The multi-speciality approach to management of localised kidney cancer

Professor Grant D Stewart MBChB[1,2,3,+], Tobias Klatte MD[1,4], Laura Cosmai MD[5], Professor Axel Bex PhD[6,7,8], Benjamin W Lamb FRCS(Urol)[2,9], Professor Holger Moch MD[10], Professor Evis Sala MD[3,11], Shankar Siva MD[12], Professor Camillo Porta MD[13,14,*], Professor Maurizio Gallieni MD[5,15,*]

*Joint senior authors

+ Corresponding author

[1]Department of Surgery, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK,

[2]Department of Urology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK,

[3]CRUK Cambridge Centre, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK,

[4]Department of Urology, Charité - Universitätsmedizin Berlin, 10115 Berlin, Germany,

[5]Division of Nephrology and Dialysis, ASST Fatebenefratelli-Sacco, Fatebenefratelli Hospital, 20121 Milan, Italy,

[6]Specialist Centre for Kidney Cancer, Royal Free Hospital, London, UK,

[7]University College London, Division of Surgery and Interventional Science, Pond Street, London NW3 2QG, UK,

[8]The Netherlands Cancer Institute, Amsterdam, The Netherlands,

[9]School of Allied Health, Anglia Ruskin University, Cambridge, UK,

[10]Department of Pathology and Molecular Pathology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland,

[11]Department of Radiology, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK,

[12]Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia,

[13]Department of Biomedical Sciences and Human Oncology, University of Bari "A. Moro", Italy,

[14]Division of Medical Oncology, AOU Consorziale Policlinico di Bari, 70124 Bari, Italy,

[15]Department of Clinical and Biomedical Sciences "Luigi Sacco", Università di Milano, 20157 Milan, Italy.

Correspondence to: Professor Grant D Stewart, Department of Surgery, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK. Telephone: +44 (0)1223 769002. Email: gds35@cam.ac.uk

Summary

Historically, kidney cancer was approached in a siloed single-speciality fashion, with urological surgeons managing the localised stages of the disease and medical oncologists caring for patients if metastases develop. However, improvements in the management of localised kidney cancer have occurred rapidly over the past two decades with greater understanding of the disease biology, diagnostic options and innovations in curative treatments. These developments are favourable for patients but provide a substantially more complex landscape for patients and clinicians to navigate, with associated challenging decisions about who to treat, how, and when. As such, the skill sets needed to manage the various aspects of the disease and guide patients appropriately outstrips the capabilities of one particular specialist, and the evolution of a multi-speciality approach to the management of kidney cancer is now essential. In this review, we summarise the current best multi-speciality practice for the management of localised kidney cancer as well as the areas in need of further research and development.

Search strategy and selection criteria

For this narrative review, we searched PubMed and Embase on 1 March 2022 for studies describing multidisciplinary management of localised renal cell carcinoma (RCC) between 1990 to 2022, as well as assessing the literature for the highest level of evidence on key topics in RCC that required explanation. We used the search terms "renal cell carcinoma", "RCC", "kidney cancer", “multi-disciplinary team” and "MDT". We applied no language restrictions.

Introduction

Worldwide renal cell cancer (RCC) is the 9th and 14th commonest cancer in men and women, respectively, being more common in the Western world than in Africa and Asia.[1] Despite founder mutations occurring in the teenage years,[2] there are no known pre-malignant states of RCC allowing a preventative treatment. As the established risk factors for RCC (smoking, hypertension, obesity) are similar for other chronic conditions (e.g., type 2 diabetes, cardiovascular disease, and lung cancer), all cost-effective primary prevention interventions have been implemented.[3] Furthermore, despite ongoing research into liquid biomarkers there are no clinically tractable early detection tools that enable diagnosis in asymptomatic people.[4] Though of great interest to clinicians, patients, and carers, population screening for RCC requires substantial further research, such as the ongoing Yorkshire Kidney Screening Trial (NCT05005195).[5] As such, RCC remains a cancer first suspected when detecting a renal mass on imaging.

Traditionally, RCC has been a surgical disease, including cytoreductive nephrectomy in the metastatic setting. This unidimensional approach is now obsolete. As shown in Figure 1, over the last two decades there have been substantial improvements in diagnostic imaging, interventional radiology, pathology, radiotherapy and peri-surgical systemic therapy, meaning that a multi-speciality approach is advantageous from the outset in the majority of RCC patients. Despite these changes, and although different data sources vary, US data show that age-standardised mortality rate from RCC has been almost static over the past 50 years (4% improvement); whereas there has been a 27% reduction in cancer mortalities for all cancers combined since 1971.[6] As such, significant work remains to improve RCC outcomes. In this review, we illustrate, using a case history approach (figure 2), the current and emerging key elements of modern, multi-speciality management of localised RCC; medical and surgical management of metastatic disease will not be covered.

Modes of presentation

RCC frequently presents incidentally. Approximately 60% of all RCC patients from stages one to four will be asymptomatic or present with symptoms unrelated to RCC, the lesion being identified on imaging undertaken for a different indication.[7] Haematuria and less commonly flank pain or a palpable mass are the commonest

RCC-related symptoms. Of patients with small RCCs, defined as <4cm diameter (clinical stage-T1a), 87% will present without any symptoms.[7] Thus, the diagnosis of patients with early stage disease, potentially curable with surgery or ablation alone, is almost always incidental. However, abnormalities in common primary care blood tests such as inflammatory markers, haemoglobin, renal and liver function start to appear from 6–8 months before diagnosis in 25-40% (depending on the test) of RCC patients, indicating the potential for earlier diagnosis.[8] Notably, there are clear links between RCC and renal medicine (Panel 1). More advanced RCC cases, particularly those that are clinically stage three (locally advanced) or four (metastatic), are more likely to present with a range of systemic symptoms such as night sweats and hypertension. Due to such cytokine and chemokine related paraneoplastic syndromes, RCC can mimic other conditions.[9]

Baseline imaging

Ultrasound (US) is often the first imaging modality identifying a patient with suspected renal mass. The main advantages of US are its widespread availability and absence of ionising radiation or nephrotoxic contrast agents, especially for patients with renal impairment. US can reliably differentiate solid masses from simple cysts. Solid lesions on US or those with suspicious features such as thickened walls/septa or solid components with blood flow on colour Doppler US or enhancement on contrast-enhanced US,[10] require further evaluation with CT or MRI.[11]

