly pursued.

[H1] Diagnosis, screening and prevention

[H2] Diagnosis

Historically, patients were diagnosed with RCC after presenting with flank pain, gross haematuria and a palpable abdominal mass. Nowadays, the majority of diagnoses result from incidental findings. This shift is a consequence of the widespread use of non-invasive radiological techniques such as ultrasonography or abdominal CT imaging performed for another reason. That being said, paraneoplasic syndromes — symptoms caused by hormones or cytokines excreted by tumour cells or by an immune response against the tumour — are not uncommon in RCC [96] and symptoms include hypercalcaemia, fever and erythrocytosis. Most of these symptoms are usually reversed after tumour resection[11]. Diagnosis is usually strongly suspected by imaging studies although RCCs can display variable radiographic appearances[97]. Typical radiological features for ccRCC include exophytic (outward) growth, heterogeneity due to intratumoral necrosis or haemorrhage and high uptake of contrast-enhancement agents[98].

[H3] Staging.

The stage of RCC reflects the tumour size, extent of invasion outside of the kidney, the involvement of lymph nodes and whether the tumour has metastasized (FIG. 5). CT imaging with contrast enhancement of the chest, abdominal cavity and pelvis is required for optimal staging. Such imaging enables assessment of primary tumour (size and whether the tumour is organ-confined or extends to perinephric fat or kidney hilum), regional spread (lymph node involvement) and distant metastases (lung, bone and distant lymph nodes). MRI can also provide additional information, especially to determine whether the tumour extends into the vasculature (vena cava tumour thrombus). Bone scan, ^{18}F-fluorodeoxyglucose PET and imaging of the brain are not systematically recommended for initial staging[14,15]. Prognostic assessment will require further laboratory testing that includes, but is not limited to, haemoglobin, leukocyte and platelet counts; serum-corrected calcium levels; and lactate dehydrogenase levels[99,100].

[H3] Genomic implications.

An age of onset of ≤46 years raises the possibility of a hereditary syndrome (Table 2) and, according to the American Society of Clinical Oncology, should trigger consideration for genetic counselling and might

serve as a useful cut-off age when establishing genetic testing guidelines[37]. Indeed, awareness of the non-renal malignancies and non-neoplastic features associated with RCC is of interest to the physician to identify hereditary syndromes[40]. Furthermore, specific therapeutic options driven by the underlying biology are now being developed for these different RCC related to cancer susceptibility syndromes[101]. Upon confirmation, patients and their families harbouring mutations are subject to specialized monitoring and treatment plans to minimize morbidity and prevent mortality.

[H2] Histopathological confirmation

Histopathological confirmation of malignancy is obtained either with renal core biopsy or on the partial or radical nephrectomy specimen. Initial biopsy is recommended before ablative therapy is undertaken (in those for whom surgery is not an option) or before initiating systemic therapy (in those who have metastatic disease)[102]. In 2016, the WHO classification of RCC was updated[5] from previous (2004) WHO[1] and International Society of Urological Pathology (ISUP) Consensus Conference[4] (2013) systems. Although most RCCs can be easily classified on the basis of histological criteria, some tumours pose a diagnostic problem because they display a combination of features characteristic of different subtypes. For instance, the presence of clear cells is not unique to ccRCC but can be observed in pRCC, chRCC and MiT family translocation RCC (tRCC)[66]. Similarly, papillary structures, characteristic of pRCC, can be present in other RCC types[103]. In challenging cases, careful evaluation of cytological features, growth pattern, immunophenotype and genetic alterations usually enables the proper diagnosis. However, a subset of RCCs (~4%) cannot be assigned to any specific category because they either present combined morphologies or display unusual features and are, therefore, designated uRCC[3,104,105]. Nevertheless, a recent molecular characterization of 62 aggressive uRCC revealed distinct subsets including *NF2* loss (26%), mTORC1 pathway activation (21%) and mutations in chromatin and DNA damage regulators (21%)[10].

At macroscopic examination, the cut surface of the ccRCC tumours is golden yellow with frequent haemorrhagic, necrotic and cystic areas. Microscopically, ccRCC usually consists of tumour cells with clear cytoplasm arranged in nests or tubules surrounded by a rich vascular network. The clear appearance of the cytoplasm is due to the accumulation of glycogen and lipids. A variable proportion of tumour cells with granular eosinophilic cytoplasm can be observed and, in some cases, these cells constitute the entire

tumour mass[3,104,105]. The most widely used grading system for ccRCC is the Fuhrman grading system, which defines four nuclear grades (1-4) in order of increasing nuclear size, irregularity and nucleolar prominence[106]. The Fuhrman nuclear grade has been shown to have prognostic value in ccRCC[30,107,108].

It should be noted that all RCC types can contain foci of high-grade malignant spindle cells (that is, sarcomatoid differentiation). Thus, sarcomatoid RCC is no longer considered as an entity but rather as a progression of any RCC type[109]. Of note, recent genomic insights from sequencing matched sarcomatous and carcinomatous RCC demonstrated enrichment in *TP53* and *CDKN2A* mutations, implicating these genetic defects as underlying causes of sarcomatoid differentiation in RCC[110-112].

[H2] Screening

Owing to the relatively low incidence of RCC, universal screening (such as that for asymptomatic micro-hematuria) has not demonstrated a positive effect on outcomes in RCC[113]. Furthermore, other biomarkers have not yet been established for screening[114,115]. Imaging remains the primary tool for RCC detection and screening. An ultrasonography screening study in 45,905 participants reported a 10-fold higher RCC-incidence than expected for a general population with improved cancer-free survival when compared with symptomatic patients[116].

Although most cases are sporadic[62], the majority of patients with RCC might have a genetic predisposition[38,117]. Although, no guideline is available regarding the selection of patients for germline mutation testing, guidelines for monitoring those with confirmed hereditary syndromes that increase the risk of RCC are available[37].

[H2] Prevention: modifiable risk factors

Smoking, obesity and hypertension are associated with increased risks of developing RCC whereas exercise and moderate consumption of alcohol and flavonoids reduce RCC risks.

[H3] Tobacco. When compared to never smokers, a relative risk for ever smokers of 1.38 (95%CI=1.27-1.50) was reported in a meta-analysis including 8,032 cases and 13,800 controls from 5 cohort studies[118]. A

dose-dependent increase in risk in both men and women was found; individuals who had quit smoking >10 years prior had a lower risk when compared to those who had quit <10 years prior. Other studies have confirmed smoking as a risk factor for RCC[119].

[H3] Obesity. A 5 kg/m^2 increase in body mass index (BMI) was found to be strongly associated with RCC[120]. Similarly, a strong association between weight gain in early and mid-adulthood (18–35 years of age) with RCC was reported[121]. Moreover, central adiposity (relative risk 1.8, 95%CI 1.2-2.5) and the waist-to-hip ratio (0.86–2.88) was positively associated with RCC in women[122]. The impact of BMI on overall survival was also studied in 1,975 patients treated with targeted agents. The authors reported on a median overall survival of 25.6 months (95%CI 23.2-28.6) in patients with high BMI versus 17.1 months (95%CI 15.5-18.5) in patients with low BMI (adjusted hazard ratio of 0.84, 95%CI 0.73-0.95)[123]. Compared with stable weight, neither steady gain in weight nor weight loss was significantly associated with risk of RCC[121.]

[H3] Hypertension and medications. Higher BMI and hypertension were independently shown to increase the long-term risk of RCC in men whereas a reduction in blood pressure lowered the risk[124]. Aspirin use was found to be associated with an increased RCC risk in one out of five studies[125]; by contrast, paracetamol (acetaminophen) exposure showed no increased risk[126]. The role of phenacetin (acetophenetidin) exposure has been inconclusive[127]. Statins were reported to significantly reduce the risk of RCC in a large analysis (*n*=483,733), with a 48% risk reduction (adjusted odds ratio 0.52, 95%CI 0.45-0.60)[128]. However, owing to the sporadic and low frequency nature, current guideline does not support the role of empiric treatment for prevention of RCC in general population; patients with hereditary syndromes should be monitored more closely and treated accordingly.

[H1] Management

For patients with surgically resectable RCC, the standard of care is surgical excision by either partial or radical nephrectomy with a curative intent. By contrast, those with inoperable or metastatic RCC typically

undergo systemic treatment with targeted agents and/or immune checkpoint inhibitors. Deciding on which treatment has been largely guided by various nomograms[30]. For example, the UCLA Integrated Staging System (UISS) and Stage Size Grade and Necrosis (SSIGN) score integrate clinical (1997 TNM stage) and pathological (Fuhrman nuclear grade) information to recommend the length and frequency of clinical follow-up and the selection of high-risk patients for adjuvant studies[129-131]. Similarly, key prognostic factors have been identified, validated and adopted to guide and stratify patients with metastatic RCC for systemic treatment, including performance status, time from diagnosis to systemic treatment and blood levels of haemoglobin, neutrophils, platelets, calcium and lactate dehydrogenase[99,132,133].

