The multispeciality approach to the management of localised kidney cancer

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Historically, kidney cancer was approached in a siloed single-speciality way, with urological surgeons managing the localised stages of the disease and medical oncologists caring for patients if metastases developed. 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 multispeciality approach to the management of kidney cancer is now essential. In this Review, we summarise the current best multispeciality practice for the management of localised kidney cancer and the areas in need of further research and development.

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Introduction

Worldwide, renal cell carcinoma—also known as kidney cancer—is the ninth most common cancer in men and the 14th most common cancer in women. Renal cell carcinoma is more common in Europe and North America than in Africa and Asia.[1] Despite founder mutations occurring in teenage years,[2] there are no known premalignant states of renal cell carcinoma allowing a preventative treatment. Because the established risk factors for renal cell carcinoma (eg, smoking, hypertension, and obesity) are similar for other preventable conditions (eg, 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 people who are asymptomatic.[4] Although population screening for renal cell carcinoma is of great interest to clinicians, patients, and carers, this approach requires substantial further research, such as the ongoing Yorkshire Kidney Screening Trial (NCT05005195).[5] As such, renal cell carcinoma is first suspected when detecting a renal mass on imaging.

Traditionally, renal cell carcinoma has been a surgical disease, including cytoreductive nephrectomy in the metastatic setting. This unidimensional approach is now obsolete. Over the last two decades there have been substantial improvements in diagnostic imaging, interventional radiology, pathology, radiotherapy, and perisurgical systemic therapy, meaning that a multispeciality approach is advantageous from the outset in most patients with renal cell carcinoma (figure 1).[6–9] Despite these changes, and although different data sources vary, data from the USA show that the age-standardised mortality rate from renal cell carcinoma has been almost static over the past 50 years (4% reduction in mortality). By contrast, since 1971, there has been a 27% reduction in cancer mortalities for all cancers combined.[10] As such, substantial work is required to improve renal cell carcinoma outcomes. In this Review, we illustrate, using a case history approach (figure 2), the current and emerging key elements of modern, multispeciality management of localised renal cell carcinoma. The medical and surgical management of metastatic disease will not be covered.

Modes of presentation

Renal cell carcinoma frequently presents incidentally. Approximately 60% of all patients with renal cell carcinoma from stages 1 to 4 will be asymptomatic or present with symptoms unrelated to renal cell carcinoma. For these patients, the lesion is identified on imaging undertaken for a different indication.[11] Haematuria and, less commonly, flank pain or a palpable mass are the most common renal cell carcinoma-related symptoms. Of patients with small renal cell carcinomas, defined as a tumour that is smaller than 4 cm in diameter (clinical stage T1a), 87% will present without any symptoms.[11] Thus, the diagnosis of patients with early-stage disease, which is potentially curable with surgery or ablation alone, is almost always incidental. However, abnormalities in common primary care blood tests (eg, inflammatory markers, haemoglobin, renal function, and liver function) start to appear from 6 to 8 months before diagnosis in 25–40% (depending on the test) of patients with renal cell carcinoma, which indicates the potential for earlier

Search strategy and selection criteria

For this Review, we searched PubMed and Embase on March 1, 2022 for studies describing multidisciplinary management of localised renal cell carcinoma between 1990 and 2022. We also assessed the literature for the highest level of evidence on key topics in renal cell carcinoma that required explanation. We used the search terms "renal cell carcinoma", "RCC", "kidney cancer" and "localised". We did not use any language restrictions.

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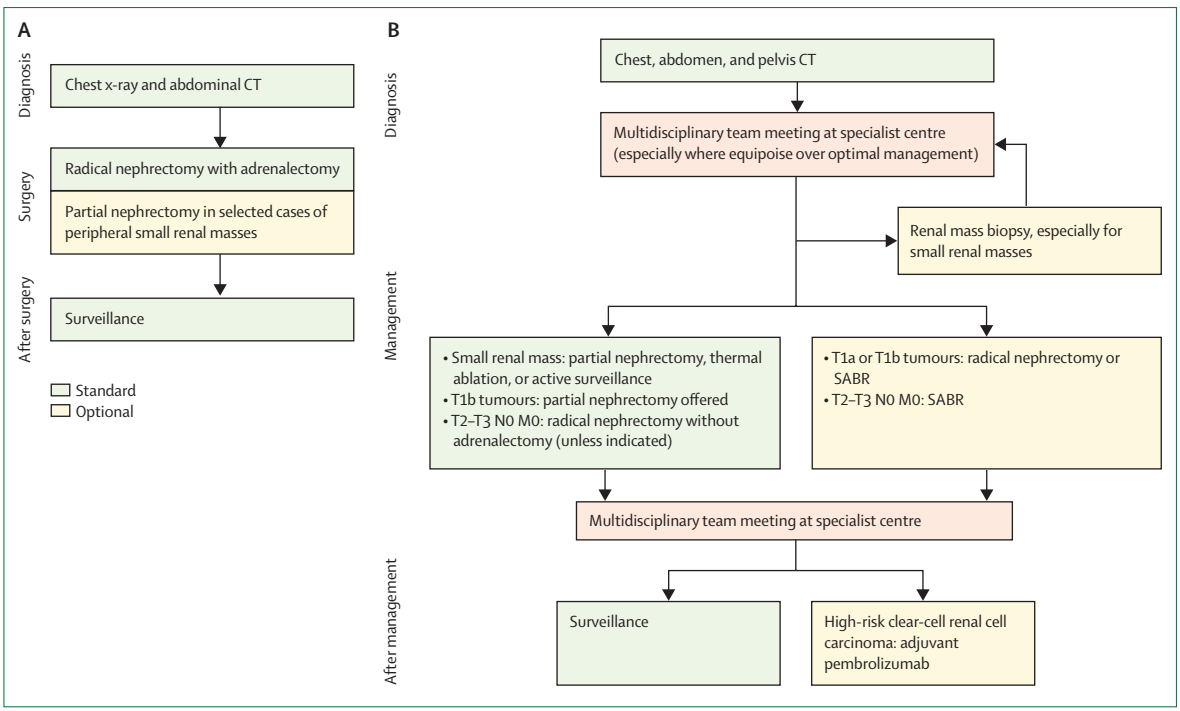