Triple-phase CT of chest, abdomen and pelvis is the standard for characterisation of solid renal masses and staging of RCC with 91% accuracy.[12] However, for patients with small renal masses (<4cm) and no systemic symptoms the risk of lung metastases is <1% and they could forego a chest CT.[13] Initial imaging of the head and bone is only recommended in the presence of specific symptoms or laboratory signs.[14] Differentiating benign from malignant renal masses is not normally possible on CT scan. Common benign lesions such as oncocytomas (~5% all renal masses) overlap with RCCs in terms of attenuation, enhancement and contrast wash-out.[15] ^{99m}Tc-sestamibi SPECT-CT shows promise for the diagnosis of oncocytomas and hybrid oncocytic/chromophobe RCCs from much more aggressive clear cell RCC (ccRCC) or papillary RCC (pRCC). The diagnostic accuracy of ^{89}Zr-girentuximab PET/CT, which targets carbonic anhydrase IX present in ccRCC but

not other RCC histological subtypes, is being evaluated in the ZIRCON study (NCT03849118). However, neither of these approaches provides confident diagnosis of absolute benignity of the lesion.[16] Thus, there is a need for an imaging biomarker to non-invasively differentiate RCC from benign renal masses. Imaging biomarkers may be developed from novel image analysis methods and machine learning approaches such as those used in radiomics, the extraction and evaluation of high-dimensional quantitative data from images, have shown promise in the grading of ccRCC, but requires substantial further development.[17] As such, currently tumour biopsy (see below) remains the most informative method of differentiating renal mass aetiology as well as RCC subtype and grade (low vs high) prior to treatment decision. Multi-parametric MRI is superior to CT for evaluating the extent of tumour thrombus in the inferior vena cava (IVC).[18]

The multidisciplinary team (MDT) meeting

After the initial imaging, each patient's case should be referred to the MDT meeting to make recommendations for treatment options. Kidney cancer MDTs variably include histopathologists, radiologists, surgeons, cancer nurse specialists, research nurses, radiation and medical oncologists, meeting typically weekly. A hub-and-spoke model ensures subspeciality expertise is available to colleagues in peripheral centres[19]. Patients generally do not attend MDT meetings, and their general health and wishes are often not known.[20] Thus, the decision about suitability for eventual active treatment continues from the MDT meeting discussion into the clinic with the patient and their relatives.

Use of MDT meetings varies Internationally from discussion of complex cases only through to discussion of all new cases. The ideal MDT should allow sufficient time for discussion of complex localised RCC cases, such as: high-complexity small renal mass management, IVC tumour thrombi and clinical trial suitability.

Role of renal tumour biopsy

Unlike virtually any other solid tumour, patients with a renal mass do not undergo a mandatory tumour biopsy to determine the aetiology of the lesion. This is an anomaly and contravenes the established rules of surgical oncology. This is despite the fact that a typical 4cm contrast-enhancing renal mass, has only an 86%

probability of being a RCC, with as few as 23% being aggressive lesions requiring invasive treatment; these figures are even lower for tumours <4cm.[21] Critics of renal tumour biopsy argue that reduced diagnostic accuracy either by non-diagnostic biopsy or sampling error in a benign lesion are reasons why a renal tumour biopsy should not be undertaken routinely. However, modern series show very high sensitivity (99·1%) and specificity (99·7%) of renal tumour biopsy for diagnosis of malignancy, and a median concordance rate between biopsy and final surgical pathology of 90·3%.[22] There are concerns around the morbidity of biopsy considering the vascularity of the organ and the depth of biopsy required to reach the tumour. However, the risks associated with biopsy are minimal, with a 0·7% risk of bleeding requiring ablation or nephrectomy.[22] Tumour seeding has been described in case reports but is very rare using a coaxial needle technique and greatly outweighed by risks of unnecessary surgery on benign lesions.[23,24] The expertise of the interventional radiologist is key in decision-making over biopsy approach, because: targeting lesions under 2 cm is significantly more challenging; and the location of the tumour within the kidney may be challenging and require the use of a CT-guided (10-15% of cases, authors (AB and GDS) personal series), rather than the default US-guided approach. Ultimately, the individual patient's preference for intervention will be a significant factor affecting the decision of undertaking a biopsy, which is not mandatory if a patient wishes to undergo surgery regardless of a benign diagnosis. Therefore, a renal mass biopsy is recommended if the diagnosis may change the treatment approach and should certainly be discussed with all patients with tumours <=4cm. For patients who elect for renal mass biopsy, multiple biopsies are preferred over fine-needle aspiration. For example, in our patient's case (figure 2), due to advanced CKD (stage 3b), a biopsy providing a definitive diagnosis was essential in ensuring that an intervention risking a further reduction in renal function (and dialysis) was only undertaken if a significant malignancy (i.e. high grade RCC) was confirmed on biopsy.[25]

There is an increasingly complete understanding of the molecular architecture of RCC.[26] The fifth edition of the World Health Organization classification of urogenital tumours,[27] introduced a molecular driven renal tumour classification, taking recent discoveries in renal tumour genomics into account. Such novel molecularly-defined epithelial renal tumours include SMARCB1-deficient medullary RCC, TFEB-rearranged

RCC, Alk-rearranged RCC and ELOC-mutated RCC. However, there are no genetic, transcriptomic, methylation or proteomic approaches that are routinely used on wither biopsy or resection tissue as an adjunct to standard histopathology to guide diagnosis, treatment or follow-up, but the global introduction of next-generation sequencing (NGS) will result in a diagnostic shift from morphology to molecular analyses. The BIONIKK trial is a recent first example of a molecularly stratified trial of systemic therapies in RCC,[28] this is an approach that should be expanded upon in the neoadjuvant and adjuvant setting.

Treatment

i. *Localised RCC (<=7 cm)*

Patients presenting with small, solid renal masses or complex renal cysts <=4 cm can, following the offer of a renal tumour biopsy, be variably offered nephron-sparing surgery, thermal ablation, stereotactic ablative radiotherapy (SABR), active surveillance or occasionally reassurance and discharge. While nephron-sparing surgery in the form of partial nephrectomy has evolved as the standard of care by default, thermal ablation and active surveillance are alternatives traditionally for frail and comorbid patients.[29] At present, these management modalities have not been compared in prospective randomized controlled trials (RCTs), but large retrospective studies with long-term follow up, of largely elderly patient cohorts, suggest similar overall survival (OS) for the various treatment options.[29] A key question is whether the risk of the lesion outweighs the risk of the competing health risks. Although no high level evidence exists to address this question, small renal mass risk models have been developed providing clear information to patients on their personalised risk.[30] Information from such models helps to reassure the frailest patients that the risks of treatment outweigh that of any small kidney cancer and they can safely be discharged from any further follow-up.

a. Active surveillance

The concept of active surveillance is regular imaging to assess tumour growth, with or without renal tumour biopsy to determine the nature of the mass. Surveillance is a particularly important option for patients with CKD (initially used in our patient's case; figure 2), especially elderly patients, who may progress to end-stage

kidney disease. Among a cohort of patients aged over 40 years, the expected mean annual reduction in eGFR is -0.39 mL/min/1·73 m^2 per year (95% confidence interval: -0·41 to -0·37), but older age is associated with faster loss of kidney function due to high systolic blood pressure, proteinuria, and smoking.[31]

