Renal cancer

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Abstract

Renal carcinoma is a reasonably common cancer in the UK. Fortunately, its diagnosis is nowadays much earlier due to the increased utilization of radiological imaging. While surveillance is an option, particularly in older/comorbid patients, nephron-sparing surgery remains the gold standard treatment for small renal masses. Laparoscopic, robotic or open partial nephrectomy have excellent cure rates. For larger tumours, radical nephrectomy may be required. This again can be performed laparoscopically, robotically or in an open manner. The classic presentation of renal mass, haematuria and loin pain is a late presentation – many of these patients will already have metastatic disease. Although non-curable, treatments are available for metastatic disease. Surgical options in the form of cytoreductive nephrectomy and metastasectomy can improve overall survival. Tyrosine kinase inhibitors, other targeted agents and immune check point inhibitors constitute the non-surgical treatments and have demonstrated increases in survival.

Keywords Cancer; carcinoma; kidney; nephron sparing ablation; partial radical nephrectomy; renal

Renal cancer facts

Renal carcinoma (RC) is the seventh most common cancer in the UK accounting for 3% of all new cancer diagnoses. Over time, this cancer has become more prevalent (Figure 1),[1] due largely to the increasing use of radiological imaging with a resulting increase in diagnosis of incidental renal masses. With detection of smaller, earlier stage tumours, a reduction in patients presenting at a late, incurable stage has occurred. Thus, the pathognomonic presentation triad of loin pain, renal mass and haematuria has thankfully become far less common. It is important to note that despite the improvement in survival, renal cancer remains a significantly deadly disease; only 56% of UK adults diagnosed expect to survive 5 years.

The main risk factors are: male sex, smoking status, hypertension and obesity. There are several genetic predispositions including Von Hippel-Lindau syndrome, Birt-Hogg Dube syndrome, hereditary papillary RCC and tuberous sclerosis amongst others.

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Renal cancer diagnosis and staging

A majority of renal masses are asymptomatic at the time of diagnosis. Over 50% of RCCs are diagnosed incidentally on imaging done for other reasons. A history of macroscopic haematuria, loin pain, renal dysfunction, family history of RCC and prior surgery should be elicited. Medical comorbidities, medications, family history of renal tumours or genetic predispositions as well as ECOG (Eastern Cooperative Oncology Group) status should be assessed. Clinical examination can reveal an abdominal mass. Assessment for cervical and supraclavicular lymphadenopathy should be made.

RCC can produce several paraneoplastic effects, including anaemia, weight loss, fever, thrombocytopenia, hypertension, hypercalcaemia (due to parathyroid-hormone-related peptide secretion)[2] and, rarely, an acute hepatitic picture known as Stauffer's syndrome. Occasionally, patients may present with only these signs or symptoms. A worse prognosis is imparted by the presence of hypoalbuminaemia, weight loss, anorexia and malaise.[3]

Laboratory tests should include full blood examination, urea and electrolytes (to assess overall renal function), alkaline phosphatase (can be elevated with bone metastases). Calcium, lactate dehydrogenase and erythrocyte sedimentation rate are markers for prognostic stratification. Urine cytology can be considered for central tumours or tumours involving the collecting system to help exclude urothelial carcinoma.

Renal masses can be classified as solid or cystic. Contrast enhanced CT and MRI have been used widely for the characterization of renal masses. Contrast enhanced ultrasound can also be considered in certain patient groups for (renal impairment, contraindication to IV contrast). Standard ultrasound can also be used to distinguish cysts from solid renal tumours. Heterogeneous, enhancing masses are typical of RCC, although no radiological investigation can reliably differentiate benign from malignant tumours nor assess the grade of the tumour. To aid decision making, total and differential renal function can be assessed indirectly with US or CT, or more accurately via isotope imaging.