Figure 1: **Changes in the management of localised kidney cancer over the past two decades**
(A) The management of localised kidney cancer in 2001. Figure adapted from Mickisch and colleagues (2001).[6] (B) The management of localised kidney cancer in 2022. Figure adapted from the EAU guidelines on renal cell carcinoma,[7] Bedke and colleagues (2021),[8] and the National Comprehensive Cancer Network guidelines.[9] EAU=European Association of Urology. SABR=stereotactic ablative radiotherapy.

diagnosis.[12] Notably, there are clear links between renal cell carcinoma and renal dysfunction (panel 1).[13–16] Patients with more advanced renal cell carcinoma, particularly those that are clinically stage 3 (locally advanced) or 4 (metastatic), are more likely to present with a range of systemic symptoms, such as night sweats and hypertension. Due to these cytokine and chemokine related paraneoplastic syndromes, renal cell carcinoma can mimic other conditions.[17]

Baseline imaging

Ultrasound is often the first imaging modality that identifies a patient with a suspected renal mass. The main advantages of ultrasound are its widespread availability and absence of ionising radiation or nephrotoxic contrast agents, especially for patients with renal impairment. Ultrasound can reliably differentiate solid masses from simple cysts. Solid lesions on ultrasound or those with suspicious features (eg, lesions with thickened walls or septa or lesions with solid components with blood flow on colour doppler ultrasound or enhancement on contrast-enhanced ultrasound)[18] require further evaluation with CT or MRI.[19] Triple-phase CT of the chest, abdomen, and pelvis is the standard investigation for the characterisation of solid renal masses and staging of renal cell carcinoma with 91% accuracy.[20] However, for patients with small renal masses (<4 cm) and no systemic symptoms, the risk of lung metastases is less than 1% and they could forego a chest CT.[21] Initial imaging of the head and bones is only recommended in the presence of specific symptoms or laboratory signs.[7] Differentiating benign from malignant renal masses is not normally possible on CT scan. Common benign lesions such as oncocytomas (approximately 5% of all renal masses) overlap with renal cell carcinomas in terms of attenuation, enhancement, and contrast washout.[22] Technetium (^{99m}Tc) sestamibi single-photon emission CT shows promise for differentiating oncocytomas, hybrid oncocytic chromophobe renal cell carcinomas, and chromophobe renal cell carcinomas from much more aggressive clear-cell renal cell carcinomas or papillary renal cell carcinomas during diagnosis. The diagnostic accuracy of zirconium (^{89}Zr) girentuximab positron emission tomography CT, which targets carbonic anhydrase 9 present in clear-cell renal cell carcinoma but not in other renal cell carcinoma histological subtypes, is being evaluated in the ZIRCON study (NCT03849118). However, neither of these approaches provides a confident diagnosis of absolute benignity of the lesion.[23] Thus, there is a need for an imaging biomarker to non-invasively differentiate renal cell carcinoma from benign renal masses. Imaging biomarkers could 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 has shown promise in the grading of clear-cell renal