In the largest reported study and systematic reviews of active surveillance, the mean tumour linear growth rate was 2-3 mm per year, and progression to metastatic disease was 1-3%.[32–34] Short-term oncological results of active surveillance appear equivalent to partial or radical nephrectomy.[35] However, more research into the triggers for intervention in patients at high risk of progressing to lethal metastatic disease is required; studies such as the currently recruiting European Active Surveillance of Renal Cell Carcinoma study[36] aim to establish these.

b. Surgery

Nephron-sparing surgery is the recommended approach for cT1 lesions (tumours <=7cm) provided the resection is technically feasible and oncologically safe.[14] Decision making over surgical approach often requires uro-radiology expertise with 3D reconstructions of the CT scans to be available for the urologist expert in partial nephrectomy (PN) to decide on the feasibility of PN. Preference for PN is based on a single prospective EORTC randomised controlled trial including patients with non-metastatic RCCs up to 5cm in diameter. The EORTC study revealed a comparable cancer-specific survival for PN versus radical nephrectomy (RN), but superior renal function preservation.[37,38] The EORTC trial closed prematurely, was underpowered, but did not demonstrate any inferiority of RN versus PN in terms of OS. All other studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and limited size.[39] Retrospective studies suggest that PN preserves renal function with a lower risk of cardiovascular complications.[40–42] Similarly, in a Cochrane review, PN for localised RCC was associated with a reduced time-to-death of any cause compared to RN, whereas serious adverse event rates, cancer-specific survival, and disease-free-survival (DFS) were similar between PN and RN.[43] This evidence resulted in guidelines recommending PN as the treatment of choice for cT1 RCC since it better preserves renal function and potentially limits cardiovascular disorders. The evidence is clearer for cT1a tumours than for cT1b tumours,

where only retrospective data suggesting improved DFS and CSS for PN.[44] The question of PN versus RN for cT1b tumours will be addressed in the forthcoming PARTIAL trial, endpoints will include complications, renal function, quality of life and cost-effectiveness.[45] Whether PN leads to decreased mortality from any cause is still unresolved. Still, in patients with pre-existing CKD or single kidney and a renal lesion requiring treatment (see biopsy section) PN is the preferred surgical treatment option as it decreases the risk of developing end-stage renal disease and the need for haemodialysis.[46]

As to the choice of the surgical approach, no prospective RCTs exist comparing open (OPN), laparoscopic (LPN), and robot-assisted laparoscopic (RAPN) partial nephrectomy. Peri-operative and short-term oncological and functional outcomes are largely comparable between RAPN and LPN when comparing highly experienced surgeons.[47] In addition, there was a decreased morbidity in the RAPN group with fewer overall and major complications, fewer transfusions, and shorter hospital stay compared to OPN.[48] In most major RCC centres, OPN is now reserved for resection of the most complex of tumours.[49] If the expertise of the surgeon and team allow, RAPN is becoming the preferred approach for the majority of PNs, although surgeon and hospital case volume are key to outcomes.[50]

c. Thermal ablation

Previous clinical trials have failed feasibility to recruit patients to assess thermal ablation vs. surgery or active surveillance for T1a/b RCCs,[51] indicating the need for urologists and interventional radiologists in the MDT who are prepared to take a balanced view in guiding patients on optimal treatments. A recent systematic review including 3,974 patients who had undergone ablation (either radiofrequency ablation or cryoablation) or PN showed higher all-cause mortality and cancer-specific mortality rates for ablation than for PN (HR: 2·11 and 3·84, respectively). No statistically significant difference in local recurrence rates or risk of metastasis was seen. Complication rates were lower for ablation than for PN (13% vs. 17·6%, $p < 0·05$). A significantly greater decrease in eGFR was observed after PN compared to ablation.[52] A major limitation of the systematic reviews in this setting are differences in patient populations with regards to age and comorbidities.[53] These limitations result in selection bias, poorer all-cause mortality and fewer long-term data for ablation compared

to PN. All systematic reviews on this subject have low confidence ratings.[53] Current data are inadequate to make any strong and clear conclusions regarding the comparative effectiveness of ablation versus PN. An ongoing cohort embedded trial (NEST) is addressing feasibility of randomisation and patient choices on ablation versus PN.[54]

d. Stereotactic ablative radiation therapy

SABR is a newer, totally non-invasive treatment modality for localised RCC. The data is rapidly emerging, a meta-analysis in 2019 included 26 predominantly retrospective studies and 372 patients.[55] The local control and grade 3-4 toxicity rates were 97·2% and 1·5%, respectively. Clinical trial data is mainly small single institutional trials. However, the International TransTasman Radiation Oncology Group (TROG) FASTRACK II multicentre trial is ongoing.[56] Data from the International Radiosurgery Oncology Consortium for Kidney (IROCK) demonstrate promising cancer specific survival of 91·9% and local control of 97·8%,[57] in addition to safety and local efficacy of SABR in patients with ≥T1b tumours[58] and patients with solitary kidneys.[59] Special populations have also been investigated through clinical trials: neoadjuvant SABR for IVC thrombus;[60] neoadjuvant SABR prior to cytoreductive nephrectomy.[61] As such, SABR is considered as novel treatment reserved for patients with T1a-T3 tumours who are not medically or technically operable (National Comprehensive Cancer Network (NCCN) Guidelines 2022).

ii. *Management of renal tumours >7cm*

Treatment of patients with cT2 (>7cm) renal tumours is generally to proceed directly to surgery. Biopsy is rarely performed as the likelihood of a RCC is much greater than for patients with SRMs. Nonetheless, patients with significant co-morbidities should be assessed by anesthetists or medicine of the elderly physicians with expertise in pre-operative assessment to determine risk of death from surgery and enable the urologists to contrast this with the risk of development of metastatic kidney cancer. A useful tool is the American College of Surgeons Risk Calculator to provide estimates of a patient's risk of postoperative morbidity/mortality.[62] Renal tumour biopsy is indicated in patients with CKD where DMSA scan indicates a

nephrectomy would push a patient close to requiring dialysis or in co-morbid patients to assist in defining the risk of the tumour to the patient i.e. if benign or low grade (G1/2) RCC then treatment might be avoided. Tools are available to quantify the risk of clinically significant CKD (i.e. GFR <45ml/min; CKD stage 3+) following kidney cancer surgery; one example incorporates age, diabetes, pre-operative eGFR, and type of nephrectomy (figure 3).[63] Such patients should undergo a nephrological assessment before planning surgery, as well as during the post-surgical follow-up (Panel 2).