Complex renal cysts (Figure 2) can be malignant and often represent a diagnostic dilemma. The Bosniak score[4] can stratify the likelihood of harbouring malignancy and is based on CT characteristics, including whether the cyst contains solid enhancing components, enhancing wall or septae as well as degree of septation, nodularity and calcification. The following risk levels for malignancy apply: Bosniak 4, 90%; Bosniak 3, 50%; Bosniak 2, 0–5%; Bosniak 1 (simple cyst), 0%.[4]

Local and nodal staging can also be based on CT of the retroperitoneum, while a CT of the chest is useful for excluding lung metastases. Renal vein or caval thrombus can be visualized on CT (Figure 3) or MRI. Whole body bone scan can identify metastatic deposits if suspected, while a brain CT may be required if focal neurological symptoms are present. PET is not currently recommended in the workup of RCC. Table 1 shows the AJCC renal cancer staging system.

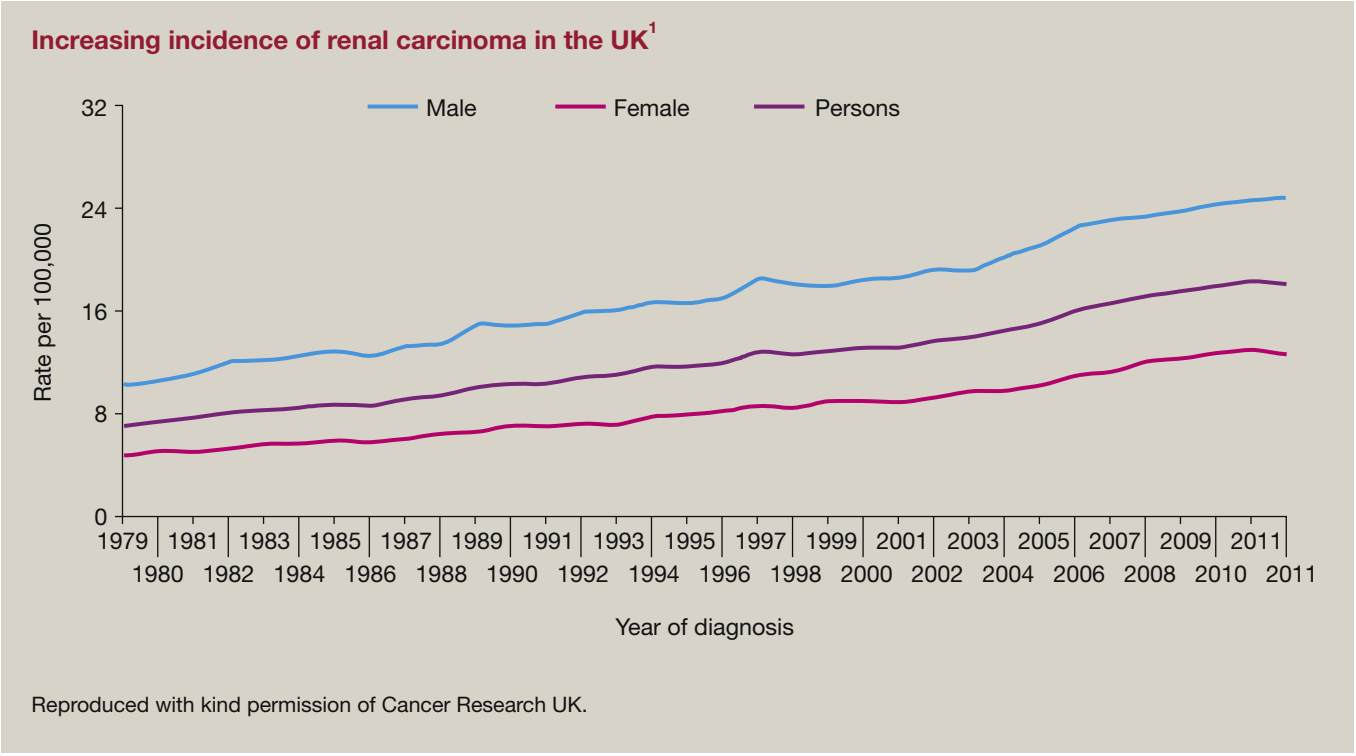


Figure 1

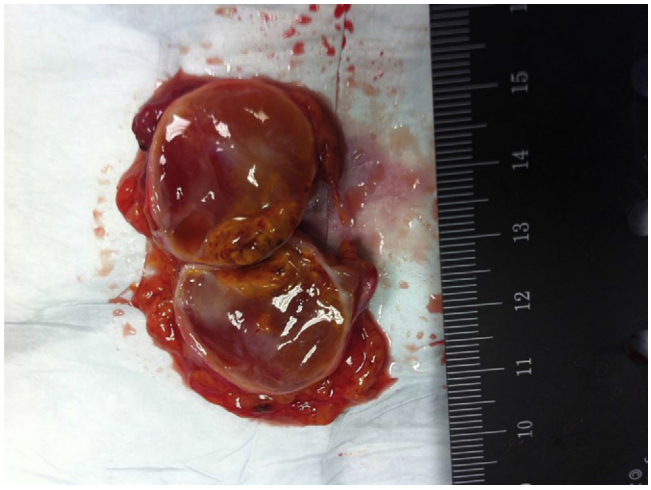


Figure 2 Cystic renal mass with solid component.

Pathological assessment/biopsy

Small renal masses (less than 4 cm), are benign 20% of the time. Larger tumours (Figure 4) are malignant in over 90% of cases. The role of biopsy is contentious; however, reasons to biopsy a renal mass include single functional kidney, bilateral tumours, prior to ablative therapy, chronic renal impairment and known other primary cancers (to rule out metastasis). Disadvantages of biopsy include complications of bleeding, infection, theoretical seeding and that occasionally, it may be difficult to differentiate certain benign and malignant tumours (e.g. oncocytoma from chromophobe RCC).