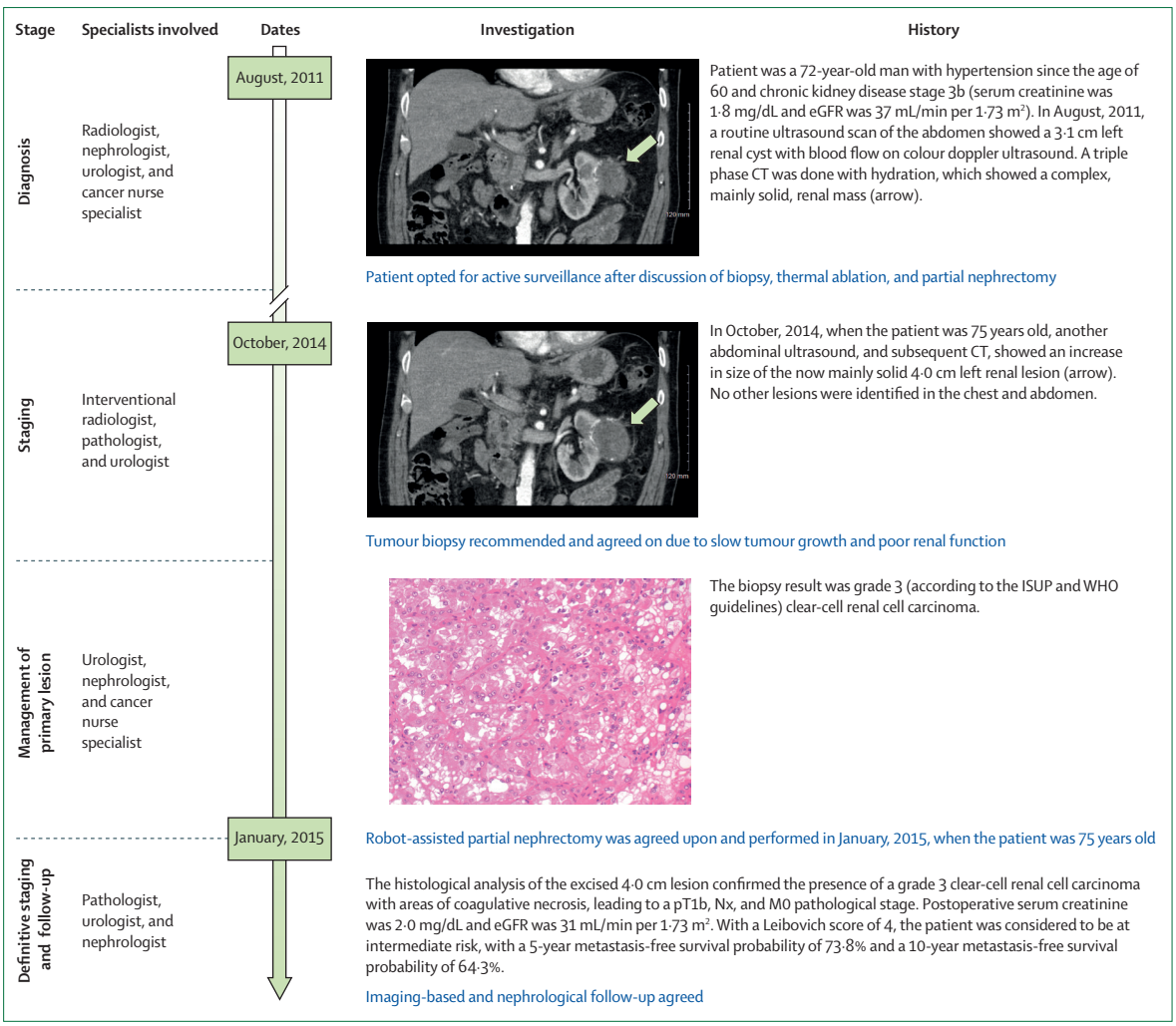

Figure 2: **Case history of a patient with renal cell carcinoma from diagnosis to staging**
ISUP=International Society of Urological Pathology.

cell carcinoma, but requires substantial further development.[24] Currently, tumour biopsy remains the most informative method of differentiating renal mass cause and renal cell carcinoma subtype and grade (low *vs* high) before treatment decision. Multiparametric MRI is superior to CT for evaluating the extent of tumour thrombus in the inferior vena cava.[25]

The multidisciplinary team meeting

After the initial imaging, each patient's case should be referred to the multidisciplinary team meeting to make recommendations for treatment options. Kidney cancer multidisciplinary team meetings variably include histopathologists, radiologists, surgeons, cancer nurse specialists, research nurses, radiation oncologists, and medical oncologists. These meetings typically occur on a weekly basis. A hub-and-spoke model ensures subspecialty expertise is available to colleagues in peripheral centres.[26] Patients generally do not attend multidisciplinary team meetings, and their general health and wishes are often not known.[27] Thus, the decision about suitability for eventual active treatment continues from the multidisciplinary team meeting discussion into the clinic with the patient and their relatives.

The use of multidisciplinary team meetings varies internationally, and sometimes even locally, from discussing only complex cases to discussing all new cases. The ideal multidisciplinary team meeting should allow sufficient time for discussion of complex localised renal cell carcinoma cases (eg, high-complexity small renal mass management, inferior vena cava tumour thrombi, and clinical trial suitability).

Role of renal tumour biopsy

Unlike patients with any other solid tumour, patients with a renal mass do not undergo a mandatory tumour biopsy to determine the aetiology of the lesion. Tumour

Panel 1: **The bidirectional relationship between renal cell carcinoma and chronic kidney disease[13]**

Chronic kidney disease is a risk factor for developing renal cell carcinoma

- Patients with stage 3 or 4 chronic kidney disease have a greater risk of developing renal cell carcinoma, with lower eGFR being associated with an increased risk of renal cell carcinoma (HR: 1·39 for eGFR=45–59 mL/min; 1·81 for eGFR=30–44 mL/min; 2·28 for eGFR <30 mL/min)[14]

There is an increased prevalence of chronic kidney disease in patients with renal cell carcinoma

- The prevalence of chronic kidney disease in patients with renal cell carcinoma at the time of diagnosis (ie, pre-surgery) is 25% higher than in the general population[15]
- Overlapping risk factors between chronic kidney disease and renal cell carcinoma could account for the high prevalence for chronic kidney disease in the oncological population
- With improvement in cancer patients' survival due to improved treatments, chronic kidney disease-related morbidity due to nephron mass loss and comorbid disease-induced complications has become increasingly relevant, ultimately affecting overall quality of life and non-cancer-related survival[16]

Treatment for renal cell carcinoma has a detrimental effect on renal function

- Interventional treatments such as surgery for renal cell carcinoma frequently result in reduction of the renal function due to the removal or damage of peritumoral normal renal parenchyma

eGFR=estimated glomerular filtration rate. HR=hazard ratio.