In cases where surgery is warranted but the nephrologists determine that with nephrectomy there will be a need for post-surgical dialysis, options to try and avoid dialysis are attempting an open partial nephrectomy or in specialist centres *ex vivo* 'bench dissection' and auto-transplantation.[64] Of note, there have been small phase II trials of neoadjuvant systemic therapy with an aim to downstage the cancer and enable a partial nephrectomy; e.g. AXIPAN trial which showed a modest reduction in tumour size but the partial nephrectomy remained complex.[65]

Active surveillance of cT2 renal masses is an area that requires further study, but there is low quality evidence to suggest that in patients who are borderline fit for surgery AS leads to acceptable oncological outcomes.[66]

In patients who are inoperable, SABR is a treatment option in patients with T2 disease associated with promising local control and low morbidity.[58] More confirmatory studies are required in this population.

Regarding surgical approach for lesions >7cm, minimally invasive surgery is usually attempted where possible, non-trial data suggests that cancer outcomes are comparable between laparoscopic and open radical nephrectomy.[67,68] Low quality data suggests no advantage to robot-assisted radical nephrectomy, which is the most expensive option.[69]

Prophylactic adenalectomy or lymph node dissection is not needed to enable cure when, on pre-surgical staging CT, these structures appear normal (lymph nodes <1cm in short axis).[70,71] Adrenal preservation is important as contralateral adrenal metastases are not uncommon for RCC patients. Endocrinologists should be involved in the peri-surgical management of patients likely to be rendered steroid dependent after bilateral adrenalectomy. This scenario is associated with significant complications and morbidity.[72]

iii. *Locally advanced disease*

Cancer cure remains possible when RCC has extended outside of the kidney itself. A unique invasive phenomenon of RCC is the extension of the tumour along the segmental renal veins into the main renal vein, IVC and in extreme examples into the right atrium of the heart. Although intuitively disease that has extended in such a gross haematogenous fashion would be thought to be incurable, up to 65% of patients with venous tumour thrombus (VTT) are alive at 5-years following surgery.[73,74] However, peri-surgical mortality is high (5-15%) and increases with the level of the VTT[75,76]. Surgery is usually performed open but in very specialized centres a minimal access robotic approach may be an option.[77] A phase II trial investigating neoadjuvant SABR for VTT has demonstrated safety of this approach.[60]

iv. *Neoadjuvant systemic therapy*

Neoadjuvant treatment is the use of non-surgical therapy prior to curative management, such as surgery, to substantially reduce the morbidity of treatment and increase the chances of treatment with curative intent. There are no established neoadjuvant therapies for RCC. However, clinical trials, including window-of-opportunity studies to assess the impact of short courses of novel combination therapies (i.e. PARP inhibitors) are ongoing.[78] Recently completed studies include the NAXIVA trial of neoadjuvant tyrosine kinase inhibitor (TKI) axitinib to downstage IVC VTT to enable less extensive and morbid surgery.[79] In NAXIVA 35% patients had a reduction in the extent of VTT and 41% had less extensive surgery than that originally planned. As the evidence for adjuvant T-cell checkpoint inhibitor use in RCC gathers pace[80], there is considerable interest in RCC as to the role of a neoadjuvant strategy in high-risk localised RCC, either as an adjunct to subsequent adjuvant treatment or as a standalone therapy, with the potential advantages of this latter strategy mentioned above. While a single arm trial (NEOAVAX) demonstrated a 30% partial response rate in primary tumours by checkpoint inhibitor combination therapy with VEGFR-TKI (avelumab plus axitinib), a randomised phase III trial (PROSPER RCC, NCT03055013) is evaluating the combined neoadjuvant-adjuvant strategy with nivolumab versus observation.[81]

Post-surgical follow-up and adjuvant systemic therapy

i. Post-interventional treatment follow-up

There are no proven adjuvant RCC treatments.[82] As such, follow-up after surgery or ablation is currently observational in nature to assess renal function status and monitor oncological control by cross-sectional imaging. Clinical assessment includes assessment of symptoms of recurrence (i.e. abdominal pain, cough, bone pain, weight loss, loss of appetite, fatigue). The frequency and modality of imaging are ill-defined by evidence and vary considerably in major guidelines.[14,83] Guideline recommendations are based on validated risk models of recurrence, a systematic review has established that of the existing validated risk stratification tools the Leibovich, Karakiewicz and Sorbellini clinico-pathological models are optimal to predict RFS, CSS and OS in ccRCC following surgery with curative intent.[84] The VENUSS score performs best for pRCC.[85] In our patient's case (figure 2) the Leibovich score was used and due to being pT1b (3 points) and grade 3 (1 point), the patient's Leibovich score of 4 translates into being intermediate risk for recurrence (Leibovich scores 3-5).[86] The EAU guidelines (table 1) recommends 6-monthly cross-sectional imaging for intermediate RCC patients for the first year, annual CT scans from 2-5 years, followed by biannual scans to 10 years follow-up.[14] It is uncertain if follow-up improves survival and how long to continue. A small Scandinavian study analysing a surveillance protocol eight years after its implementation suggests a survival benefit for patients who were followed within a structured surveillance protocol versus patients who were not.[87] However, analysis of the European multicentre RECUR database showed that more frequent imaging leading to the earlier detection of recurrence did not impact on OS compared to less frequent imaging.[88]

Imaging based follow-up is hugely resource intensive, for each single patient treated for RCC recurrence who remained alive with no evidence of disease, the number of follow-up imaging tests needed was 542, climbing to 697 for high-risk patients.[88] No prospective comparative studies of different follow-up regimens have ever been performed. There is a need for research to evaluate dynamic patient competing risk and cancer risk stratification models but also the intensiveness of imaging-based follow-up.

It is also unknown if specific follow-up by nephrologists changes the natural history of the disease (Panel 2). Our patient (Figure 2) has CKD stage 3b and progression to end-stage kidney disease is a likely possibility,

preventing this can favourably impact the patient's OS and the drop in quality-of-life of undergoing dialysis, as well as impacting on the type of oncological treatment options if metastatic RCC develops.[89]

ii. Adjuvant therapy

As indicated above, a step change is needed to achieve improvement in RCC survival, which appears to have lagged behind improvements seen in other cancer types.[6] Impactful adjuvant treatment of localised RCC patients at substantial risk of developing metastasis would benefit a large proportion of RCC patients and enable that survival improvement.

Following five clinical trials reporting the outcomes of adjuvant TKIs in RCC, surveillance remains the standard-of-care following surgical excision. However, adjuvant treatment with T-cell checkpoint inhibitors appears to be more promising. The recently published Keynote-564 study, in patients with ccRCC at high risk of recurrence including complete metastasectomy, showed that after 1 year of treatment with adjuvant pembrolizumab (PD-1 inhibitor) there was a significant DFS benefit over placebo (HR 0·68, 95% CI 0·53–0·87; P=0.002), with overall survival (OS) data awaited.[80] If ongoing adjuvant checkpoint inhibitor trials[90] continue to demonstrate a significant survival advantage they are likely to become standard-of-care. However, with these expensive treatments come the risks of significant adverse events some of which can be life changing/threatening. As such, it is plausible that the use of prognostic models of post-surgical cancer recurrence will soon move beyond simply informing patients of their risk of recurrence and rationale for their follow-up regimen to an enhanced role of determining eligibility for adjuvant treatment and supporting decision making around the possible benefits and harms of these treatments at an individual level.