[H2] Surgery

Surgical treatment of RCC is related to the clinical stage of the disease and to the general condition of the patient (FIG. 5). Although typically reserved for localized disease, both partial and radical nephrectomy can also be used with cytoreductive intent in patients with metastatic disease. Indeed, randomized controlled trials (RCTs) demonstrating the benefit of this approach date from the 1990s, when cytokine-based therapies dominated the systemic therapy landscape. Furthermore, although most patients included in RCTs of targeted therapies also underwent cytoreductive nephrectomy, the current role of excision of the primary tumour in these patients has yet validated . However, according to main international guidelines many centres in offer cytoreductive nephrectomy if there is a substantial disease volume at the primary site but only a low burden of metastatic disease[134]

[H3] Partial nephrectomy. The goal of partial nephrectomy is to completely remove the primary tumour while preserving the largest possible amount of healthy renal parenchyma. Partial nephrectomy is indicated for patient with T1 tumours (according to the Union for International Cancer Control TNM staging system) **[Au:OK?, ok]** and a normal contralateral kidney (elective indication). Moreover, partial nephrectomy is strongly recommended (imperative absolute indications) in patients with RCC who have only one kidney (anatomically or functionally), in those with bilateral synchronous RCC and in those with von Hippel-Lindau syndrome. Similarly, imperative relative indications include conditions that can impair renal function (for example, kidney stones, hypertension, diabetes and pyelonephritis). Indeed, partial nephrectomy offers lower renal function impairment[135-137] and equivalent oncological survival outcomes

compared with radical nephrectomy in those with T1 tumours[138,139]. More controversial is the favourable impact of partial nephrectomy on overall survival[140,141] because conventional wisdom dictates that removal of the whole kidney is better in terms of oncological outcome. In this scenario, surgical feasibility remains the main factor influencing the final decision making process.

In the past decade, nephrometry scoring systems have been proposed to predict the complexity of the partial nephrectomy procedure and predict perioperative outcomes according to the anatomical and topographical tumour characteristics (Table 3)[142]. The R.E.N.A.L. and PADUA nephrometry systems are still the most popular and most used tools to preoperatively classify tumours [143]. These first-generation systems, along with the Centrality Index system, mainly factor in tumour-related anatomical parameters, including face location (that is, anterior or posterior faces, accordingly to their coverage by the anterior or posterior layers of the renal fascia, respectively), longitudinal polar location, rim location (that is, whether the tumour is located at the lateral or medial rim of the kidney), degree of tumour extension into the parenchyma, renal sinus involvement, upper urinary collecting system involvement and clinical maximal diameter of the tumour. Clinical studies demonstrated that such nephrometry systems were able to predict the risk of bleeding and post-operative complications in patients who underwent partial nephrectomy [142]. Thus, they represent valid tools for counselling patients and selecting the ideal candidate for partial nephrectomy according to surgeon experience [143]. Second-generation nephrometry systems, such as Diameter-Axial-Polar system, Zonal NePhRo scoring system and Arterial Based Complexity System, should be externally validated and tested head-to-head against a first-generation system before being introduced in the clinical practice.

Laparoscopic partial nephrectomy (LPN) and robot-assisted partial nephrectomy (RAPN) are the main alternative to classical open partial nephrectomy (OPN). However, RAPN and OPN are more appropriate in the treatment of more-complex cases (based on expert opinion). Conversely, LPN should be reserved for small tumours (usually ≤4 cm in size) in patients without complex features as defined according to nephrometry systems (low- or intermediate-risk categories). Available meta-analyses have demonstrated that RAPN provides equivalent perioperative outcomes to LPN, but a significantly shorter warm ischaemia time[144,145]. Moreover, RAPN seems to be significantly better than OPN in terms of perioperative

complications, estimated blood loss and hospital stay[146,147]. Conversely, transfusion rate, ischaemia time, estimated glomerular filtration rate change and early cancer outcomes are similar between the two approaches[147]. International guidelines recommended the use of both approaches according to the surgeon and patient preferences.

Finally, partial nephrectomy can also involve simple enucleation — entirely sparing the healthy parenchyma around the tumour. Alternatively, classic enucleoresection whereby a thin layer of healthy parenchyma is removed or polar or wedge resection whereby a wider excision of healthy parenchyma is performed are also viable options. A minimal tumour-free surgical margin following partial nephrectomy seems appropriate to avoid the increased risk of local recurrence[24]. Positive surgical margins have been reported in 1-6% of cases regardless the type of used surgical technique[148]. Haematuria, perirenal haematoma and urinary fistulas are the most common complications of partial nephrectomy procedures. Less frequent postoperative complications can be represented by acute renal impairment and infection[149].

[H3] Radical nephrectomy. Classical radical nephrectomy consists in the removal of kidney, perirenal fat tissue, adrenal gland and regional lymph nodes. However, in patients with tumour $\leqslant$5 cm in size, located at the inferior pole, the adrenal gland can be spared. Similarly, regional lymph nodes dissection can be reserved for patients with clinically positive nodes detected by CT or during the surgical procedure [150]. Radical nephrectomy can be considered in cases with multiple small renal tumours, in cases in which the tumour extends into the vasculature and can be a laparoscopic or open procedure (FIG. 6). In most patients with stage I and II tumours, radical nephrectomy is currently performed using a traditional laparoscopic approach; the open approach remains the gold standard for the treatment of more complex cases. In experienced hands, the robot-assisted approach can represent a potential alternative to open surgery in cases with venous tumour thrombus.

Data recently extracted from the US National Cancer Data Base support the use of cytoreductive nephrectomy in those with metastatic disease even while they receive systemic targeted therapies. Indeed, the median overall survival was 17.1 months in cytoreductive nephrectomy cases versus 7.7 months in non-cytoreductive nephrectomy group[151].

[H2] Active surveillance and ablative therapies

Active surveillance and ablative techniques such as cryotherapy or radiofrequency ablation are alternative strategies for elderly patients and/or those with competing health risks and limited life expectancy that renders them unsuitable for surgery[15,24].

A definite protocol for active surveillance has yet to be defined. The most common approach consists of alternating between ultrasonography imaging and CT or MRI every 3 months in the first year, every 6 months in the second year and annually thereafter. Intervention should be considered for growth to >3-4 cm or by >0.4-0.5 cm per year[152]. Data from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry in the United States showed that in a well-selected cohort of patients with up to 5 years of prospective follow-up, active surveillance was not inferior to primary intervention in terms of both overall survival and cancer-specific survival [26].

Ablative technology must be able to completely destroy all viable tumour tissue with no area of viable tumour left. Both cryotherapy and radiofrequency ablation can be performed using a laparoscopic or percutaneous approach under a CT or ultrasound guidance. A meta-analysis of case series showed 89% and 90% of efficacy for cryoablation and radiofrequency ablation, respectively[25]; complication rates are 20% and 19%. Available low quality studies suggest a higher local recurrence rate for ablative therapies compared with partial nephrectomy[153].

[H2] Medical management

The past 10 years have seen the approval of a number of targeted therapeutic agents and one immunotherapy agent for the treatment of metastatic RCC (FIG. 7). However, in the adjuvant setting after surgery, the situation is less clear and a randomised trial (ASSURE) of sunitinib versus sorafenib versus placebo showed no benefit for either drug therapy in terms of disease-free survival[131]. Notably, a recent study in the adjuvant setting reported a disease-free survival benefit for 1 year of sunitinib therapy in

comparison with observation in the S-TRAC trial[130]. A number of other trials of adjuvant targeted therapies (such as PROTECT and SORCE) have completed accrual and will report outcomes in the next 12 months.

[H3] Targeted therapies. Given the highly vascular nature of RCCs, it is unsurprising that several therapies are available to exploit this feature. Indeed, tyrosine kinase inhibitors targeting the VEGF signalling axis approved in the first-line and second-line settings for the treatment of metastatic RCC in United States and European Union are sorafenib, sunitinib, pazopanib, axitinib, lenvatinib and cabozantinib[154-159]. All approvals have been as single agents except the combinations of lenvatinib with everolimus; additionally, the anti-VEGF monoclonal antibody bevacizumab is approved for use with interferon-α[160,161]. Broadly speaking, sunitinib, pazopanib and the combination of bevacizumab and interferon-α are approved as first-line options whereas axitinib and cabozantinib are approved in the second line. The mTOR inhibitors everolimus and temsirolimus are approved as single agents in the second-line setting and in the first line in patients with poor risk status[162,163]. Indeed, arguably the landmark trial of first-line systemic therapy of metastatic RCC was the phase 3 study of sunitinib versus interferon-α reported in 2007 in which the superiority of sunitinib in terms of response rate, progression free and overall survival was reported[155]. This trial established sunitinib as the standard of care and the drug remains the comparator for all currently recruiting phase 3 studies of new drugs.