Renal cancer types

Clear cell renal cell carcinoma (ccRCC) is the most common type of RC. It is characterized by abundant clear cytoplasm due to the abundance of glycogen, on microscopy. The other RCCs include papillary RCC, with type 1 boasting a more favourable prognosis than type 2. Chromophobe RCC has the most favourable prognosis, due to its relative slow growth. Other types of renal cortical tumours include renal medullary carcinoma, carcinoma of the collecting duct (Bellini), acquired cystic disease associated RCC, angiomyolipoma (AML) and oncocytoma amongst others. A WHO/ISUP grade will be assigned based on the degree of nuclear atypia. This replaces the previous Fuhrmann grading system. TNM stage, tumour grade and RCC subtype provide important prognostic information.

Treatment of RCC

There are various approaches to managing RCC. The choice depends on patient factors such as age, comorbidities and renal function. Tumour factors also direct treatment, including size and location of tumour, as well as stage and grade of disease.

Surveillance

Small renal masses (SRMs) are tumours less than 4 cm in diameter. Some of these are benign and even if malignant, they generally pose a low annual metastatic potential of 3% or less. They tend to grow at roughly 3 mm a year. As such, older comorbid patients can often be safely monitored without the need for intervention.

Surgical treatment

For many years radical nephrectomy (RN) has remained the surgical operation of choice for the treatment of renal masses.

Figure 3 CT image of right renal tumour with caval thrombus.

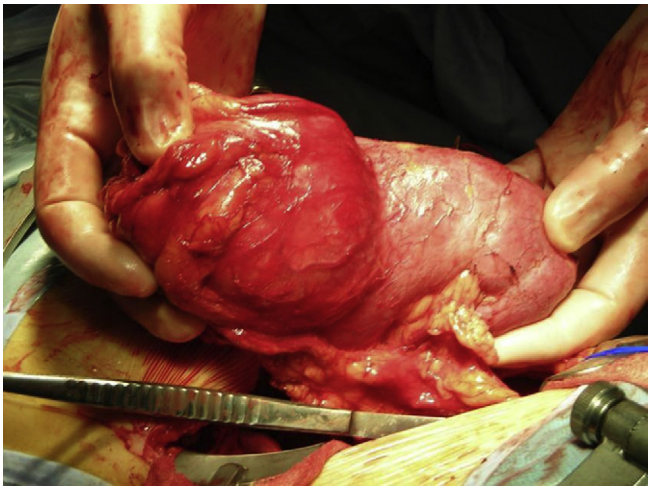


Figure 4 A large renal tumour arising from the upper pole of the left kidney.