biopsies not being mandatory is an anomaly and contravenes the established rules of surgical oncology. However, a typical 4 cm contrast-enhancing renal mass has only an 86% probability of being a renal cell carcinoma, with as few as 23% of masses being aggressive lesions requiring invasive treatment. These figures are even lower for tumours smaller than 4 cm.[28] 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 patient cohorts 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%.[29] 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 embolisation or nephrectomy.[29] Tumour seeding has been described in case reports but is very rare using a coaxial needle technique and is greatly outweighed by risks of unnecessary surgery on benign lesions.[30,31] In fact, the accuracy and safety of renal tumour biopsies is superior to biopsies of other systems.[32] The expertise of the interventional radiologist is key in making decisions about the biopsy approach because targeting small lesions (ie, ≤1 cm) is substantially more challenging than targeting larger lesions, and the location of the tumour within the kidney might be challenging and require the use of a CT-guided (10–15% of cases authors' [AB and GDS] personal case series of patients), rather than the default ultrasound-guided, approach. Ultimately, the individual patient's preference for intervention will be a substantial 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 could change the treatment approach and should certainly be discussed with all patients with tumours smaller than, or equal to, 4 cm. For patients who elect for renal mass biopsy, multiple biopsies, with the aim of ensuring a diagnosis can be made and to counter grade heterogeneity, are preferred over fine-needle aspiration. For example, in our case study (figure 2), due to the patient having advanced chronic kidney disease (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 malignancy that was likely to be aggressive (eg, high-grade renal cell carcinoma) was confirmed on biopsy.[33]

There is an increasingly complete understanding of the molecular architecture of renal cell carcinoma.[34] The fifth edition of the WHO classification of urogenital tumours[35] introduced a molecule-driven renal tumour classification, taking discoveries in renal tumour genomics into account. Such novel molecularly defined epithelial renal tumours include SMARCB1-deficient medullary renal cell carcinoma, TFEB-altered renal cell carcinoma, Alk-rearranged renal cell carcinoma, and ELOC-mutated renal cell carcinoma. However, there are no genetic, transcriptomic, methylation, or proteomic approaches that are routinely used on either biopsy or resection tissue as an adjunct to standard histopathology to guide diagnosis, treatment, or follow-up, but the introduction of next-generation sequencing 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 renal cell carcinoma,[36] which is an approach that should be expanded upon in the neoadjuvant and adjuvant setting.

Treatment

Management of localised renal cell carcinoma (≤7 cm)

Patients presenting with small, solid renal masses or complex renal cysts smaller than, or equal to, 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. Although nephron-sparing surgery in the form of partial nephrectomy has evolved as the standard of care by default, ablation and active surveillance are alternatives, traditionally for patients who are frail or have comorbidities.[37] At present, these management modalities have not been compared in prospective randomised controlled trials, but large retrospective studies with long-term follow-up or studies with mostly older patient cohorts suggest similar overall survival for the various treatment options.[37] A key question is whether the risk of the lesion outweighs the risk of the competing health risks. Although no high-quality evidence exists to address this question, risk models of small renal mass management have been developed that provide clear information to patients on their personalised risk.[38] Information from such models helps to reassure patients who are frail that the risks of treatment outweigh that of any small kidney cancer and that they can safely be discharged from any further follow-up.

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 chronic kidney disease (initially used for the patient in our case study; figure 2), especially older patients, who might progress to end-stage kidney disease. Among a cohort of patients aged over 40 years, the expected mean annual reduction in estimated glomerular filtration rate (eGFR) is -0·39 mL/min/1·73 m² per year (95% CI: –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.[39]

In the largest reported study and in 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%.[40–42] Small renal mass growth rates are similar between cancers and non-cancers. Furthermore, the absence of tumour growth does not rule out cancer, but slower growing tumours seem less likely to progress to metastatic disease.[43] Short-term oncological results of active surveillance appear equivalent to partial or radical nephrectomy.[44] 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[45] aim to establish these triggers.

Surgery

Nephron-sparing surgery is the recommended approach for cT1 lesions (tumours ≤7 cm), provided the resection is technically feasible and thus oncologically safe.[7] Decision making over surgical approach often requires uroradiological expertise. Urologists who are experts on partial nephrectomy should be provided with 3D reconstructions of the CT scans to help them make decisions about the feasibility of partial nephrectomy. The preference for partial nephrectomy was formulated on a single prospective randomised controlled trial done by the European Organization for Research and Treatment of Cancer (EORTC) that included patients with non-metastatic renal cell carcinomas up to 5 cm in diameter. The EORTC study revealed a comparable cancer-specific survival for partial nephrectomy versus radical nephrectomy, but superior renal function preservation.[46,47] This trial closed prematurely and was underpowered, but did not show any inferiority of renal nephrectomy versus partial nephrectomy in terms of overall survival. All other studies comparing the oncological outcomes of partial nephrectomy and radical nephrectomy are retrospective and include cohorts of varied and limited sizes.[48] Retrospective studies suggest that partial nephrectomy preserves renal function with a lower risk of cardiovascular complications than radical nephrectomy.[49–51] Similarly, in a Cochrane review, partial nephrectomy for localised renal cell carcinoma was associated with decreased mortality from any cause than radical nephrectomy. However, serious adverse event rates, cancer-specific survival, and disease-free survival were similar between partial and radical nephrectomy.[52] This evidence resulted in guidelines recommending partial nephrectomy as the treatment of choice for cT1 renal cell carcinoma because it preserves renal function more and potentially limits cardiovascular disorders. The evidence is clearer for cT1a tumours than for cT1b tumours, for which only retrospective data suggest improved disease-free survival and cancer-specific survival following partial nephrectomy.[53] The question of partial versus radical nephrectomy for cT1b tumours will be addressed in the forthcoming PARTIAL trial. The outcomes evaluated in this trial will include complications, renal function, quality of life, and cost-effectiveness.[54] Whether or not partial nephrectomy truly leads to decreased mortality from any cause is still unresolved. However, for patients with pre-existing chronic kidney disease or solitary kidneys and a renal lesion requiring treatment, partial nephrectomy is the preferred surgical treatment option because it decreases the risk of developing end-stage renal disease and reduces the need for haemodialysis.[55]