No clinically usable markers are available to select patients for particular therapies, despite intensive efforts. As such, the average duration of disease control with these drugs is 8-9 months in the first line setting and 5-6 months in the second line setting. Most of the phase 3 RCTs leading to the approval of these agents have excluded patients with nccRCC (Box 1) and as such this evidence base relates largely to ccRCC. Furthermore all of these agents are given continuously until disease progression in the absence of major toxicity. Furthermore, alternative schedules such as those electively interrupting therapy for prolonged periods have not been reported from RCTs.

[H3] Immunotherapy. Cytokines such as interferon-α and high dose IL-2 that enhance anti-tumour immune activity have been used since the 1990s to treat metastatic RCC and were standards of care prior to the introduction of sunitinib[164]. Both drugs typically benefit only a small subset of patients (generally those

with intrinsically favourable disease biology) and are associated with significant toxicity, particularly in the case of high-dose IL-2. Many studies are currently investigating combinations of anti-VEGF therapy with new-generation of immunotherapy agents in the form of T-cell immune checkpoint inhibitors such as the antibodies against programmed cell death protein 1 ligand 1 (PDL1), which include avelumab and atezolizumab, and antibodies against programmed cell death protein 1 (PD1), which include nivolumab and pembrolizumab). PD1 negatively regulates T cell function and its ligand PDL1 is highly expressed by cancer cells; accordingly, blockade of the PD1–PDL1 axis promotes T cell activation and immune killing of the cancer. Another combination under investigation (Checkmate 214, NCT02231749) is nivolumab with ipilimumab, an inhibitor of the T-cell checkpoint cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4 also downregulates T cell function; its inhibition by these antibodies promotes T cell activation.

Nivolumab was approved in United States and European Union after the Checkmate 025 RCT showed an overall survival benefit compared with everolimus in patients who had failed prior therapy with sunitinib and pazopanib[165]. However, the response rate to nivolumab was only 25% (5% for everolimus) and most patients treated did not experience significant tumour shrinkage. Although these check point inhibitors show promise, predicting response is difficult. In Checkmate 025, for example, PDL1 expression did not correlate with response, as had been reported in other trials in other cancer types [165]. The reason for this observation is unknown, but PD-L1 expression is dynamic in space and time and archival (paraffin-embedded) material from the primary tumour used in Checkmate 025 might not have been representative of PD-L1 expression at metastatic tumour sites.

Finally, nivolumab is well tolerated compared with everolimus. Furthermore, it has been possible to combine nivolumab (and other anti-PD1 or anti-PDL1 therapies) with ‘clean’ (that is, more-specific, less-toxic and easier to combine) anti-VEGF therapies such as axitinib and bevacizumab, leading to a number of phase 3 studies of such combinations in metastatic RCC.

[H1] Quality of life

Quality of life and patient reported outcomes have become an important way to assess therapeutic strategies in the treatment of patients with RCC. Adverse events are important to consider and these are summarized in Table 4. Although oncological outcomes such as survival are more objective, validated quality of life measures have been developed to help assess the patient experience.

For localized RCC, a systematic review was performed which included data from 29 studies that included randomized and non-randomized studies[149]. It noted that quality of life outcomes after partial nephrectomy were superior to those of radical nephrectomy regardless of approach or technique. Interestingly, no good evidence suggested that cryotherapy or radiofrequency ablation had better quality of life outcomes compared to nephrectomy.

For metastatic RCC, quality of life measures become more important as treatment is usually palliative and patients continually balance quality versus quantity of life. A validated 15-question tool called the Functional Assessment of Cancer Therapy (FACT)–Kidney Cancer Symptom Index (FKSI) is the most specific to kidney cancer [166]. A subscale of this, the FKSI-DRS (disease-related symptoms) has nine kidney cancer-specific questions on the topics of lack of energy, pain, weight loss, bone pain, fatigue, shortness of breath, cough, fever and haematuria. Other more-general questionnaires exist and have been used in RCC clinical trials, including the Functional Assessment of Cancer Therapy General (FACT-G), the EuroQOL EQ-5D and Visual Analogue Scale (VAS)[167]. These tools enable investigators to assess quality of life; however, limitations including questionnaire burden, incomplete answering and defining a truly clinically significant minimal difference in quality of life scores remain.

In the phase 3 registration trial of first-line sunitinib versus interferon-α in the metastatic setting, the FKSI, FKSI-DRS, FACT-G, EQ-5D and EQ-VAS demonstrated a consistent favourable difference in quality of life for sunitinib [155]. This finding can probably be attributed to the favourable adverse effect profile of sunitinib, which is associated with less fatigue than interferon-α, and higher efficacy of sunitinib (31% response rate) compared with interferon-α (6%).

Quality of life was assessed with FKSI-19, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Cancer Therapy Satisfaction Questionnaire (CTSQ) and Seville Quality of Life Questionnaire (SQLQ) in the COMPARZ clinical trial comparing first line sunitinib versus pazopanib[156]. Measurements were taken at baseline and at day 28 of each treatment cycle, which is typically the point of highest sunitinib toxicity (including soreness in mouth, throat, hands and feet). Improved quality of life scores were observed in those patients taking pazopanib versus those taking sunitinib.

The immune checkpoint inhibitors have also had quality of life analyses reported[167]. In the Checkmate 025 study of nivolumab used the FKSI-DRS score, these were performed at baseline and every 4 weeks up to study week 104 after which assessments were reduced. Median time to health-related quality of life improvement was shorter in patients given nivolumab (4.7 months, 95% CI 3.7–7.5) than in patients given everolimus (median not reached). The overall survival of patients was longer in those who had high baseline health-related quality of life scores who then improved than those with similar baseline whose scores then deteriorated. The shortest overall survival was observed in those with low baseline scores who then deteriorated.

[H1] Outlook

With the considerable advances in the molecular biology and management of RCC over the past several decades, it is not without reason that one could describe the current era of knowledge and available treatments as the ‘golden age’ of research. If we are to progress further, advances in diagnosis, local management and systemic therapy are needed to achieve >80% long-term survival that might define the future ‘diamond age’ of kidney cancer research and therapy (FIG. 7). Areas that currently show promise include developing strategies for treating high-risk patients, biomarkers to guide treatment and preventing and overcoming drug resistance.

[H2] Biomarkers to guide treatment

Although wide ranging clinical outcomes can be attributed to tumour heterogeneity in RCC, opportunities to further improve clinical outcomes on the basis of individual tumour characteristics (so called precision medicine) is an emerging field. Given that nivolumab, cabozantinib and lenvatinib were only recently

approved, and few correlative studies have been reported, potential biomarkers for VEGF and mTOR inhibitors currently have the most promise.

Biomarkers can range from clinical parameters (such as blood pressure) and endogenous substances (such as plasma proteins) to pathobiological features specific to individual tumours (such as mutations). For example, as an on-target clinical biomarker, hypertension (systolic blood pressure ≥140mmHg) in patients receiving VEGF inhibitors has been shown to be associated with longer progression free survival and overall survival[168]. Additionally, many studies have looked into circulating biomarkers[169], among which high levels of IL-6, IL-8, hepatocyte growth factor and osteopontin were associated with shorter progression free survival in patients receiving pazopanib and sunitinib[170,171] whereas high levels of lactate dehydrogenase were associated with better overall survival in those receiving temsirolimus but not interferon-α[172].

Genetic biomarkers are also beginning to be studied for associations with treatment outcome in various metastatic settings[173-175]. For example, RECORD-3, a large randomized phase 2 trial (*n*=471), demonstrated the better first-line efficacy of sunitinib (progression free survival of 10.7 months) over first-line everolimus (progression free survival of 7.9 months)[22]. Interestingly, genomic biomarker analysis of patients enrolled in RECORD-3 showed that *BAP1* mutations were associated with 8.1 month progression free survival with first line sunitinib but 5.5 month with first-line everolimus — a significant difference. By contrast *PBRM1* mutations showed no such association[20], which is consistent with a VEGF inhibitor outlier study[173] and warrants further validation. That *BAP1* mutations were associated with inferior outcomes on everolimus[20] is surprising given their reported higher mTORC1 activity than *PBMR1* mutant tumours[70]. Furthermore, patients with *KDM5C* mutations were associated with a much longer first-line progression-free survival with sunitinib (20.6 months) than everolimus (9.8 months)[20]. As mutual exclusivity was detected between mutations of *BAP1* and *PBRM1* or *KDM5C*[20], molecular subgrouping of metastatic ccRCC based on these three genes could be of clinical value in the future. In addition, case-based mTOR inhibitor outlier studies recognized activation mutations of *MTOR* and bi-allelic inactivation of *TSC1* or TSC2 as potential biomarkers for long-term responders[69,73,75,76].

