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Maintain a high index of suspicion for kidney cancer

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Abstract

Kidney cancer accounts for 4% of total malignancies in men and 3% in women. More than 80% of kidney cancers are renal cell carcinomas (RCC). Early stage and localised disease is potentially curable in around 90% of patients. However, metastatic disease has historically been associated with poor prognosis; 10% survival at five years post diagnosis. More than 50% of RCC cases are detected incidentally on imaging, often at a late stage. Patients may present with mass-related localised symptoms, constitutional symptoms and symptoms of metastatic disease. There is a male predominance for RCC in a ratio of 3:2. Incidence increases with advancing age with more than 50% of cases diagnosed in people aged over 70. Risk factors include smoking, obesity and hypertension. Patients with acquired cystic kidney disease, those with end-stage renal disease, patients receiving haemodialysis or who have had a renal transplant are all at an increased risk of RCC. Ultrasound is the optimal initial investigation to screen individuals with suspected RCC. NICE recommends that patients aged 45 and over with isolated haematuria, in the absence (or following treatment) of a urinary tract infection, are referred for investigation of a potential renal malignancy.

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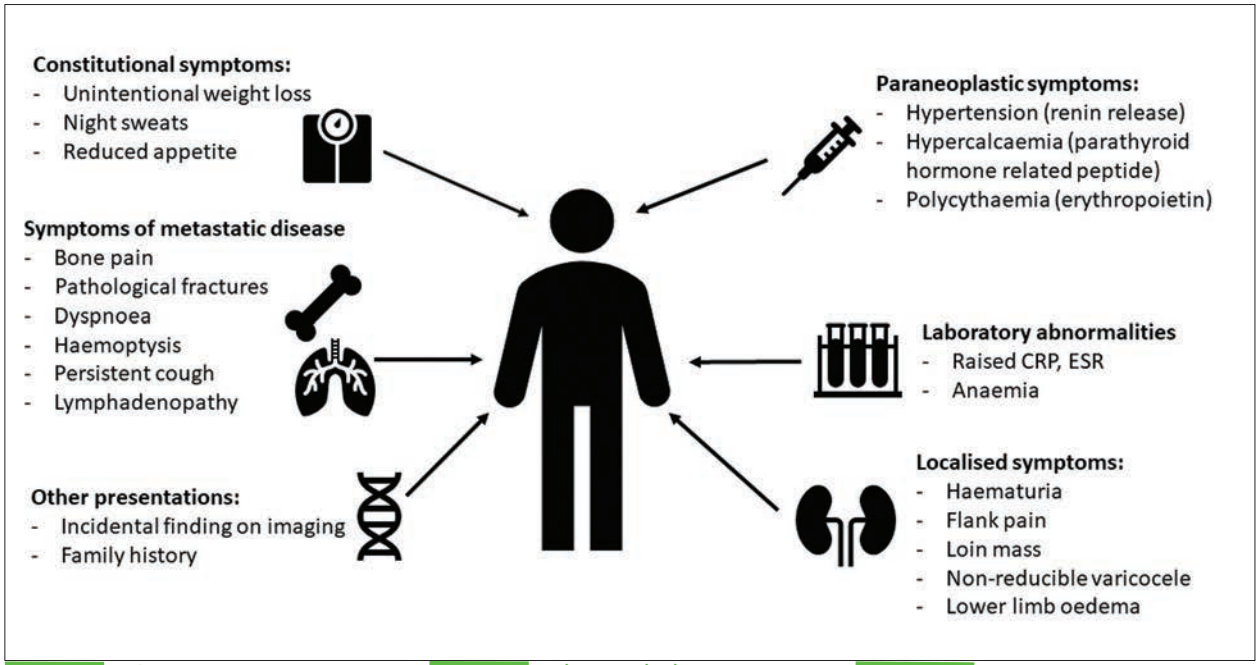

BOX 1
Summary of the clinical presentations of kidney cancer

How do patients present in primary care?

KIDNEY CANCER ACCOUNTS FOR 4% OF TOTAL MALIGNANCIES IN MEN AND 3% IN WOMEN.[1]

In the UK, cases have been predicted to rise by 26% by 2035 to 32 cases per 100,000 people in part due to an ageing population.[2] However, there is evidence worldwide that the incidence of kidney cancer is plateauing.[3]

The term kidney cancer refers to a large array of both parenchymal and urothelial malignancies. More than 80% of kidney cancers are renal cell carcinomas (RCC) of which clear cell (ccRCC) (illustrated in figures 1 and 2, p22) is the predominant subtype, accounting for around 75% of RCC cases.[4] Hence, RCC will be the focus of this article.