Regarding the choice of the surgical approach, the current principal issue of debate is robotic-assisted laparoscopic partial nephrectomy (RAPN) versus open partial nephrectomy (OPN). However, no prospective randomised controlled trials exist comparing these techniques.[56] Retrospective data suggest a decreased morbidity in the RAPN group with fewer overall complications, fewer major complications, fewer transfusions, and shorter hospital stay than OPN.[56] In most major renal

Score

Age (years)	
<65	0
≥65	1
Diabetes	
No	0
Yes	1
Preoperative eGFR (mL/min per 1·73 m2)	
60–69	5
70–79	4
80–89	3
≥90	0
Management plan	
Partial nephrectomy	0
Radical nephrectomy	3

Risk level (score)	Probability of stage 3b chronic kidney disease (%)
Negligible (0–3)	1%
Low (4–6)	10%
Moderate (7–8)	25%
High (9–10)	**50%**

Figure 3: **A clinical score to predict clinically relevant chronic kidney disease after nephrectomy**
The pre-operative clinical factors are scored (left panel) to provide the probability of stage 3b chronic kidney disease (right panel). Used with permission from Ellis and colleagues (2020).[71] eGFR=estimated glomerular filtration rate

cell carcinoma centres, OPN is now reserved for resection of the most complex tumours.[57] If the expertise of the surgeon and team allow, RAPN is becoming the preferred approach for the majority of partial nephrectomies, although surgeon and hospital case volume are key to outcomes.[58]

Thermal ablation

Previous clinical trials have failed feasibility to recruit patients to assess thermal ablation versus surgery or active surveillance for T1a and T1b renal cell carcinomas,[59] indicating the need for urologists and interventional radiologists in the multidisciplinary team who are prepared to take a balanced view in guiding patients on optimal treatments. A systematic review from 2018 including 3974 patients who had undergone ablation (either radiofrequency ablation or cryoablation) or partial nephrectomy showed higher all-cause mortality rates (hazard ratio [HR]: 2·11) and cancer-specific mortality rates (3·84) for ablation than for partial nephrectomy. No statistically significant difference in local recurrence rates or risk of metastasis was seen. Complication rates were lower for ablation than for partial nephrectomy (13% *vs* 17·6%; p<0·05). A significantly greater decrease in eGFR was observed after partial nephrectomy than after ablation.[60] A major limitation of these systematic reviews is inherent differences in patient populations with regards to age and comorbidities.[61] These limitations result in selection bias, poorer all-cause mortality, and fewer long-term data for ablation than for partial nephrectomy. All systematic reviews on this subject have low confidence ratings.[61] Current data are inadequate to make any strong and clear conclusions regarding the comparative effectiveness of ablation versus partial nephrectomy. An ongoing cohort embedded trial (NEST) is addressing the feasibility of randomisation and patient choices for ablation compared with partial nephrectomy.[62]

Stereotactic ablative radiation therapy

Stereotactic ablative radiation therapy (SABR), a totally non-invasive treatment modality, has recently been applied to localised renal cell carcinoma. The data are rapidly emerging: a meta-analysis in 2019 included 26 predominantly retrospective studies and 372 patients.[63] In this meta-analysis, the local control rate was 97·2% and the grade 3–4 toxicity rate was 1·5%. The existing prospective clinical trials are all small, single institutional studies. However, the multicentre TransTasman Radiation Oncology Group FASTRACK II trial is ongoing.[64] Data from the International Radiosurgery Oncology Consortium for Kidney show promising cancer-specific survival of 91·9% and local control of 97·8%,[65] in addition to safety and local efficacy of SABR for patients with tumours that are larger than, or equal to, the T1b grading,[66] and for patients with solitary kidneys.[67] Special populations have also been investigated through clinical trials: neoadjuvant SABR for inferior vena cava thrombus[68] and neoadjuvant SABR before cytoreductive nephrectomy.[69] As such, SABR is considered a novel treatment reserved for patients with T1a–T3 tumours who are not medically or technically operable (according to the 2022 National Comprehensive Cancer Network guidelines).[9]

Management of localised renal cell carcinoma (>7 cm)

Patients with cT2-stage (>7 cm) renal tumours are generally treated directly with surgery. Biopsy is rarely done as the likelihood of a renal cell carcinoma is much greater for patients with tumours larger than 7 cm than for patients with small renal masses. However, patients with frailty or substantial comorbidities, or both, should be assessed by anaesthesiologists or geriatricians with expertise in presurgical assessment to determine risk of death from surgery and enable the urologists to weigh this against the risk of the patient developing metastatic kidney cancer. A useful tool is the American College of Surgeons Risk Calculator, which provides estimates of a patient's risk of postsurgical morbidity and mortality.[70] Renal tumour biopsy is recommended for patients with chronic kidney disease when a dimercaptosuccinic acid scan indicates a nephrectomy would push the patient close to requiring dialysis. Renal tumour biopsy is also recommended for patients with many comorbidities to assist in defining the risk of the tumour to the patient (ie, if the patient has benign or low grade [G1 or G2] renal cell carcinoma), which means surgical treatment might be avoided.