[H2] Managing high-risk patients

A significant number (~30%) of patients with non-metastatic disease (based on clinical and pathological evaluation at the initial diagnosis) have occult metastases that will eventually become clinically evident. How to identify and better manage these high-risk patients presents a major challenge for operating urologists. As we begin to appreciate the impact that prevalent RCC mutations (in *PBRM1*, *SETD2*, *BAP1*, *KDM5C*, *PTEN*, and *TP53*) have on clinical outcomes, incorporating specific mutational information into prognostic nomograms will become increasingly useful. For example, transcription signatures such as ClearCode34[86], and other biomarkers in the blood and urine, might be incorporated into validated predictive biomarkers for RCC recurrence after surgery. Similarly, predicting treatment response to systemic therapy might be plausible and will reduce cost and improve RCC cancer patient care. Our improving ability to identify high-risk patients with RCC and formulate personalized treatment and follow-up plans based on multi-omics holds the promise to quickly reduce the incidence of patients developing overt metastatic disease and render long-term survival.

[H2] Emerging therapies and changes to treatment

Several promising new drugs with novel mechanisms of action are in various stages of clinical trials. For immunotherapeutics, ipilimumab, an anti-CTLA-4 antibody, in combination with nivolumab has shown remarkable response rate of ~40% in the Checkmate 016 trial[176]. Additionally, the efficacy of autologous dendritic cell-based immunotherapy, which consists of expanding patient's own dendritic cells *in vitro* followed by the introduction of tumour RNA before re-infusion back to the patient, in combination with sunitinib has been examined and showed early promise[177].

In the realm of targeted therapeutics, inhibitors specifically targeting HIF-2 have been developed[178,179]. As kidney cancer is characterized by aberrant glycolysis (with aberrant glutamine and tryptophan metabolism[65,180,181]), it is of interest to learn if the glutaminase inhibitor CB-839[182] and the indolemaine-2,3-dioxygenase inhibitor INCB024360[183] could yield additional clinical benefits when added to existing therapies. Finally, as many of these novel therapeutic agents act on modulating the anti-cancer response in patients, further understanding of the intricate relationship between individual an kidney cancer cell and its

respective immune microenvironment would be critical for the future success in designing combination treatment to improve survival[87,184-187].

Given the increasing understanding of tumour biology and the increasing number of treatment options, how treatments are selected in the future will undoubtedly change (FIG. 8). As well as those already discussed, potential measures of high values personalized vaccination[188], targeted radiotherapy to enhance anti-tumour immune response[189] and selective cytoreductive nephrectomy in patients who were initially inoperable but later showed marked shrinkage of tumours after systemic treatments. Additionally, neoadjuvant or adjuvant[190] immunotherapy or targeted therapy could become integrated into the current treatment algorithms.

[H2] Preventing and overcoming drug resistance

Model systems and clinical experience have shown that inhibiting RCC activity with multiple drugs specific to different targets is superior to single-agent approaches[23,191,192]. However, such approaches tend to produce more toxicities — on and off-target. For example, the combination of sunitinib and everolimus in treating metastatic RCC subjected patients to severe toxicity[193]. Nevertheless, bevacizumab, a more tolerable VEGF pathway inhibitor than sunitinib, plus everolimus is well tolerated and has been shown to be efficacious in treating nccRCC with papillary features[194]. The success of polypharmacy relies on efficient and correct targeting of both primary and secondary (bypass) pathways[69,195]. In ccRCC, VEGF is the primary pathway due to the universal *VHL* loss; secondary targets can include mTORC1, MET and IL-8 but not EGFR or PI3K pathways when one takes into consideration of available clinical[158,159,169,196,197] and preclinical studies[92,198-200].

Given the availability of targeted therapies (FIG. 7), immediate challenge is to design the most effective and specific regimen through combining or sequencing drugs to prevent resistance in individual patients[201]. Interestingly, a recent study in melanoma patients who relapsed after the initial treatment response on PD-1 blockade revealed invaluable insights on how tumour cells might develop resistance to immunotherapies, including defects in interferon-receptor signalling and in antigen presentation [202]. As immune checkpoint inhibitors functions independently of specific oncogenic pathways and incur distinct resistance

mechanisms[202], the combination of these drugs with targeted therapies is of great clinical interests[203] and theoretically can prevent the emergence of escape mechanisms from either agent.

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Author contributions

Introduction (J.J.H); Epidemiology (M.P.); Mechanisms/pathophysiology (S.S., J.J.H. and C.S.); Diagnosis screening and prevention (L.A. and M.S.); Management (V.F. and J.L.); Quality of life (D.Y.H.); Outlook (J.J.H.); and Overview of Primer (J.J.H.).

Competing interests

J.J.H. is a consultant for Novartis, Eisai and Chugai and received research funding from Pfizer, Novartis, Eisai and Cancer Genomics Inc. C.S. is a consultant for Roche, Pfizer, Boehringer Ingelheim, Novartis, Celgene, Servler, Eli Lilly, and Glaxo Smithkline, and owns stock options from Achilles Therapeutics, Epic Biosciences, Grail, and Apogen Biotech. L.A. is a consultant for Pfizer, Novartis, Sanofi, Amgen, Bristol-Myers Squibb, Bayer and Cerulean, and received research funding from Pfizer and Novartis. M.S. is a consultant for Pfizer, Bristol-Myers Squibb, Ipsen, Exelixis, Eisai, Roche, Novartis and Astellas. D.Y.H. is a consultant for Pfizer, Novartis and Bristol-Myers Squibb. J.L. received research funding from Novartis, Pfizer, Bristol-Myers Squibb, and Merck Sharp & Dohme. M.P.P., S.S. and V.F. declare no competing interests.

Display items

Box 1 | Limitations in the management of nccRCC.

From the perspective of surgical management, the presence of non-clear cell histology rarely has a bearing on treatment and, in fact, histological subtype is often unknown pre-operatively. Limited data are available to guide medical management of non-clear cell renal cell carcinoma (nccRCC) as a consequence of the exclusion in general of non-clear cell histologies from registration trials of targeted agents over the past 10 years. Importantly, the tumours classed as nccRCC are fundamentally different; there is no reason to suppose that a therapy effective for papillary RCC would be effective for chromophobe or indeed any other subtype of kidney cancer. Nevertheless, some trials have been carried out and have broadly established sunitinib as a reasonable first line option in nccRCC, although the efficacy is less than for clear cell renal carcinoma (ccRCC). Most patients with metastatic nccRCC are treated with targeted agents approved for ccRCC, with the data favouring VEGF inhibitors over mTORC1 inhibitors[204,22,205]. Unfortunately, most patients with nccRCC succumb to their diseases within 18 months despite systemic treatment[12,13,204,205,206], and currently there is no evidence base for the treatment of nccRCC with checkpoint inhibitors. Encouragingly, a recent phase 2 trial reported everolimus plus bevacizumab as an effective combination in treating nccRCC in patients whose tumours display papillary features, achieving an overall response rate at 43% and a median progression free survival at 12.9 months[194]. Arguably, everolimus plus bevacizumab should be considered as the comparison arm in trials in rare RCC subtypes displaying predominant papillary morphology (papillary RCC type I and type II, and unclassified RCC with papillary features). Overall, the advances made are encouraging, but drug therapies tailored specifically to subtype remains an unmet need. Initiatives such as rarekidneycancer.org set up by experts and patient advocates are important steps to encourage rapid communication among patients with rare kidney cancer, doctors specialized in nccRCC and trialists.

Figure 1. Distinct subtypes of RCC. Approximately 75% of renal cell carcinomas (RCCs) are a | clear cell RCC (ccRCC). b | Papillary RCCs make up ~15% of all kidney cancers and are divided into two types based on staining features: b | type 1 (basophilic) and c | type 2 (eosinophilic). d | Chromophobe RCCs make up ~5% of kidney tumours. Other minor subtypes include e | MiT family translocation RCCs and f | collecting duct RCCs. Additional minor subtypes include medullary RCC, clear cell papillary RCC, acquired cystic disease-associated RCC, tubulocystic RCC, mucinous tubular and spindle RCC, succinate dehydrogenase-deficient RCC, hereditary leiomyomatosis, renal cell carcinoma-associated RCC and oncocytoma. Tumours not fitting into any of these categories are designated unclassified RCC. Scale bar = 200 μm.