Principles and management of hereditary kidney cancer.

Inherited forms of RCC account for 5% of all cases. The most common hereditary condition is von Hippel-Lindau disease (VHL). However, due to modern sequencing approaches several new syndromes have been identified in recent years, e.g. SDHB-deficient RCC, hereditary leiomyomatosis and RCC (HLRCC)-syndrome associated RCC and papillary RCC-syndrome.[91] Many patients are aware they have such a familial syndrome

due to family history. However, when patients <46 years are diagnosed with a new RCC a medical genetics referral should be considered, as 70% of hereditary RCCs develop prior to this age. In VHL, multiple foci of RCC can develop throughout life and a biopsy is not usually required. Surgery to excise all lesions is usually performed when the largest lesion reaches 3cm. The same principal can be followed in other syndromes except for HLRCC which metastasise early and should be resected promptly.[91]

Conclusions

In this review, we highlighted the rapid evolution of modern multi-speciality management of RCC over the past 20 years, but also the key areas requiring further research. Maintaining renal function and the optimal oncological treatment be it surgery, ablation, SABR, observation or systemic therapies now require the input of specialists from across medicine in decision making, treatment delivery and follow-up. Novel next-generation molecular technologies and risk stratified decision making tools will help to personalise treatments and, when integrated with the patient's own co-morbidities, will allow truly tailored care. This integrated approach, which still needs to be cemented in clinical practice, will ensure the best outcomes for patients with this often complex condition.

Acknowledgements

We are grateful to Dr Anne Warren for her assistance with the case history.

Contributors

GDS, CP and MG conceived the work and contributed to the design of the research. GDS, TK, SS, CP, SS, MG, HM, ES, BWL, AB and LC prepared the manuscript. All authors edited and approved the final version of the manuscript.

Declaration of interests

GDS has received educational grants from Pfizer, AstraZeneca, and Intuitive Surgical; consultancy fees from Pfizer, Merck, EUSA Pharma, and CMR Surgical; Travel expenses from Pfizer and Speaker fees from Pfizer. LC acted as a speaker and/or consultant for Astra Zeneca, General Electric, MSD, Novartis and Pfizer. CP acted as speaker and/or consultant for Angelini, Astra Zeneca, BMS, Eisai, EUSA, General Electric, Ipsen, Merck, MSD, Novartis, Pfizer, acted as a protocol steering committee member for BMS, Eisai and EUSA, received travel support from Roche, and acted as an Expert Testimony for EUSA and Pfizer. ES is a co-founder of Lucida Medical, a research consultant for Amazon, received travel support from Siemens and GSK, and speaker's bureau for Siemens and GSK. BWL has previously received funding for training MDTs in assessment and quality improvement methods from Somerset, Wiltshire, Avon & Gloucestershire Cancer Alliance Network and Penninsula Cancer Alliance Network. MG received travel expenses and speaker fees from Astra Zeneca and General Electric. AB has received honoraria for participation in advisory boards for Pfizer, Novartis, and Ipsen, and is principal investigator of a neoadjuvant trial supported by a restricted educational grant from Pfizer. HM is on advisory boards for Bayer, Astra Zeneca, Janssen, Roche, and Merck. TK has acted as a speaker for Pfizer and Janssen. SS has no conflicts of interest.

Acknowledgements

Funding source – nil. Professor Grant D Stewart's and Professor Evis Sala's contribution to this research was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014) and the Cancer Research UK Cambridge Centre [C9685/A25177]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. As corresponding author Professor Stewart confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Panel 1. The bidirectional relationship between RCC and chronic kidney disease (CKD).[92]

Relationship between RCC and CKD	**Details**
CKD is a risk factor for developing RCC	Greater risk of developing RCC in patients with CKD stage 3 or 4, with lower eGFR being associated with an increased risk of RCC (HR, 1·39 for eGFR=45-59ml/min; HR, 1·81 for eGFR=30-44ml/min; HR, 2·28 for eGFR<30ml/min).[93]
Increased prevalence of CKD in RCC patients	The prevalence of CKD in RCC at the time of diagnosis (i.e. pre-surgery) is 25% higher as compared to the general population.[94] Overlapping risk factors between CKD and RCC may account for the high prevalence for CKD in the oncological population. With improvement of cancer patients' survival, CKD-related morbidity due to nephron mass loss, as well as to comorbid disease-induced complications, has become more and more relevant, ultimately impacting on overall quality of life and non-cancer-related survival.[95]
Detrimental effect of RCC treatment on renal function	Interventional treatments such as RCC surgery frequently result in reduction of the renal function due to the removal or damage of peritumoral normal renal parenchyma.

Panel 2. Nephrological management before and after surgery for RCC, especially relevant to patients predicted to have CKD stage 3+ (eGFR <45ml/min) after surgery.

Point in treatment journey	**Assessment**
Pre-surgery	The nephrologist should inform the patients and their caregivers on the likelihood and the consequences of worsening kidney function. Indeed, patients with pre-existing CKD have a significantly higher risk of morbidity, including acute kidney injury, and mortality during the perioperative period and on the long term; patients with localized RCC are more likely to die from CKD-related complications, rather than from their kidney malignancy.[96] Thus, their management should focus on preserving renal function, reducing cardiovascular risk, and long-term CKD care. Optimization of glycaemic and blood pressure control should be mandatory to reduce deterioration of GFR postoperatively.[97]
During and perisurgery	Euvolemia should be aimed for to maintain renal perfusion. Nephrological follow-up is crucial, as it is the avoidance of nephrotoxins.
Follow-up	Surgical-induced CKD is associated with a low incidence of progressive annual renal function decrease, while patients' comorbidities have a higher impact on CKD evolution98. The first goal of the nephrologist is to minimize the risk of worsening of renal function by eliminating all modifiable risk factors for renal damage, including the management of comorbidities potentially affecting renal function (e.g. hypertension or diabetes). Secondly, the nephrologist should support oncologists in managing treatment-related renal adverse event, in those patients needing oncological treatments, either in the adjuvant setting, or in the case of development of recurrent metastatic disease (about 30% of the cases). Finally, the nephrologist should be involved in the choice of the best radiological procedure to use for follow-up purposes, mainly deciding if, when and how to use CT contrast medium. The follow-up, comprehensive of eGFR, blood pressure determination, creatinine-protein ratio, should be customized according to the residual renal function, and eventual concomitant treatments. Finally, the nephrologist should also deal with oncological patients on dialysis or with kidney transplant, including if and when to start the former, or to allow the latter.