Tools are available to quantify the risk of clinically significant chronic kidney disease (ie, eGFR <45 mL/min; chronic kidney disease stage 3 or 4) following kidney cancer surgery. One example of such a tool incorporates

For the **American College of Surgeons Risk Calculator** see https://riskcalculator.facs.org/RiskCalculator/

Panel 2: **Nephrological management before, during, and after surgery for renal cell carcinoma**

Nephrological assessments are especially relevant for patients predicted to have chronic kidney disease that is stage 3–5 (eGFR <45 mL/min) after surgery.

Pre-surgery

- The nephrologist should inform the patients and their caregivers about the likelihood and the consequences of worsening kidney function
- Patients with pre-existing chronic kidney disease have a substantially higher risk of morbidity, including acute kidney injury, and mortality during the perioperative period and in the longer term[15]
- The management of patients with pre-existing chronic kidney disease should focus on preserving renal function, reducing cardiovascular risk, and long-term chronic kidney disease care
- Optimisation of glycaemic and blood pressure control should be mandatory to reduce deterioration of GFR postoperatively[72]

During surgery and perisurgery

- Euvolemia should be aimed for to maintain renal perfusion
- Nephrotoxins should be avoided

Post surgical follow-up

- Surgically induced chronic kidney disease is associated with a low incidence of progressive annual renal function decrease, whereas patients' comorbidities have a higher effect on the progression of chronic kidney disease[73]
- The first goal of the nephrologist is to minimise 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 (eg, hypertension or diabetes)
- Secondly, the nephrologist should support oncologists in managing treatment-related renal adverse events, in those patients needing oncological treatments, either in the adjuvant setting, or if the patient develops recurrent metastatic disease
- The nephrologist should be involved in the choice of optimal follow-up radiological procedure to use, mainly deciding if, when, and how to use CT contrast media
- Because the risk of intravenous contrast-induced nephropathy has been redefined by the literature,[74] and the risk of suboptimal restaging after primary treatment greatly outweighs the risk of inducing further kidney injury,[75] a more liberal approach to the use of CT contrast media is justified to guarantee prompt diagnosis of cancer recurrence
- A shared protocol for the use of contrast media in patients with chronic kidney disease should be implemented in cancer centres[76]
- Nephrological follow-up, comprising of eGFR, blood pressure, and creatinine–protein ratio, should be customised according to the residual renal function and concomitant treatments
- The nephrologist should also deal with oncological patients on dialysis or with kidney transplant, including if, and when, to start dialysis, or whether to allow a kidney transplant

eGFR=estimated GFR. GFR=glomerular filtration rate.

age, diabetes, presurgical eGFR, and type of nephrectomy (figure 3).[71] Such patients should undergo a nephrological assessment before planning surgery and during the postsurgical follow-up (panel 2).[72–76]

For patients who warrant surgery but the nephrologists determine that with nephrectomy there will be a need for postsurgical dialysis, options to avoid dialysis include attempting an open partial nephrectomy or, in specialist centres, an ex vivo bench dissection and autotransplantation.[77] There have been small phase 2 trials of neoadjuvant systemic therapy with an aim to downstage the cancer and enable a partial nephrectomy. For example, the AXIPAN trial showed a modest reduction in tumour size following axitinib therapy but the partial nephrectomy remained complex.[78]

Active surveillance of T2-stage 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, active surveillance leads to acceptable oncological outcomes.[79] SABR is a burgeoning treatment option for patients with T2-stage disease associated with promising local control and low morbidity.[66] More confirmatory studies are required in this population.

Regarding surgical approach for patients with lesions larger than 7 cm, minimally invasive surgery is usually attempted where possible, and non-trial data suggests that cancer outcomes are similar between laparoscopic and open radical nephrectomy.[80,81] Low-quality data suggest no advantage to robotic-assisted radical nephrectomy, which is the most expensive surgical approach.[82]

Prophylactic adrenalectomy or lymph node dissection is not needed as a treatment when, on presurgical staging CT, these structures appear normal (lymph nodes <1 cm in short axis).[83,84] Adrenal preservation is important because contralateral adrenal metastases are not uncommon for patients with renal cell carcinoma. Endocrinologists should be involved in the perisurgical management of patients who are likely to be rendered steroid dependent after bilateral adrenalectomy, which is a scenario associated with substantial complications and morbidity.[85]

Locally advanced disease

Cancer cure remains possible when renal cell carcinoma has extended outside of the kidney itself. A unique invasive phenomenon of renal cell carcinoma is the

	3 months	6 months	12 months	18 months	2 years	3 years	>3 years
Low risk of disease recurrence	--	CT	--	CT	--	CT	CT once every 2 years
Intermediate risk of disease recurrence	--	CT	CT	--	CT	CT	CT once every year and after 5 years CT once every 2 years
High risk of disease recurrence	CT	CT	CT	CT	CT	CT	CT once every year and after 5 years CT once every 2 years

Follow-up should be intensified in patients after partial nephrectomy for tumours larger than 7 cm or in patients with a positive surgical margin. This schedule was developed on the basis of expert opinion.[7] Empty cells indicate that no follow-up is required at these timepoints for that risk level. EAU=European Association of Urology.