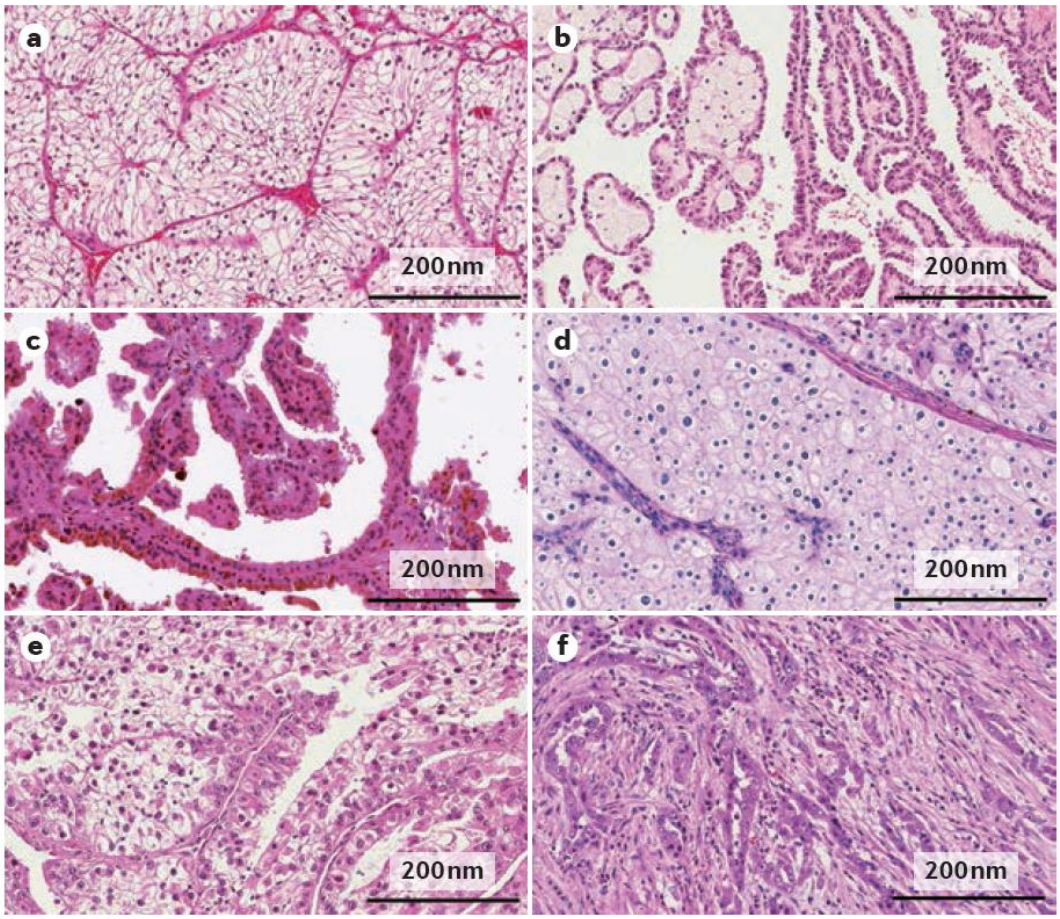


Figure 2. Globalkidney cancer incidence. Estimated age-standardized rates (ASRs) of incidence for both sexes (per 100,000 persons) in 2012. Rates are generally higher in developed countries, with the highest incidence the Czech Republic (reasons unknown). Data from GLOBOCAN database; http://globocan.iarc.fr.

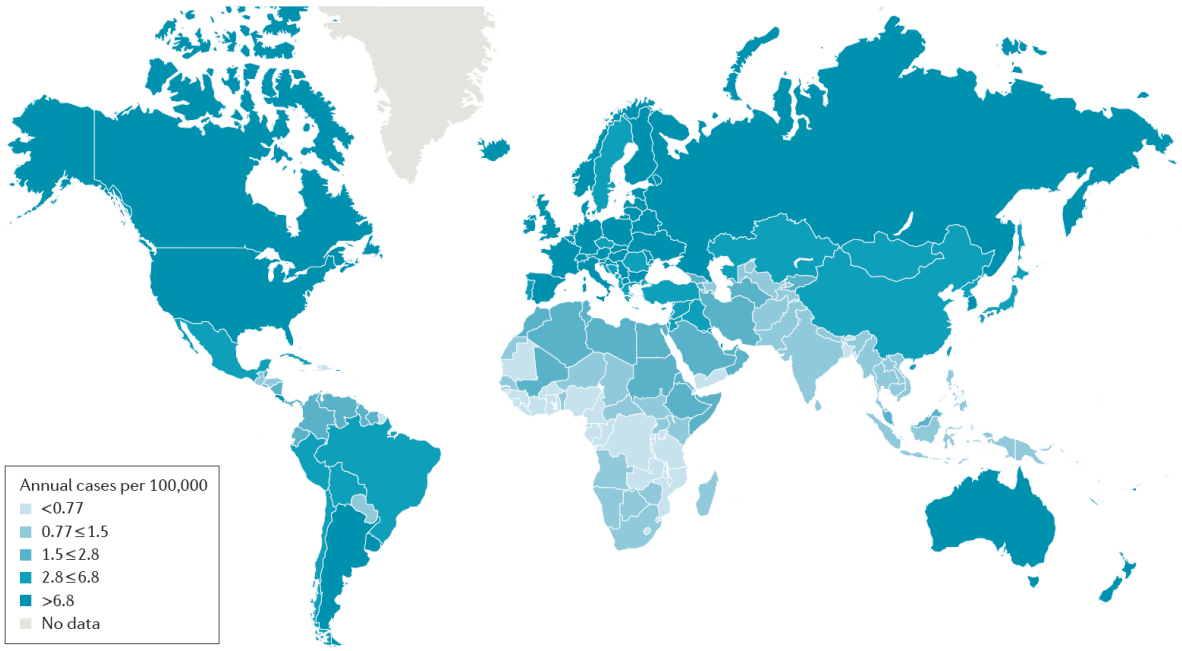


Figure 3. *VHL* inactivation in ccRCC and its implication in targeted therapy. Loss of *VHL* is the most frequent genetic feature of clear cell renal cell carcinoma (ccRCC). Its loss relieves the cell of negative regulation of the hypoxia inducible factors (HIFs), which results in increase HIF target gene expression and ensuing changes in cellular metabolism and signalling that enhances cell survival. For example, increased vascular endothelial growth factor (VEGF) expression increases angiogenesis in concert with increased signalling from growth factor receptors in endothelial cells in the tumour microenvironment (including fibroblast growth factor (FGF) and hepatocyte growth factor (HGF)). Collectively, these changes provide the targets for therapeutic agents to impede tumour growth, as indicated. FGFR, FGF receptor VEGFR, VEGF; TSC, tuberous sclerosis complex; PI3K, phosphatidylinositol 4,5-bisphosphate 3-kinase; AKT, RAC-α serine/threonine-protein kinase; Rheb, GTP-binding protein Rheb; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; S6K1, ribosomal protein S6 kinase; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; HRE, HIF response element; MET, hepatocyte growth factor receptor.