Early stage and localised disease is potentially curable in around 90% of patients, while metastatic disease has historically been associated with poor prognosis; 10% survival at five years post diagnosis.[1] Case mortality for RCC has stabilised, despite the increasing incidence, through earlier detection with more sensitive imaging and novel therapeutic options for those with advanced disease.[5]

However, the often vague and variable symptoms of RCC still make an earlier clinical diagnosis challenging.

How should patients be investigated?

CLINICAL PRESENTATION

More than 50% of RCC cases are detected incidentally on imaging (often at a late stage), reflecting the occult nature of the disease.[6] Patients may present with mass-related localised symptoms, constitutional symptoms, symptoms of metastatic disease and/or abnormal laboratory investigation results as summarised in box 1, above.

Local tumour invasion of the renal vein can present with a non-reducing varicocele.[7] In severe cases the tumour can extend into the inferior vena cava causing bilateral lower limb oedema.[8]

Up to 30% of patients with symptomatic RCC have features related to a paraneoplastic syndrome.[6] These are caused by secretion of tumour-derived hormones e.g. erythropoietin in polycythaemia, parathyroid hormone-related peptide in hypercalcaemia or renin in hypertension.[6]

Abnormal laboratory investigation findings can include anaemia, raised CRP or elevated ESR in the absence of infection.

Up to 30% of patients will present with metastatic disease and corresponding symptoms such as swelling due to lymphadenopathy, bone pain caused by bone metastases and respiratory symptoms (dyspnoea, haemoptysis) due to lung metastases.[6]

What are the treatment options?

RISK FACTORS

There is a male predominance for RCC in a ratio of 3:2 and the incidence increases with advancing age with more than 50% of cases diagnosed in people over 70 years old.[1]

There are well known risk factors associated with increased incidence of RCC such as cigarette smoking, obesity and hypertension.

Evidence is emerging for some aetiological factors having protective effects, such as higher caffeine intake, moderate alcohol consumption and »

increased intake of cruciferous vegetables all associated with lower RCC incidence.[3,9]

A history of chronic kidney disease is associated with an increased risk of RCC and in the presence of symptoms should raise clinical suspicion of a tumour. Patients with acquired cystic kidney disease, those with end-stage renal disease, patients receiving haemodialysis or who have had a renal transplant are all at increased risk of RCC.[3,10] Inherited autosomal dominant polycystic kidney disease does not appear to have an association with RCC.

RCC is not a cancer that is typically linked with occupational exposure to chemicals and should not be confused with the increased risk of urological cancers, such as transitional cell carcinoma, with exposure to aniline dyes used in textile, rubber and plastic industries.[11]

However, exposure to trichloroethylene (a chemical used as a metal degreaser in the automobile industry) has been shown to predispose individuals to RCC.[12]

Approximately 2-3% of all RCCs are hereditary and several autosomal dominant syndromes have been described.[11] Von Hippel-Lindau disease is the most common and is associated with retinal, central nervous system and renal tumours. Patients with tuberous sclerosis, which presents with developmental delay, epilepsy and hamartomas in the central nervous system, skin and kidneys are at increased risk of RCC.

Familial ccRCC is another autosomal dominant condition that should be suspected if two or more family members present at a young age (under 50) with bilateral RCC.[13,14] Patients with a family history of RCC, those presenting at a young age, patients presenting with bilateral RCC or in association with syndromic features should be referred for genetic testing.[6]

INVESTIGATION

Ultrasound remains the optimal initial investigation to screen individuals with suspected RCC. An urgent ultrasound of kidneys and urinary bladder should be requested.

Other investigations including full blood picture (anaemia/polycythaemia), electrolyte profile (baseline renal function), bone profile (hypercalcaemia) and CRP/ESR are all useful.

Urinalysis combined with a urinary albumin: creatinine ratio (ACR) can be helpful to investigate and differentiate different causes of haematuria. Haematuria in association with nitrites and/or leucocytosis could represent a simple urinary tract infection (UTI) while haematuria associated with significant proteinuria (ACR >70 mg/mmol) is more likely to represent an intrinsic renal disease. Isolated haematuria without proteinuria or evidence of infection should raise suspicion of a renal or urological structural disease or malignancy.