Table: **Chest and abdomen CT follow-up schedule according to the EAU guidelines following treatment for renal cell carcinoma, considering tumour risk profile and treatment efficacy**

extension of the tumour along the segmental renal veins into the main renal vein, inferior vena cava, and, in extreme examples, into the right atrium of the heart. Although disease that has spread so extensively might be thought to be incurable, up to 65% of patients with venous tumour thrombus are alive 5 years after surgery.[86,87] However, perisurgical mortality is high (5–15%) and increases with the extent of the venous tumour thrombus.[88,89] Surgery is usually performed open but in very specialised centres a minimal access robotic approach could be an option.[90] A phase 2 trial investigating neoadjuvant SABR for venous tumour thrombus has shown the safety of this approach.[68]

Neoadjuvant systemic therapy

Neoadjuvant treatment is the use of non-surgical therapy before 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 renal cell carcinoma. However, clinical trials, including window-of-opportunity studies to assess the effect of short courses of novel combination therapies are ongoing.[91] Completed studies include the NAXIVA trial of the neoadjuvant tyrosine kinase inhibitor axitinib to downstage inferior vena cava venous tumour thrombus to enable less extensive and morbid surgery.[92] In NAXIVA 35% of patients had a reduction in the extent of venous tumour thrombus and 41% of patients had less extensive surgery than the originally planned surgery. There are multiple phase 2 clinical trials of neoadjuvant tyrosine kinase inhibitor therapy using a range of different agents,[93] mainly with the aim of downstaging the primary disease (median tumour size percentage reduction ranging from 9·6% to 28·3%). In the future, more phase 3 neoadjuvant renal cell carcinoma trials are needed.

As the evidence for adjuvant T-cell checkpoint inhibitor use in renal cell carcinoma increases,[94] there is considerable interest in the role of a neoadjuvant strategy in high-risk localised renal cell carcinoma, either as an adjunct to subsequent adjuvant treatment or as a standalone therapy. Although a single arm trial (NEOAVAX) showed a 30% partial response rate in primary tumours by checkpoint inhibitor combination therapy with VEGFR-TKI (avelumab plus axitinib),[95] a randomised phase 3 trial (PROSPER RCC, NCT03055013) is evaluating the combined neoadjuvant-adjuvant strategy with nivolumab versus observation in patients with M0 disease or M1 disease planned to be resected or definitively treated (ie, M1 no evidence of disease).[96]

Postinterventional follow-up and adjuvant systemic therapy

Postinterventional treatment follow-up

Follow-up after surgery or ablation is currently observational to assess renal function status and monitor oncological control by cross-sectional imaging. Clinical assessment includes an assessment of symptoms of recurrence (ie, abdominal pain, cough, bone pain, weight loss, loss of appetite, and fatigue). The frequency and modality of imaging are not well defined by evidence and vary considerably in major guidelines.[7,97] Guideline recommendations are made on the basis of validated risk models of recurrence. A systematic review has established that, out of the existing validated risk stratification tools, the Leibovich, Karakiewicz, and Sorbellini clinico-pathological models are optimal to predict recurrence-free survival, cancer-specific survival, and overall survival for clear-cell renal cell carcinoma following surgery with curative intent.[98] The VENUSS score performs best for papillary renal cell carcinoma.[99] For the patient in our case study (figure 2), the Leibovich score was used and due to the patient's tumour being pT1b (3 points) and grade 3 (1 point), the patient's Leibovich score of 4 translates into being having an intermediate risk of recurrence (Leibovich scores 3–5).[100] The European Association of Urology (EAU) guidelines (table) recommend cross-sectional imaging every 6 months for patients with intermediate renal cell carcinoma for the first year, annual CT scans for the following 2–5 years, and biennial scans for up to 10 years follow-up.[7]

It is uncertain whether follow-up improves survival and how long follow-up should be continued. A small Scandinavian study analysing a surveillance protocol 8 years after its implementation suggests a survival benefit for patients who were followed up within a structured surveillance protocol compared with patients who were not.[101] However, analysis of the European multicentre

RECUR database showed that more frequent imaging leading to the earlier detection of recurrence did not lead to higher overall survival than less frequent imaging.[102]

Imaging-based follow-up is hugely resource intensive. According to the RECUR database, overall 542 follow-up imaging tests were required for each patient treated for renal cell carcinoma recurrence who remained alive with no evidence of disease, whereas 697 imaging tests were needed for patients at high-risk of recurrence.[102] No prospective comparative studies of different follow-up regimens have ever been done. There is a need for research to evaluate dynamic-patient competing risk models, cancer risk stratification models, and 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). The patient in our case study (figure 2) has chronic kidney disease (stage 3b) and progression to end-stage kidney disease is a possibility. Preventing the progression to end-stage kidney disease could favourably affect the patient's overall survival and could prevent the drop in quality-of-life due to dialysis. Furthermore, preventing disease progression could affect the oncological treatment options if metastatic renal cell carcinoma develops.[103]

Adjuvant therapy

As indicated above, a step change is needed to achieve improvement in renal cell carcinoma survival, which appears to have lagged behind improvements seen in other cancer types.[10] Effective adjuvant treatment for patients with localised renal cell carcinoma who are at substantial risk of developing metastasis would benefit a large proportion of patients with renal cell carcinoma and would enable that survival improvement.