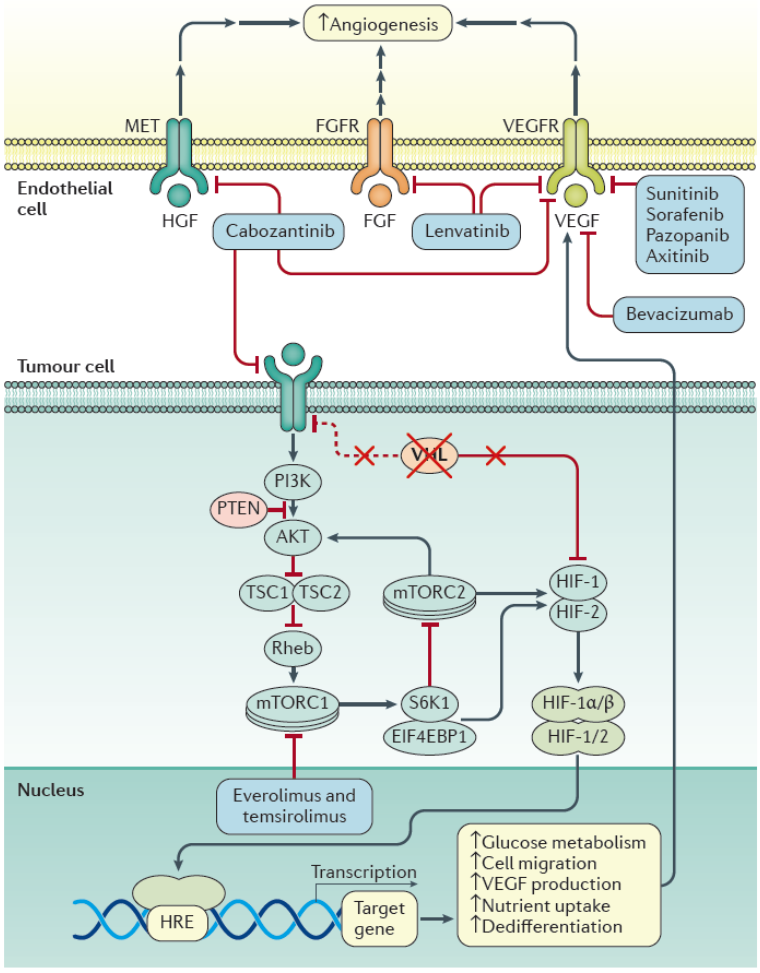


Figure 4. Cancer evolution and tumour heterogeneity in ccRCC. Although *VHL* mutation and 3p loss of heterozygosity are early events that are evident in all clear cell renal cell carcinoma (ccRCC) cells regardless of the region of the tumour sampled, common driver mutations (for example, *SETD2*, *MTOR* and *KDM5C* mutations) are present heterogeneously — suggestive of subclonal evolution of the tumour. a | Cancer subclones originate from the most recent common ancestor cell (MRCA) in which a normal cell acquires all functional capacities to become cancer cell. b | Genomic heterogeneity can result from the sequential, parallel accumulation of mutations, contributing to the heterogeneity and the evolution of ccRCC. In this example, 'R' represents the genomic characteristics of the primary tumour and 'M' represents the genomic characteristics of the metastatic sites, numbered accordingly. The major genetic lesions acquired after *VHL* mutation feature in different samples and are indicated on the branches. c | However, some evidence suggests that tumours can converge by way of parallel evolution. Here, a hypothetical beaded river model depicts the sequential convergence of *SETD2* and *KDM5C* mutations through different spatiotemporally distinct genetic events.

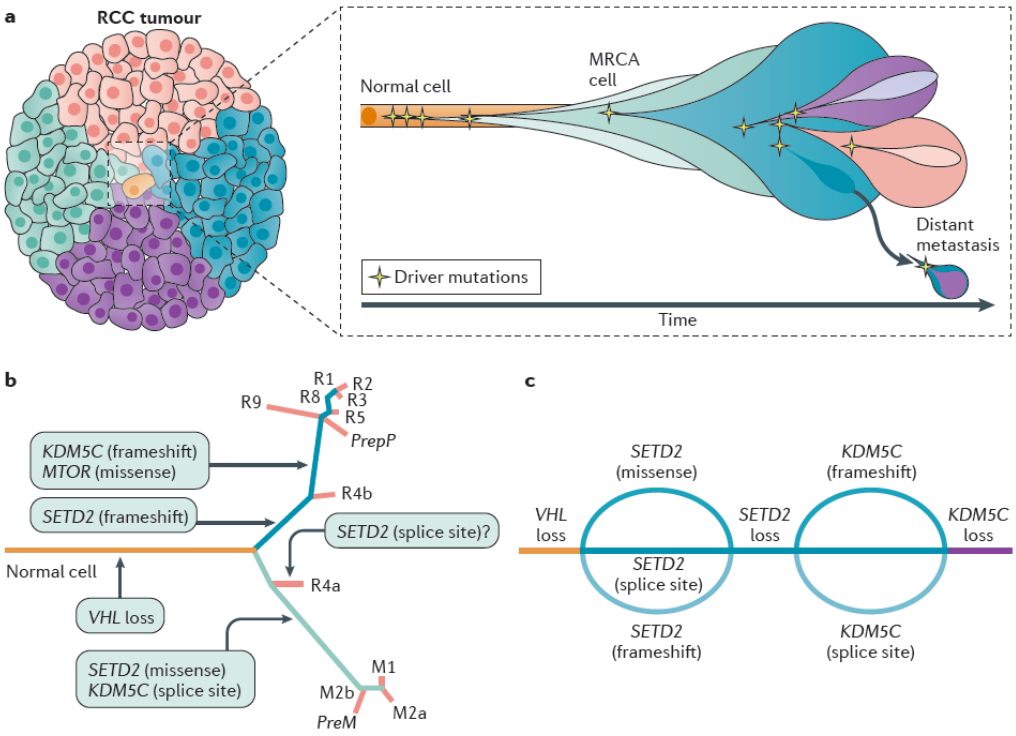


Figure 5. Stages of kidney cancer and recommended treatments. Staging renal cell carcinoma (RCC) is based on size, position and lymph node involvement[15]. For example, a stage I or II tumour is enclosed wholly in the kidney. Stage III tumours can extend into major veins or adrenal glands within Gerota's fascia (the layer of connective tissue encapsulating the kidneys and adrenal glands) or can involve one regional lymph node involvement. Stage IV tumours can invade beyond Gerota's fascia and/or have distant metastases. *Until the introduction of newer targeted therapies beginning in 2005, the 5-year survival of stage IV RCC was <10%. Treatment is largely guided by stage[15,24]. For example, those with stage I RCC who are fit for surgery are recommended partial nephrectomy. However, radical nephrectomy is also an option; for elderly patients or those who cannot undergo surgery owing to comorbidities, active surveillance or ablative therapies are recommended. In patients with stage III RCC, radical nephrectomy is recommended with lymph node dissection in those with clinical enlarged lymph nodes, but systemic therapies might be the only available option for those with extensive disease and poor performance status.

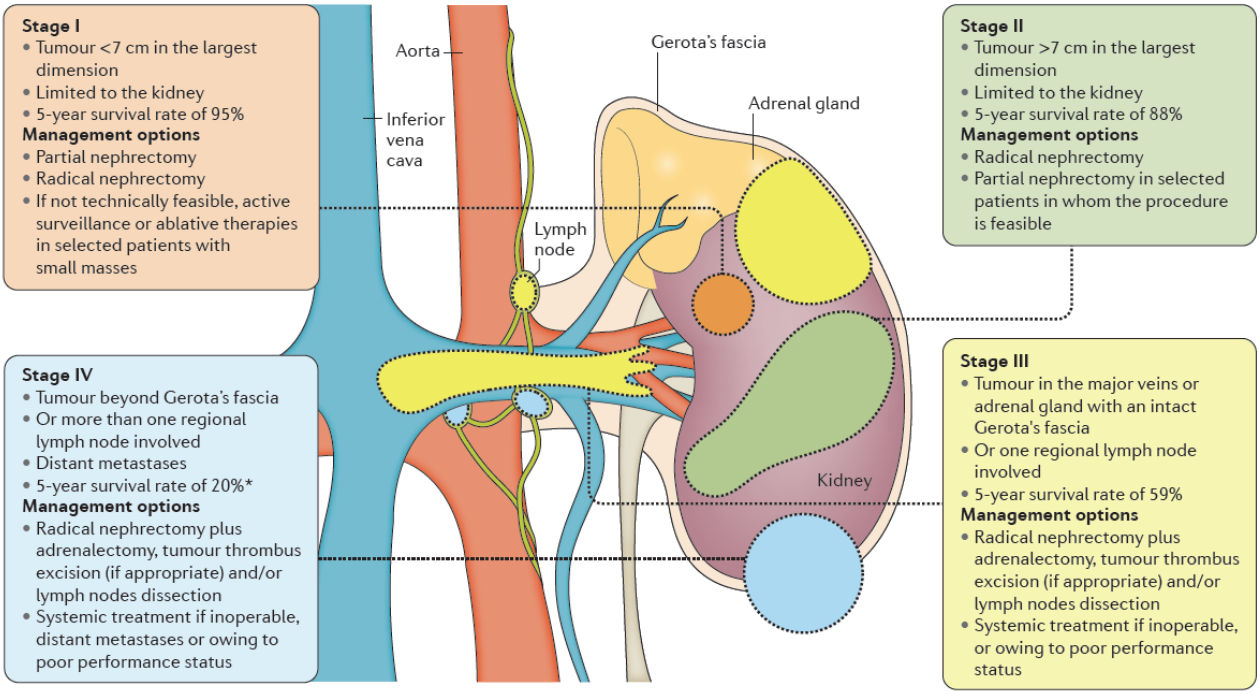


Figure 6. Indications for radical nephrectomy. a | Radical nephrectomy could be considered in cases with multiple small renal tumours (circled). b | Conversely, radical nephrectomy and contextual excision of neoplastic thrombus into renal vein or cava vein tumour thrombus is the gold standard treatment for patients with venous involvement.