Renal cancer staging system (American Joint Committee on Cancer)

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumour >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumour >7 cm in greatest dimension, limited to the kidney
T2a	Tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumour >10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumour grossly extends into the vena cava below the diaphragm
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1

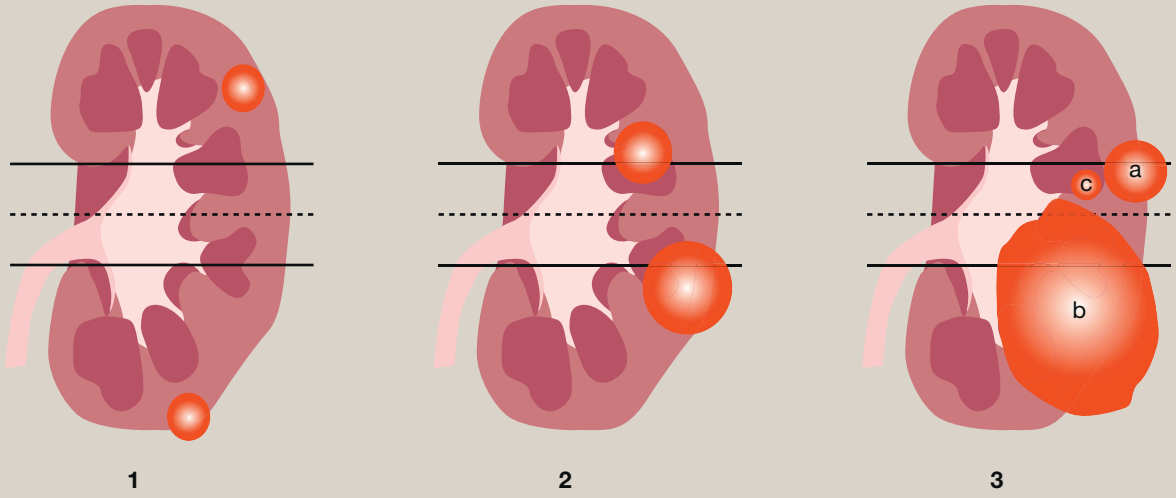
However, its negative impact on renal function and chronic kidney disease[5] has encouraged the concept of nephron sparing treatment. Nephron-sparing surgery (NSS) currently remains the standard of treatment where possible. The underlying principle is that preservation of nephrons is beneficial and that this should be attained with equivalent oncological cure rates compared with radical nephrectomy (RN). For stage T1 disease (tumours up to 7 cm, confined to the kidney), it appears that partial nephrectomy (PN) may yield equivalent oncological outcomes to RN.[6,7] It is not only size that determines suitability for PN; The PADUA and RENAL scores (Figure 5) incorporate other anatomical factors (e.g. proximity to hilum, involvement of collecting system/renal sinuses, exo/endophytic nature and position) which can be used to delineate surgical and medical perioperative risk. Increasingly, more complex tumours are being managed with PN, with acceptable complication rates.[8]

NSS options include open (Figure 6), laparoscopic and increasingly robotic-assisted partial nephrectomy. It appears that there is an overall reduction in impairment of renal function compared with RN.[9] Whether this translates to improved cancer specific and overall survival improvements is still contentious. In patients with pre-existing renal dysfunction, PN infers a survival benefit.[10] Disadvantages include an increased risk of bleeding (3% vs 1%), urine leak and the potential of a positive surgical margin. Clamping of the renal artery is general required with excision of the tumour, followed by renorraphy. A warm ischaemia time of 30 minutes or less is acceptable. Otherwise, cooling the kidney in ice slush may allow for longer cool-ischaemia times often required for more complex cases.[11] It is unclear whether agents such as mannitol, used intraoperatively, minimize impairment of renal function. The main predictor of post PN renal function seems to be preoperative function, quality and quantity of renal tissue preserved, as well as both type and duration of ischaemia.[12] The benefits of minimally invasive surgery are clearly established. These aside, oncological outcomes seem similar between robotic/laparoscopic and open procedures.[13]

Radical nephrectomy (R) (Figure 7) is an option for certain complex T1 tumours (insufficient remaining parenchyma after

RENAL Nephrometry score

	1pt	2pts	3pts
(R)adius (maximal diameter in cm)	≤4	>4 but <7	≥7
(E)xophytic/endophytic properties	≥50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* *Suffix 'h' asisigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)



From Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location, and depth. J Urol 2009; 182:844e853 (with kind permission).