The NICE guideline *NG12. Suspected cancer: recognition and referral* recommends that patients aged 45 and over with isolated haematuria, in the absence (or following treatment) of a UTI, are referred for investigation of a potential renal malignancy, see table 1, p23.[15] (Visible haematuria should raise suspicion of urological malignancy such as bladder or prostate cancer.) Clinicians should also be aware of the updated recommendations regarding referral for suspected bladder cancer, see table 1, p23.

In secondary care, after ultrasound examination of renal tracts further imaging such as CT or MRI will be requested. This provides additional information regarding tumour extension, anatomy of the contralateral kidney and potential metastatic spread contributing to staging. If appropriate, pathological specimens will be obtained in order to get a tissue diagnosis as the RCC subtypes can have varying treatment options and prognoses.

FIGURE 1
Renal cell carcinoma. A large renal tumour has replaced the lower half of the kidney. The upper half has normal anatomy. The kidney is surrounded by visceral fat

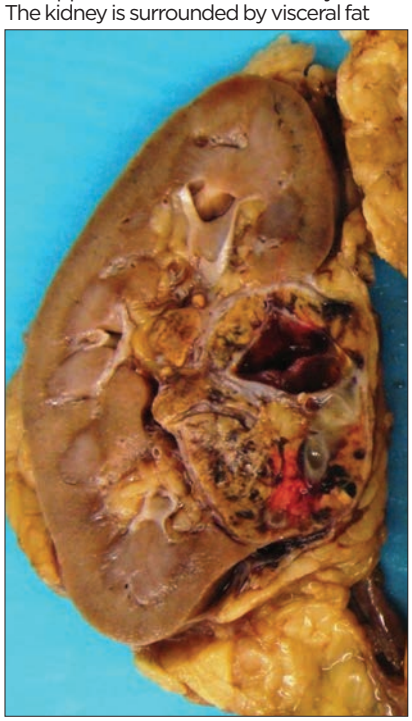

FIGURE 2
Histological specimen demonstrating clear cell renal cell carcinoma

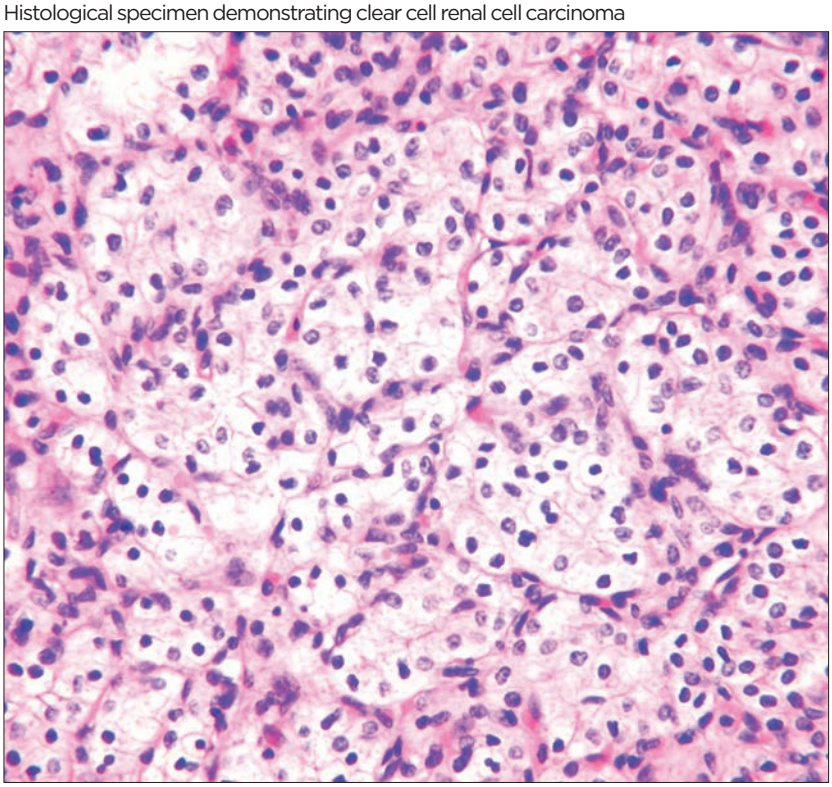

Table 1

Summary of NICE recommendations for referral for suspected renal or bladder cancer (adapted from NICE NG12)[15]