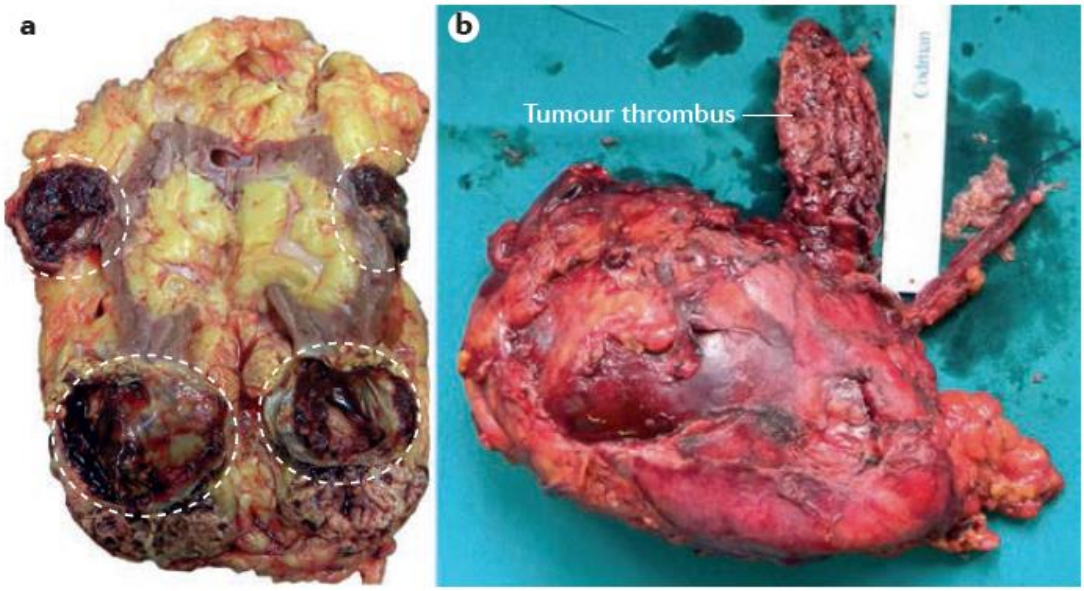


Figure 7. Therapeutic evolution and survival outcome of metastatic ccRCC through the four different eras. a | Prior to 2004, two drugs were available to treat RCC (with a median survival of ~15 months). This so-called dark age of treatments was followed by the modern age (2005-2014), which saw seven additional regimens gain approval (increasing median survival to ~30 months). Currently, the golden age has already witnessed the introduction of three drugs, with more anticipated over the next decade. b | These advances promise to be translated to a significant number of patients (~50%) achieving durable remissions under active surveillance by 2025 with a median survival of ~5 years. The ultimate goal is the future diamond age of drug approvals is >80% of patients with metastatic ccRCC long-term survival. Dashed lines represent predicted survival.

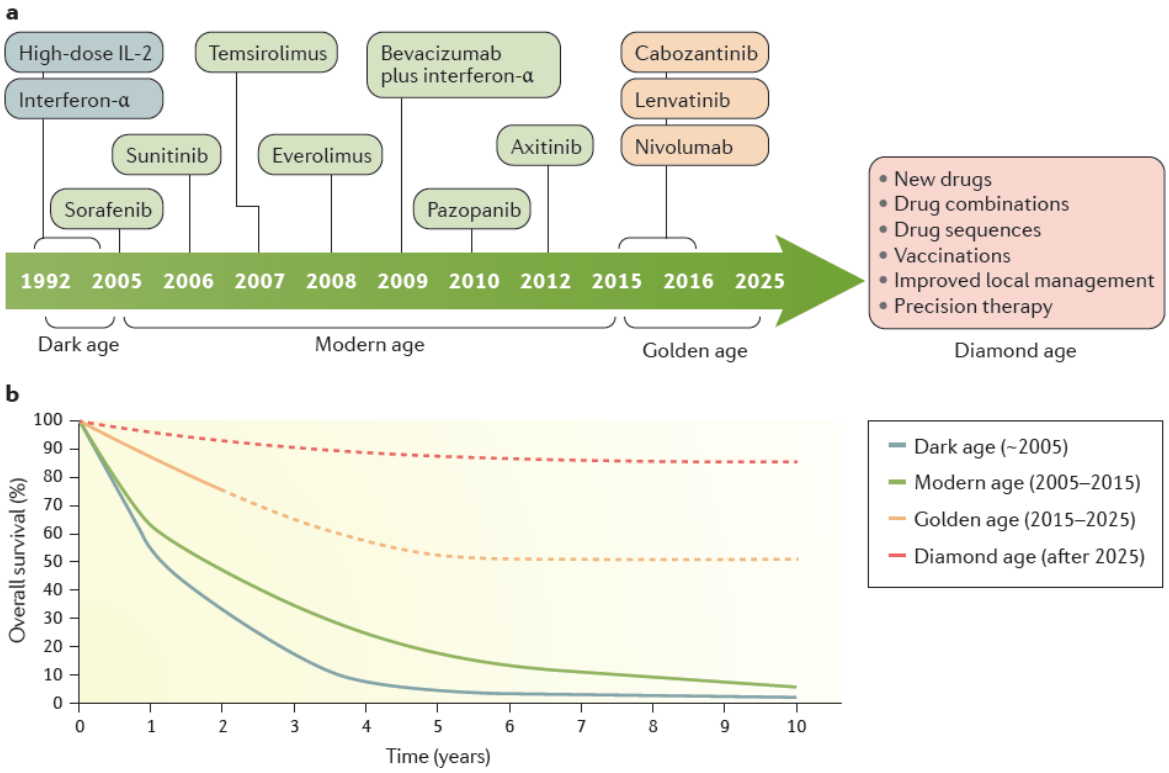
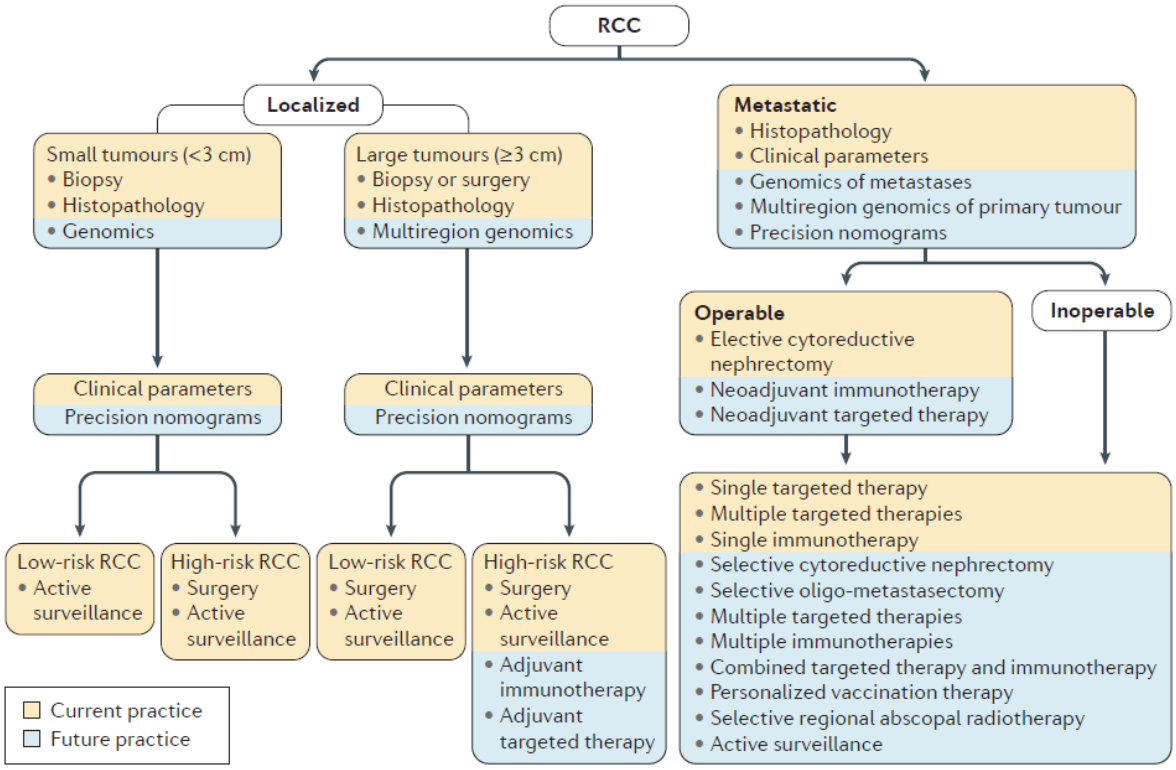


Figure 8. Treatment algorithms for renal cell carcinoma. Given the advances in renal cell carcinoma (RCC) research, how patients are treated — based on their individual tumour characteristics — will likely change in the future.