Figure 5

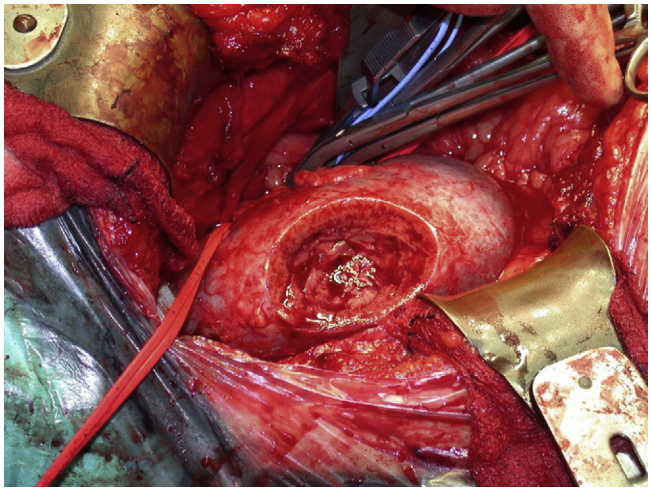


Figure 6 Open partial nephrectomy.

Figure 7 Radical nephrectomy specimen, with caval tumour thrombus.

PN, renal vein thrombosis, unfavourable position) as well as the standard treatment for the remainder of higher grade masses. It can be performed open, purely laparoscopic or robotically assisted. RN involves excision of the kidney including Gerota's fascia, and may include excision of the ipsilateral adrenal gland and regional lymph nodes. However, lymphadenectomy and its extent, remains debatable. RCC can, in locally advanced cases, spread via tumour thrombus into the lumen and wall of the vena cava. Such cases infer a significantly worse prognosis, but cure is still possible.

Tumour ablation

For patients with smaller tumours, who are not fit or suitable for PN, yet warrant treatment, ablative techniques such as cryotherapy and radiofrequency ablation (RFA) are options. Although less invasive, areas of concern remain a higher local recurrence rate compared with PN and the difficulty of radiological follow-up. Definitive studies are lacking in relation to morbidity and long term oncological outcomes.

Metastatic disease

Unfortunately metastatic disease on the whole is fairly resistive to chemotherapeutic agents. Immunotherapies such as interferon-alpha and interleukin-2 were utilized previously, but were poorly tolerated. Targeted agents, in particular tyrosine kinase inhibitors (TKIs), form the current basis of non-surgical management for favourable risk clear cell RCC. Immune checkpoint blockade is now recommended for patients with intermediate or poor risk disease and for those patients who have failed targeted therapy[14]

Cytoreductive nephrectomy had previously demonstrated an improved long-term survival when used together with immunotherapy (interferon-α). A recent study has demonstrated no survival advantage for patients with intermediate or poor risk disease when compared to TKI therapy alone.[15] However, a benefit is demonstrated in appropriately selected patients with good risk disease or where complete metastasectomy can also be performed. Bone and brain disease are exclusions, and seem to be better palliated with radiotherapy. Both radiotherapy and radiological embolization can be utilized as palliative measures.

Summary

RCC remains a common cancer within the UK – its incidence is increasing due to widespread radiological investigation. Its presentation is predominantly asymptomatic and incidental. Depending on patient and tumour factors, surveillance, partial, or radical nephrectomy form the mainstay of treatment, while tumour ablation can be utilized for particular subgroups. Targeted therapy, cytoreductive nephrectomy with or without metastasectomy, can be used for metastatic disease. ◆

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