Renal cancer

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for renal cancer if they are aged 45 and over and have:

- Unexplained visible haematuria without urinary tract infection or
- Visible haematuria that persists or recurs after successful treatment of urinary tract infection

Bladder cancer

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are:

- aged 45 and over and have:
  - o unexplained visible haematuria without urinary tract infection or
  - o visible haematuria that persists or recurs after successful treatment of urinary tract infection, or
- aged 60 and over and have unexplained non visible haematuria and either dysuria or a raised white cell count on a blood test

Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained urinary tract infection

TREATMENT

Treatment will be guided by disease stage, tumour size, pathological subtype, patient performance status and comorbidities.[5,6] Patients should be actively involved in treatment decisions and overall goals of management.

Localised disease

For patients with disease limited to the kidney there are a range of options. In older patients, or patients with significant comorbidities who have an incidentally detected small RCC, a surveillance approach may be adopted.[5] In these patients RCC-specific mortality is usually low and risk of progression to metastatic disease is less than 2%.[16] Patients can have surveillance via ultrasound, CT or MRI imaging and only in evidence of progressive disease will intervention be considered.

Radiofrequency ablation therapy may be offered in elderly, comorbid patients considered unfit for surgery who have smaller tumours < 3 cm.[5] This may also be offered to patients with multiple tumours, chronic kidney disease or patients with a single kidney.

For patients on a palliative management plan, symptoms such as haematuria or loin pain are occasionally treated with embolisation therapy.[5]

For the majority of patients with RCC limited to the kidney the ultimate goal is surgical intervention to achieve cure. Partial nephrectomy is usually offered as first line in T1 (tumours limited to the kidney < 7 cm) and T2 (tumours limited to the kidney > 7 cm) lesions where a patient has a single kidney or chronic kidney disease.[17] This strategy is 'nephron sparing', limits the reduction in overall renal function, and is now the favoured approach. It is particularly useful in cases of hereditary RCC where multiple tumours are likely to occur over a patient's lifetime.[5,6]

In other patients with tumours > 7 cm or those that extend into local structures (adrenal tissue, inferior vena cava below the diaphragm but not beyond Gerota's fascia) attempt at curative therapy is by radical nephrectomy.[5]

There is no evidence of a difference in survival outcomes between open and laparoscopic nephrectomy in patients with RCC and hence guidelines recommend a laparoscopic technique as it is associated with reduced morbidity and shorter hospital stay.[5,18]

Interval radiological surveillance is required post-surgical resection of RCC as 20-30% will experience a relapse (often in the form of pulmonary metastases).[19] Frequency of surveillance is often based on pathological subtype and whether surgical margins are disease free.[6] Despite these high rates of relapse there are currently limited therapeutic options for adjuvant chemotherapy or immunotherapy.

Only one immune checkpoint inhibitor, pembrolizumab, has a guideline recommendation for adjuvant use in aggressive ccRCC.[5,20] Results of further studies of checkpoint inhibitor use in adjuvant therapy are awaited.

Metastatic disease

Since the introduction of the first targeted systemic therapy for metastatic RCC in 2006, therapeutic options have rapidly increased with notable improvements in outcomes for patients.[1]

Targeted systemic therapies are designed to act on aberrant molecular pathways which promote tumour growth. Some malignancies such as RCC develop mechanisms to dampen or avoid the native immune response to a tumour by acting on immune checkpoints. Immunotherapy, with immune checkpoint inhibitors, blocks the evasive behaviour of the tumour cells and hence allows upregulation of immune-mediated action against the tumour.

For naïve metastatic RCC, immune checkpoint inhibitors that target PD-1, such as nivolumab, are the backbone of treatment. These immune checkpoint inhibitors are often paired with either a tyrosine kinase inhibitor such as axitinib, which acts on vascular endothelial growth factor to reduce angiogenesis, or a second immune checkpoint inhibitor which targets CTLA-4 such as ipilimumab.[5,21]

There is growing evidence that combined immune checkpoint inhibitor regimens may result in a higher proportion of patients achieving durable remissions.[21]