806 **Table 1. Non-clear-cell renal cell carcinomas**
807

Tumour type	Subtype	Cytogenetic alterations	Genes mutated	Gross appearance	Histological features*
Papillary	Type 1	Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p	*MET*	• Mixed cystic/solid consistency • Often whitish in colour and may display haemorrhage and necrosis • Frequently with a well-demarcated pseudocapsule	• Single layer of cuboid tumour cells • Thin, basophilic papillae with scant pale cytoplasm and low nuclear grade • Concentric lamellated calcifications (psamomma bodies) • Foamy macrophage infiltration
	Type 2	Gains of 8q, loss of 1p and 9p	*CDKN2A* *SETD2* *NRF2*		• Heterogeneous, thick papillae and eosinophilic cytoplasm, high nuclear grade, and pseudostratification • Concentric lamellated calcifications • Foamy macrophage infiltration
Chromophobe	Classic	Loss of chromosomes 1, 2, 6, 10, 13, 17 and 21	*TP53* *PTEN*	• Large, well-circumscribed grey to tan-brown coloured tumour • Occasional central scar	• Tumour cells with prominent membrane and pale cytoplasm • Voluminous cytoplasm (cytoplasmic accumulation of acid mucopolysaccharides)
	Eosinophilic				• Large tumor cells with fine eosinophilic granules • Distinct cell borders • Voluminous cytoplasm
MiT family translocation	NA	Recurrent translocations involving Xp11.2 (*TFE3*) or 6p21(*TFEB*)	*TFE3* *TFEB*	• Yellowish tissue • Often studded by haemorrhage and necrosis	• Papillary or nested architecture • Abundant clear or eosinophilic cytoplasm
Collecting duct	NA	Losses at 8p, 16p, 1p, 9p, and gains at 13q	Unknown	• Partially cystic • White-grey appearance • Often exhibit invasion into the renal sinus	• Tubulopapillary pattern • Often with cells taking columnar pattern with hobnail appearance • Presence of mucinous material • Desmoplastic stroma
Medullary	NA	Poorly described, but thought to be normal karyotype	*SMARCB1*	• Tan/white appearance • Poorly defined • Capsule • Extensive haemorrhage and necrosis	• Poorly differentiated, eosinophilic cells • Inflammatory infiltrative cells • Sheet-like or reticular pattern common
Oncocytoma	NA	• Loss of chromosome 1 and Y and CCND1 rearrangement	Mitochondrial genes (*COX1*, *COX2*, *ND4* and *CYTB*)	• Mahogany colour • Circumscribed • Occasional central scar	• Polygonal cells with abundant eosinophilic cytoplasm

				• Rarely with necrosis	• Uniform, round nuclei

Adapted from Ref. [208]. NA, no applicable. *No consensus is currently available describing the immune infilitration of non-clear-cell renal cell carcinomas.

811 **Table 2. Hereditary syndromes associated with renal cell carcinoma**

Syndrome (Phenotype MIM reference)	Gene (position)	Protein	Incidence of developing kidney tumour (%)	Median age at diagnosis (years)	Other phenotypic features
Clear cell renal cell carcinoma*					
von Hippel Lindau disease (193300)	*VHL* (3p25-26)	pVHL	25-45	40	• Hemangioblastoma • Pancreatic neuroendocrine tumours • Pheochromocytoma • Renal cysts • Pancreatic cysts • Ovary cystadenoma • Epididymal cystadenoma
***BAP1* mutant disease (614327)**	*BAP1* (3p21)	BRCA-associated protein	No data	No data	• Breast cancer • Uveal melanoma • Mesothelioma • Other cutaneous melanocytic tumors
SDH-associated kidney cancer (185470, 602413, 602690 and 115310)	*SDHB* (1p36), *SDHC* (1q21) and *SDHD* (11q23)	Succinate dehydrogenase subunits B, C and D	5-15	30	• Paraganglioma • Carotid body tumors • Pheochromocytoma • Gastrointestinal stromal tumour GIST
Papillary renal cell carcinoma					
Hereditary leiomyomatosis and renal cell cancer (150800)‡	*FH* (1q43)	Fumarate hydratase	2-21	46	• Uterine leiomyosracomas • Breast cancer • Bladder Cancer • Cutaneous leiomyomas • Uterine leiomyomas
Hereditary papillary kidney cancer (605074)§	*MET* (7q31)	Hepatocyte growth factor receptor	No data	<60	No additional features
Multiple tumour types					
Birt-Hogg-Dubé syndrome (135150)‖	*FLCN* (17p11.2)	Folliculin	34	50	• Fibrofolliculomas and trichodiscomas • Pulmonary cysts • Pneumothorax
Tuberous sclerosis complex (191100 and 191092)¶	*TSC1* (9q34) and *TSC2* (16p13)	Hamartin and tuberin	2-4	30	• Subependymal giant cell astrocytomas • Angiomyolipomas • Renal cysts • Facial angiofibroma • Ungal and periungal fibromas • Hypomelanotic macule, Forehead plaque • Cardiac rhabdomyomas • Connective tissue nevus
Cowden syndrome (multiple hamartoma syndrome; 158350)#	*PTEN* (10q23)	PTEN	34	40	• Breast Cancer • Endometrial cancer • Thyroid cancer • Prostate cancer • Macrocephaly • Intestinal hamartomatous polyps

					• Benign skin tumors (multiple trichilemmomas, papillomatous papules and acral keratoses) • Dysplastic gangliocytoma of the cerebellum
Hyperparathyroidism jaw tumour syndrome (145001)**	*HRPT2* (1q31)	Parafibromin	No data	No data	• Parathyroid carcinomas • Uterine carcinomas • Renal cysts and hamartomas • Hyperparathyroidism • Parathyroid glands tumours • Jaw fibromas

*Familial clear cell kidney cancer with chromosome 3 translocation is another possible syndrome associated with clear cell renal cell carcinoma, but the genetic lesions and associated data are unknown. ‡Papillary renal cell carcinoma type 2. §Papillary renal cell carcinoma type 1. ||Hybrid tumours; oncocytomas; and chromophobe, papillary and clear cell renal cell carcinomas. ¶Angiomyolipomas, epithelioid angiomyolipomas, renal cysts, oncocytomas and papillary and clear cell renal cell carcinomas. #Clear cell, papillary and chromophone renal cell carcinomas. **Mixed tumours (epithelial and connective tissue), papillary renal cell carcinomas and nephroblastomas. MIM, Mendelian Inheritance in Man database.

Table 3. Nephrometry scoring systems to predict partial nephrectomy complexity and outcomes.

Nephrometry system	Parameters included	Outcomes prediction	External validation
R.E.N.A.L. nephrometry [25]	Tumour size Exophytic rate Polar location Renal sinus involvement UCS involvement Face location	Blood loss Warm ischaemia time UCS lesion Overall complications Functional outcomes Benign or malignant tumour Tumour grade	Yes
PADUA classification [153]	Tumour size Exophytic rate Polar location Rim location Renal sinus involvement UCS involvement Face location	Blood loss Ischaemia time UCS lesion Overall complications Functional outcomes	Yes
Centrality Index [135]	Tumour radius Tumour depth (horizontal and vertical distances)	Ischaemia time Functional outcomes	Yes
Diameter–Axial–Polar system [136]	Diameter Axial distance Polar distance	Blood loss Ischaemia time Functional outcomes	No
Zonal NePhRo scoring system [137]	Nearness Physical zone Tumour radius Organization of the tumour	Perioperative complications	No
Arterial Based Complexity Scoring System [138]	Size of the renal arterial branches needing to be dissected or transected to achieve complete excision of the renal tumour	Ischaemia time Urinary fistula	No

UCS, upper collecting system.

822 **Table 4. Selected adverse events and quality of life of the approved agents**

Drug	Adverse events	Improvement in quality of life?	Reference
Axitinib	Hypertension, diarrhoea, hypothyroidism and hand–foot syndrome	Yes versus sorafenib	[157]
Bevacizumab	Proteinuria, hypertension and bleeding	Not reported	[160]
Cabozantinib	Diarrhoea, hand–foot syndrome, hypertension, nausea and hypothyroidism	Not reported	
Everolimus	Stomatitis, hypercholesterolaemia, hyperglycaemia and pneumonitis	No versus placebo	[209]
Nivolumab	Colitis, pneumonitis and endocrinopathies	Yes versus everolimus	[165]
Pazopanib	Diarrhoea, hypertension, liver function test abnormalities and hand–foot syndrome	No versus placebo, Yes versus sunitinib	[156]
Sorafenib	Hypertension, diarrhea, hand–foot syndrome and rash	Yes versus placebo	[154]
Sunitinib	Diarrhoea, hand–foot syndrome, mucositis and hypertension	Yes versus IFN	[155]
Temsirolimus	Stomatitis, hyperglycaemia, hypercholesterolaemia and oedema	Yes versus IFN	[210]

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