Table 1. CT chest/abdomen follow-up schedule according to the EAU guidelines following treatment for RCC, considering tumour risk profile and treatment efficacy. Follow-up should be intensified in patients after PN for tumours >7 cm or in patients with a positive surgical margin. This schedule is based on expert opinion.[14]

Risk of recurrence	**Follow-up schedule**						
	3 months	**6 months**	**12 months**	**18 months**	**2 years**	**3 years**	**> 3 years**
Low		CT	-	CT		CT	CT once every 2 years
Intermediate		CT	CT		CT	CT	CT once every year, after 5 years CT once every 2 years
High	CT	CT	CT	CT	CT	CT	CT once every year, after 5 years CT once every 2 years

Figure legends

Figure 1. Changes in management of localised kidney cancer over the past two decades.

Figure 2. Case history of a patient with renal cell carcinoma from diagnosis to staging (CNS; cancer nurse specialist).

Figure 3. A clinical score to predict clinically relevant CKD following nephrectomy. The pre-operative clinical factors are scored (left panel) to provide a predicted risk of CKD3b (right panel). Used with permission.[63]

References

1 Kidney cancer statistics | World Cancer Research Fund International. WCRF International. https://www.wcrf.org/dietandcancer/kidney-cancer-statistics/ (accessed Jan 29, 2022).
2 Mitchell TJ, Turajlic S, Rowan A, et al. Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal. Cell 2018; 173: 611-623.e17.
3 Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. World J Urol 2018; 36: 1341–53.
4 Flitcroft JG, Verheyen J, Vemulkar T, et al. Early detection of kidney cancer using urinary proteins: a truly non-invasive strategy. BJU Int 2021; published online Sept 27. DOI:10.1111/bju.15601.
5 Usher-Smith J, Simmons RK, Rossi SH, Stewart GD. Current evidence on screening for renal cancer. Nat Rev Urol 2020; 17: 637–42.
6 Kratzer TB, Siegel RL, Miller KD, Sung H, Islami F, Jemal A. Progress Against Cancer Mortality 50 Years After Passage of the National Cancer Act. JAMA Oncology 2021; published online Nov 11. DOI:10.1001/jamaoncol.2021.5668.
7 Vasudev NS, Wilson M, Stewart GD, et al. Challenges of early renal cancer detection: symptom patterns and incidental diagnosis rate in a multicentre prospective UK cohort of patients presenting with suspected renal cancer. BMJ Open 2020; 10: e035938.
8 Zhou Y, Walter FM, Mounce L, et al. Identifying opportunities for timely diagnosis of bladder and renal cancer via abnormal blood tests: a longitudinal linked data study. Br J Gen Pract 2022; 72: e19–25.
9 Hegemann M, Kroeger N, Stenzl A, Bedke J. Rare and changeable as a chameleon: paraneoplastic syndromes in renal cell carcinoma. World J Urol 2018; 36: 849–54.
10 Bertolotto M, Cicero C, Perrone R, Degrassi F, Cacciato F, Cova MA. Renal Masses With Equivocal Enhancement at CT: Characterization With Contrast-Enhanced Ultrasound. American Journal of Roentgenology 2015; 204: W557–65.
11 Diagnostic Imaging for Solid Renal Tumors: A Pictorial Review - IOS Press. https://content.iospress.com/articles/kidney-cancer/kca180028 (accessed Jan 10, 2021).
12 Sheth S, Scatarige JC, Horton KM, Corl FM, Fishman EK. Current Concepts in the Diagnosis and Management of Renal Cell Carcinoma: Role of Multidetector CT and Three-dimensional CT. RadioGraphics 2001; 21: S237–54.
13 Voss J, Drake T, Matthews H, et al. Chest computed tomography for staging renal tumours: validation and simplification of a risk prediction model from a large contemporary retrospective cohort. BJU Int 2020; 125: 561–7.
14 Professionals S-O. EAU Guidelines: Renal Cell Carcinoma. Uroweb. https://uroweb.org/guideline/renal-cell-carcinoma/ (accessed Feb 20, 2022).
15 Paño B, Soler A, Goldman DA, et al. Usefulness of multidetector computed tomography to differentiate between renal cell carcinoma and oncocytoma. A model validation. BJR 2020; 93: 20200064.
16 Roussel E, Capitanio U, Kutikov A, et al. Novel Imaging Methods for Renal Mass Characterization: A Collaborative Review. European Urology 2022; published online Feb 22. DOI:10.1016/j.eururo.2022.01.040.
17 Ursprung S, Beer L, Bruining A, et al. Radiomics of computed tomography and magnetic resonance imaging in renal cell carcinoma—a systematic review and meta-analysis. Eur Radiol 2020; 30: 3558–66.
18 Ghoreifi A, Djaladat H. Surgical Tips for Inferior Vena Cava Thrombectomy. Curr Urol Rep 2020; 21: 51.
19 Cosmai L, Porta C, Perazella MA, et al. Opening an onconephrology clinic: recommendations and basic requirements. Nephrol Dial Transplant 2018; 33: 1503–10.

20 Lamb BW, Brown KF, Nagpal K, Vincent C, Green JSA, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. Ann Surg Oncol 2011; 18: 2116–25.
21 Bhindi B, Thompson RH, Lohse CM, et al. The Probability of Aggressive Versus Indolent Histology Based on Renal Tumor Size: Implications for Surveillance and Treatment. European Urology 2018; 74: 489–97.
22 Marconi L, Dabestani S, Lam TB, et al. Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumour Biopsy. Eur Urol 2016; 69: 660–73.
23 Macklin PS, Sullivan ME, Tapping CR, et al. Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from a UK Tertiary Referral Centre. Eur Urol 2019; 75: 861–7.
24 Tran MGB, Barod R, Bex A. Re: Philip S. Macklin, Mark E. Sullivan, Charles R. Tapping, et al. Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from a UK Tertiary Referral Centre. Eur Urol 2019;75:861-7. Eur Urol 2019; 75: e179–80.
25 Aguilar Palacios D, Li J, Mahmood F, Demirjian S, Abouassaly R, Campbell SC. Partial Nephrectomy for Patients with Severe Chronic Kidney Disease-Is It Worthwhile? J Urol 2020; 204: 434–41.
26 Mitchell TJ, Rossi SH, Klatte T, Stewart GD. Genomics and clinical correlates of renal cell carcinoma. World J Urol 2018; published online Aug 11. DOI:10.1007/s00345-018-2429-x.
27 Classification of Tumours of the Urinary System and Male Genital Organs, 5th edn. Lyon: International Agency for Research on Cancer;, 2022.
28 Vano Y, Elaidi RT, Bennamoun M, et al. LBA25 Results from the phase II biomarker driven trial with nivolumab (N) and ipilimumab or VEGFR tyrosine kinase inhibitor (TKI) in naïve metastatic kidney cancer (m-ccRCC) patients (pts): The BIONIKK trial. Annals of Oncology 2020; 31: S1157.
29 Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. Cancer 2010; 116: 3119–26.
30 Psutka SP, Gulati R, Jewett MAS, et al. A Clinical Decision Aid to Support Personalized Treatment Selection for Patients with Clinical T1 Renal Masses: Results from a Multi-institutional Competing-risks Analysis. European Urology 2021; 0. DOI:10.1016/j.eururo.2021.11.002.
31 Toyama T, Kitagawa K, Oshima M, et al. Age differences in the relationships between risk factors and loss of kidney function: a general population cohort study. BMC Nephrology 2020; 21: 477.
32 Jewett MAS, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011; 60: 39–44.
33 Smaldone MC, Kutikov A, Egleston BL, et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer 2012; 118: 997–1006.
34 Klatte T, Berni A, Serni S, Campi R. Intermediate- and long-term oncological outcomes of active surveillance for localized renal masses: a systematic review and quantitative analysis. BJU Int 2021; 128: 131–43.
35 Patel N, Cranston D, Akhtar MZ, et al. Active surveillance of small renal masses offers short-term oncological efficacy equivalent to radical and partial nephrectomy. BJU Int 2012; 110: 1270–5.
36 Mir MC, Capitanio U, Bertolo R, et al. Role of Active Surveillance for Localized Small Renal Masses. Eur Urol Oncol 2018; 1: 177–87.
37 Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011; 59: 543–52.
38 Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014; 65: 372–7.