Systemic targeted therapies that were previously the mainstay of treatment of metastatic RCC such as sutinib (a tyrosine kinase inhibitor), everolimus (an mTOR mammalian target of rapamycin inhibitors which prevent tumour cell division and angiogenesis) and bevacizumab (a monoclonal antibody to vascular endothelial growth factor) are now more likely to be used in advanced disease where other treatment options have failed or are not tolerated.[5,6,21]

FUTURE CONSIDERATIONS: IMPROVING OUTCOMES

Technological advances are rapidly increasing the range of treatment options available to patients with RCC. Robotic surgical techniques hold the promise of more refined operative options for patients with larger or anatomically complex tumours.[22]

Results of multiple phase III trials are awaited that will help inform optimal systemic therapy and immunotherapy regimens for patients with metastatic disease and the use of systemic therapies for adjuvant treatment.[23] Furthermore, there are promising novel »

key points

SELECTED BY

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Kidney cancer accounts for 4% of total malignancies in men and 3% in women. More than 80% of kidney cancers are renal cell carcinomas (RCC). Early stage and localised disease is potentially curable in around 90% of patients. However, metastatic disease has historically been associated with poor prognosis; 10% survival at five years post diagnosis. More than 50% of RCC cases are detected incidentally on imaging, often at a late stage. Patients may present with mass-related localised symptoms, constitutional symptoms and symptoms of metastatic disease. Abnormal laboratory investigation results can include anaemia, raised CRP or elevated ESR in the absence of infection.

There is a male predominance for RCC in a ratio of 3:2. Incidence increases with advancing age with more than 50% of cases diagnosed in people aged over 70. Risk factors include smoking, obesity and hypertension. High caffeine intake, moderate alcohol consumption and increased cruciferous vegetable intake may be protective. Patients with acquired cystic kidney disease, those with end-stage renal disease, patients receiving haemodialysis or who have had a renal transplant are all at an increased risk of RCC.

Ultrasound is the optimal initial investigation to screen individuals with suspected RCC. Other investigations including full blood count, electrolyte profile, bone profile and CRP/ESR are all useful. Urinalysis combined with a urinary albumin: creatinine ratio can be helpful in investigating and differentiating different causes of haematuria. NICE recommends that patients aged 45 and over with isolated haematuria, in the absence (or following treatment) of a urinary tract infection, are referred for investigation of a potential renal malignancy.

Treatment is guided by disease stage, tumour size, pathological subtype, patient performance status and comorbidities. In older patients, or patients with significant comorbidities who have an incidentally detected small RCC, a surveillance approach may be adopted.

For most patients with RCC limited to the kidney the ultimate goal is surgical intervention to achieve cure. Partial nephrectomy is usually offered as first line in T1 (tumours limited to the kidney < 7 cm) and T2 (tumours limited to the kidney > 7 cm) lesions where a patient has a single kidney or chronic kidney disease. In other patients with tumours > 7 cm or those that extend into local structures attempt at curative therapy is with radical nephrectomy. For metastatic disease targeted systemic therapies designed to act on aberrant molecular pathways which promote tumour growth are used. Robotic surgical techniques hold the promise of more refined operative options for patients with larger or anatomically complex tumours.

therapeutic agents and targets being developed such as LAG-3 immune checkpoint inhibitors which may assist in improving outcomes.[23,24]

However, the main challenge to improving outcomes in RCC remains detection of early disease. With few promising potential biomarkers available for RCC,[25] awareness and appropriate timely investigation by clinicians remains the best strategy at present.

CONCLUSIONS

GPs are likely to encounter a significant number of patients with kidney cancer during their career. Maintaining a high index of clinical suspicion and arranging appropriate early investigations offers patients the best chance of diagnosis at an early stage of the disease.

Unexplained visible haematuria in people aged 45 and over should trigger referral for suspected renal cancer.

For subtler presentations of RCC, basic blood and urine testing, in conjunction with ultrasound, can provide the necessary information to guide secondary care referral.

The treatment options available are expanding rapidly. Therefore, knowledge of the treatment options and potential side effects can help both primary and secondary care work together to support patients with RCC.

Competing interests: None

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Useful information

Cancer Research UK
Patient information and links to clinical trials in kidney cancer
www.cancerresearchuk.org/about-cancer/kidney-cancer

NHS Choices
Basic overview of kidney cancer and links to patient support
www.nhs.uk/conditions/kidney-cancer/

Macmillan Cancer Support
Kidney cancer information and support
www.macmillan.org.uk/cancer-information-and-support/kidney-cancer

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