Following five clinical trials reporting the outcomes of adjuvant tyrosine kinase inhibitors for renal cell carcinoma, sunitinib was the only drug approved for adjuvant therapy by the US Food and Drug Administration (FDA).[104] Until 2021, surveillance was standard practice after surgical excision.[104] On the basis of data from the Keynote-564 study, adjuvant pembrolizumab (a PD-1 inhibitor) was approved by the US FDA, the European Medicines Agency Committee for Medicinal Products for Human Use, and given a weak recommendation by the EAU and European Society for Medical Oncology guidelines.[8,105] This trial showed that, in patients with clear-cell renal cell carcinoma at high risk of recurrence (including a subgroup of patients [n=58; 6%] after complete metastasectomy), after 1 year of treatment with adjuvant pembrolizumab there was a significant disease-free survival benefit compared with the placebo (HR 0·68; 95% CI 0·53–0·87; p=0·002).[94] In contrast to previous adjuvant tyrosine kinase inhibitor trials, at a median follow-up of 24·1 months, overall survival showed an early, yet not statistically significant, trend in favour of the pembrolizumab group compared with the placebo (0·54; 0·30–0·96; p=0·0164). However, conclusive data on overall survival are not available yet because only very few deaths have occurred. Potential benefits of adjuvant pembrolizumab must be balanced against the risks of overtreating of patients who are cured by surgery alone, a 14·7% higher all-cause grade 3–5 adverse event rate (32·4%) compared with placebo (17·7%), costs of the drug and administration, and an absence of data from other ongoing adjuvant checkpoint inhibitor trials.[96] If these data mature to show a statistically significant overall survival advantage, adjuvant checkpoint inhibitors will probably become the standard of care. However, with these expensive treatments come the risks of adverse events, which could potentially be life changing or life threatening. As such, it is plausible that the use of prognostic models of postsurgical cancer recurrence will soon move beyond simply informing patients of their risk of recurrence and the 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.[106]

Principles and management of hereditary kidney cancer

Inherited forms of renal cell carcinoma account for 5% of all cases. The most common hereditary condition is von Hippel-Lindau disease. However, due to modern sequencing approaches several new syndromes have been identified in the past three decades. These syndromes include SDHB-deficient renal cell carcinoma, hereditary leiomyomatosis and renal cell cancer syndrome-associated renal cell carcinoma, and papillary renal cell carcinoma syndrome.[107] Many patients are aware that they have a familial syndrome because of their family history. However, when patients older than 46 years are diagnosed with a new renal cell carcinoma a medical genetics referral should be considered, because 70% of hereditary renal cell carcinomas develop before this age. In von Hippel-Lindau disease, multiple foci of renal cell carcinoma can develop throughout life and a biopsy is not usually required. Surgery to excise all lesions is usually done when the largest lesion reaches 3 cm. The same principal can be followed in other syndromes except for hereditary leiomyomatosis and renal cell cancer syndrome-associated renal cell carcinoma, which metastasises early and should be resected promptly.[107]

The HIF-2α inhibitor belzutifan has shown activity in patients with von Hippel-Lindau disease-related renal cell carcinomas and non-renal cell carcinoma neoplasms associated with von Hippel-Lindau disease.[108] This treatment, which is well tolerated, might reduce the burden of often repeated surgery throughout the life of patients with von Hippel-Lindau disease.

Conclusions

In this Review, we highlighted the rapid evolution of modern multispeciality management of renal cell

carcinoma over the past 20 years, but also the key areas in this field that require further research. Maintaining renal function and choosing the optimal oncological treatment (eg, surgery, ablation, SABR, observation, or systemic therapies) now require the input of specialists from across medicine for 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 comorbidities, 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 complex condition.

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 and AstraZeneca; consultancy fees from MSD and EUSA Pharma; speaker fees from Pfizer; and has leadership roles for The Urology Foundation and Kidney Cancer UK. LC acted as a speaker and consultant for General Electric. AB has received honoraria for participation in advisory boards for Eisai and Ipsen and has an educational grant from Pfizer. BWL is a consultant for Digital Surgery; received speaker honoraria from AstraZeneca; and has a leadership role at the British Association of Urological Surgeons (Oncology). HM is a consultant for Roche; has received honoraria from Roche, Bayer, AstraZeneca, MSD, and Janssen; and has leadership roles for the International Agency for Research on Cancer WHO. ES has stock in Lucida Medical; is a research consultant for Amazon Web Services; and acted as a speaker for GE Healthcare. SS has received education grants from Varian, Reflexion, and Bayer Pharmaceuticals; is a speaker for AstraZeneca; and has leadership roles for RSS, TROG Cancer Research, and IASLC. CP acted as speaker or consultant, or both, for Eisai, MSD, Bristol Myers Squibb, AstraZeneca, Ipsen, EUSA Pharma, Angelini, and MSD. The contribution of GDS aand ES to this research was supported by the National Institute for Health Research (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, GDS confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. TK and MG declare no competing interests.

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