39 MacLennan S, Imamura M, Lapitan MC, et al. Systematic review of perioperative and quality-of-life outcomes following surgical management of localised renal cancer. Eur Urol 2012; 62: 1097–117.
40 Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? J Urol 2009; 181: 55–61; discussion 61-62.
41 Capitanio U, Terrone C, Antonelli A, et al. Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. Eur Urol 2015; 67: 683–9.
42 Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS, Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. Cancer 2008; 112: 511–20.
43 Kunath F, Schmidt S, Krabbe L-M, et al. Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. Cochrane Database Syst Rev 2017; 5: CD012045.
44 Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1b and T2 Renal Tumors: A Systematic Review and Meta-analysis of Comparative Studies. Eur Urol 2017; 71: 606–17.
45 The PARTIAL study a randomised trial of the clinical and cost effectiveness of PARTIAL vs radical nephrectomy for clinically localised renal cell carcinoma - NIHR Funding and Awards. https://fundingawards.nihr.ac.uk/award/NIHR133561 (accessed March 5, 2022).
46 Lane BR, Demirjian S, Derweesh IH, et al. Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate. Eur Urol 2015; 68: 996–1003.
47 Alimi Q, Peyronnet B, Sebe P, et al. Comparison of Short-Term Functional, Oncological, and Perioperative Outcomes Between Laparoscopic and Robotic Partial Nephrectomy Beyond the Learning Curve. J Laparoendosc Adv Surg Tech A 2018; 28: 1047–52.
48 Peyronnet B, Seisen T, Oger E, et al. Comparison of 1800 Robotic and Open Partial Nephrectomies for Renal Tumors. Ann Surg Oncol 2016; 23: 4277–83.
49 Rintoul-Hoad S, Fernando A, Nair R, Challacombe B, O'Brien T. Open nephron-sparing surgery in patients with a complex tumour in a solitary kidney: technical, oncological and functional outcomes. BJU Int 2021; 128: 431–4.
50 Tran MGB, Aben KKH, Werkhoven E, et al. Guideline adherence for the surgical treatment of T1 renal tumours correlates with hospital volume: an analysis from the British Association of Urological Surgeons Nephrectomy Audit. BJU Int 2020; 125: 73–81.
51 Soomro N, Lecouturier J, Stocken DD, et al. Surveillance versus ablation for incidentally diagnosed small renal tumours: the SURAB feasibility RCT. Health Technology Assessment 2017; 21: 1–68.
52 Rivero JR, De La Cerda J, Wang H, et al. Partial Nephrectomy versus Thermal Ablation for Clinical Stage T1 Renal Masses: Systematic Review and Meta-Analysis of More than 3,900 Patients. J Vasc Interv Radiol 2018; 29: 18–29.
53 Abu-Ghanem Y, Fernández-Pello S, Bex A, et al. Limitations of Available Studies Prevent Reliable Comparison Between Tumour Ablation and Partial Nephrectomy for Patients with Localised Renal Masses: A Systematic Review from the European Association of Urology Renal Cell Cancer Guideline Panel. Eur Urol Oncol 2020; 3: 433–52.
54 Neves JB, Cullen D, Grant L, et al. Protocol for a feasibility study of a cohort embedded randomised controlled trial comparing NEphron Sparing Treatment (NEST) for small renal masses. BMJ Open 2019; 9: e030965.
55 Correa RJM, Louie AV, Zaorsky NG, et al. The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. Eur Urol Focus 2019; 5: 958–69.

56 Siva S, Chesson B, Bressel M, et al. TROG 15.03 phase II clinical trial of Focal Ablative STereotactic Radiosurgery for Cancers of the Kidney - FASTRACK II. BMC Cancer 2018; 18: 1030.
57 Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer 2018; 124: 934–42.
58 Siva S, Correa RJM, Warner A, et al. Stereotactic Ablative Radiotherapy for ≥T1b Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK). International Journal of Radiation Oncology, Biology, Physics 2020; 108: 941–9.
59 Correa RJM, Louie AV, Staehler M, et al. Stereotactic Radiotherapy as a Treatment Option for Renal Tumors in the Solitary Kidney: A Multicenter Analysis from the IROCK. J Urol 2019; 201: 1097–104.
60 Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for Renal Cell Carcinoma Inferior Vena Cava Tumor Thrombus-Safety Lead-in Results of a Phase 2 Trial. Int J Radiat Oncol Biol Phys 2021; 110: 1135–42.
61 Singh AK, Winslow TB, Kermany MH, et al. A Pilot Study of Stereotactic Body Radiation Therapy Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma. Clin Cancer Res 2017; 23: 5055–65.
62 ACS Risk Calculator - Home Page. https://riskcalculator.facs.org/RiskCalculator/index.jsp (accessed Jan 23, 2022).
63 Ellis RJ, Del Vecchio SJ, Gallagher KMJ, et al. A Simple Clinical Tool for Stratifying Risk of Clinically Significant CKD after Nephrectomy: Development and Multinational Validation. J Am Soc Nephrol 2020; 31: 1107–17.
64 Vrakas G, Sullivan M. Current Review of Renal Autotransplantation in the UK. Curr Urol Rep 2020; 21: 33.
65 Lebacle C, Bensalah K, Bernhard J-C, et al. Evaluation of axitinib to downstage cT2a renal tumours and allow partial nephrectomy: a phase II study. BJU Int 2019; 123: 804–10.
66 Mehrazin R, Smaldone MC, Kutikov A, et al. Growth kinetics and short-term outcomes of cT1b and cT2 renal masses under active surveillance. J Urol 2014; 192: 659–64.
67 Hemal AK, Kumar A, Kumar R, Wadhwa P, Seth A, Gupta NP. Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. J Urol 2007; 177: 862–6.
68 Jeon SH, Kwon TG, Rha KH, et al. Comparison of laparoscopic versus open radical nephrectomy for large renal tumors: a retrospective analysis of multi-center results. BJU Int 2011; 107: 817–21.
69 Crocerossa F, Carbonara U, Cantiello F, et al. Robot-assisted Radical Nephrectomy: A Systematic Review and Meta-analysis of Comparative Studies. Eur Urol 2021; 80: 428–39.
70 Blom JHM, van Poppel H, Maréchal JM, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol 2009; 55: 28–34.
71 Lane BR, Tiong H-Y, Campbell SC, et al. Management of the adrenal gland during partial nephrectomy. J Urol 2009; 181: 2430–6; discussion 2436-2437.
72 Neumann HPH, Tsoy U, Bancos I, et al. Comparison of Pheochromocytoma-Specific Morbidity and Mortality Among Adults With Bilateral Pheochromocytomas Undergoing Total Adrenalectomy vs Cortical-Sparing Adrenalectomy. JAMA Netw Open 2019; 2: e198898.
73 Parra J, Drouin SJ, Hupertan V, Comperat E, Bitker MO, Rouprêt M. Oncological outcomes in patients undergoing radical nephrectomy and vena cava thrombectomy for renal cell carcinoma with venous extension: a single-centre experience. Eur J Surg Oncol 2011; 37: 422–8.
74 Gu L, Li H, Wang Z, et al. A systematic review and meta-analysis of clinicopathologic factors linked to oncologic outcomes for renal cell carcinoma with tumor thrombus treated by radical nephrectomy with thrombectomy. Cancer Treat Rev 2018; 69: 112–20.

75 Kirkali Z, Van Poppel H. A critical analysis of surgery for kidney cancer with vena cava invasion. Eur Urol 2007; 52: 658–62.
76 Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int 2004; 94: 33–41.
77 Campi R, Tellini R, Sessa F, et al. Techniques and outcomes of minimally-invasive surgery for nonmetastatic renal cell carcinoma with inferior vena cava thrombosis: a systematic review of the literature. Minerva Urol Nefrol 2019; 71: 339–58.
78 Ursprung S, Mossop H, Gallagher FA, et al. The WIRE study a phase II, multi-arm, multi-centre, non-randomised window-of-opportunity clinical trial platform using a Bayesian adaptive design for proof-of-mechanism of novel treatment strategies in operable renal cell cancer - a study protocol. BMC Cancer 2021; 21: 1238.
79 Stewart GD, Welsh SJ, Ursprung S, et al. NAXIVA: A phase II neoadjuvant study of axitinib for reducing extent of venous tumor thrombus in clear cell renal cell cancer (RCC) with venous invasion. JCO 2021; 39: 275–275.
80 Choueiri TK, Tomczak P, Park SH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med 2021; 385: 683–94.
81 Dynamic changes of the immune infiltrate after neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). | Journal of Clinical Oncology. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4573 (accessed March 6, 2022).
82 Blick C, Ritchie AWS, Eisen T, Stewart GD. Improving outcomes in high-risk, nonmetastatic renal cancer: new data and ongoing trials. Nat Rev Urol 2017; published online Aug 1. DOI:10.1038/nrurol.2017.123.
83 Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow Up - American Urological Association. https://www.auanet.org/guidelines/guidelines/renal-mass-and-localized-renal-cancer-evaluation-management-and-follow-up (accessed March 12, 2022).
84 Usher-Smith JA, Li L, Roberts L, et al. Risk models for recurrence and survival after kidney cancer: a systematic review. BJU Int 2021; published online Dec 16. DOI:10.1111/bju.15673.
85 Rosiello G, Larcher A, Fallara G, et al. Head-to-head comparison of all the prognostic models recommended by the European Association of Urology Guidelines to predict oncologic outcomes in patients with renal cell carcinoma. Urol Oncol 2022; : S1078-1439(21)00558-5.
86 Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003; 97: 1663–71.
87 Beisland C, Guðbrandsdottir G, Reisæter LAR, Bostad L, Hjelle KM. A prospective risk-stratified follow-up programme for radically treated renal cell carcinoma patients: evaluation after eight years of clinical use. World J Urol 2016; 34: 1087–99.
88 Dabestani S, Beisland C, Stewart GD, et al. Intensive Imaging-based Follow-up of Surgically Treated Localised Renal Cell Carcinoma Does Not Improve Post-recurrence Survival: Results from a European Multicentre Database (RECUR). Eur Urol 2019; 75: 261–4.
89 Antonelli A, Minervini A, Sandri M, et al. Below Safety Limits, Every Unit of Glomerular Filtration Rate Counts: Assessing the Relationship Between Renal Function and Cancer-specific Mortality in Renal Cell Carcinoma. Eur Urol 2018; 74: 661–7.
90 Marconi L, Sun M, Beisland C, et al. Prevalence, Disease-free, and Overall Survival of Contemporary Patients With Renal Cell Carcinoma Eligible for Adjuvant Checkpoint Inhibitor Trials. Clin Genitourin Cancer 2021; 19: e92–9.
91 Carlo MI, Hakimi AA, Stewart GD, et al. Familial Kidney Cancer: Implications of New Syndromes and Molecular Insights. Eur Urol 2019; 76: 754–64.
92 Hu SL, Chang A, Perazella MA, Okusa MD, Jaimes EA, Weiss RH. The Nephrologist's Tumor: Basic Biology and Management of Renal Cell Carcinoma. JASN 2016; 27: 2227–37.

93 Lowrance WT, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the Risk of Incident Cancer. JASN 2014; 25: 2327–34.
94 Chang A, Finelli A, Berns JS, Rosner M. Chronic kidney disease in patients with renal cell carcinoma. Adv Chronic Kidney Dis 2014; 21: 91–5.
95 Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2008; 351:1296-305
96 Lowrance WT, Ordoñez J, Udaltsova N et al. CKD and the risk of incident cancer. J Am Soc Nephrol 2014; 25:2327-34
97 Hung PH, Tsai HB, Hung KY et al. Increased risk of end-stage renal disease in patients with renal cell carcinoma: a 12-year nationwide follow-up study. Medicine (Baltimore) 2014; 93:e52.
98 Marconi L, Desai MM, Ficarra V et al. Renal Preservation and Partial Nephrectomy: Patient and Surgical Factors. Eur Urol Focus 2016; 2:589-600.