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Prompt investigation improves outcomes for kidney cancer

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Dr Éadaoin Hannon
MBChB MRCP
Specialist Registrar in Nephrology

Professor Alexander P. Maxwell
Consultant Nephrologist
Regional Nephrology Unit, Belfast City Hospital, Belfast, UK

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AUTHORS
Dr Éadaoin Hannon
MBChB MRCP
Specialist Registrar in Nephrology

Professor Alexander P. Maxwell
Consultant Nephrologist

Regional Nephrology Unit, Belfast City Hospital, Belfast, UK

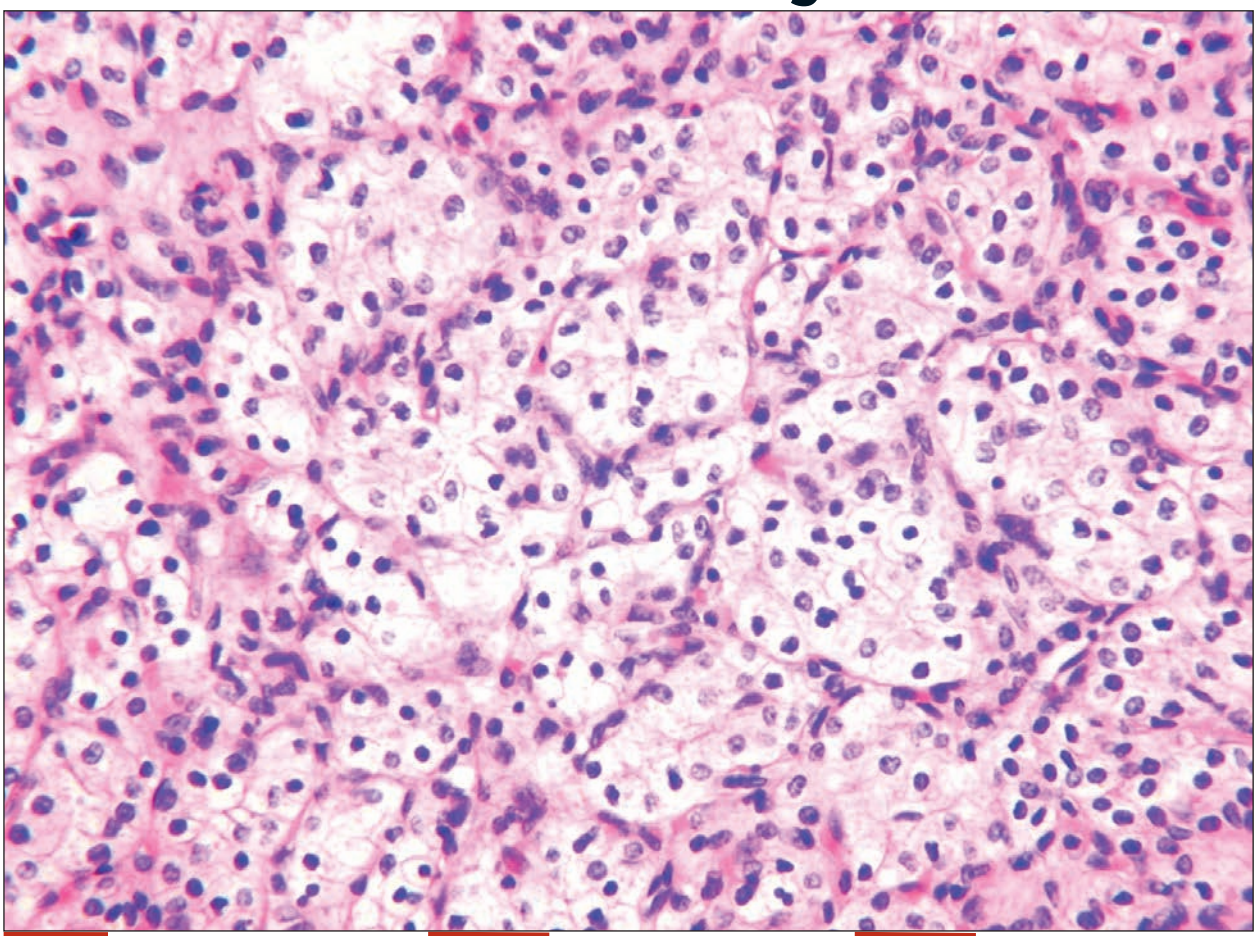

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FIGURE 1 Histological specimen demonstrating clear cell renal cell carcinoma

How do patients present in primary care?

KIDNEY CANCER IS THE SEVENTH MOST COMMON CANCER IN THE UK, ACCOUNTING FOR 3% OF all new cases in 2015.[1]

Incidence rates for kidney cancer are projected to rise by 26% between 2014 and 2035, to 32 cases per 100,000 people per annum.[2] This prediction reflects both an ageing population, 50% of new kidney cancer cases in the UK are diagnosed in people aged 70 and over,[1] and the rising prevalence of obesity, a recognised risk factor for cancer.

Renal cell carcinoma (RCC) is the focus of this article and accounts for 80% of kidney cancers, of which clear cell (ccRCC), see figure 1 above, is the main subtype (around 75%).[1,3] There is a male preponderance in a ratio of 3:2.[4]

What investigations should be carried out?

The diagnosis of kidney cancer can be challenging because of its varied and non-specific symptoms and limited early warning signs. More than half of RCCs are detected incidentally[3,4] on radiological imaging reflecting its often occult presentation.

'More than 8 in 10 patients with an early stage diagnosis will survive their disease for at least five years'

Nevertheless, it is recognised that a GP referral is the most common route to diagnosing kidney cancer.[1] With a high level of clinical suspicion and prompt investigation, kidney cancer can be diagnosed at an early stage and this is associated with improved survival. More than 8 in 10 patients with an early stage diagnosis will survive their disease for at least five years but this falls to 1 in 10 for patients with late stage kidney cancer at diagnosis.[1] »

What are the treatment options available?

Table 1

Presentations of kidney cancer

Local	Constitutional	Biochemical	Incidental
Haematuria	Weight loss	Anaemia	Mass on USS/CT
Flank pain	Pyrexia and/or night sweats	Raised ESR or CRP	Family history
Loin mass		Polycythaemia	Hypertension
		Hypercalcaemia	Right-sided varicocoele

CLINICAL FEATURES

Primary care consultation may be triggered by one of the varied presentations outlined in table 1, above.

RCC should be suspected in the presence of:

- Localising symptoms such as flank pain, a loin mass or haematuria
- Constitutional upset including weight loss, pyrexia and/or night sweats
- Unexplained laboratory test results

Abnormal test results in a symptomatic patient may include anaemia and a raised ESR or C-reactive protein in the absence of infection. Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCC[4] and are caused by secretion of tumour-derived hormones. These syndromes can be associated with polycythaemia (erythropoietin), hypercalcaemia (parathyroid hormone related peptide) or hypertension (renin).

'Between 25 and 31% of individuals with kidney cancer will have metastatic disease at diagnosis'

Between 25 and 31% of individuals with kidney cancer will have metastatic disease at diagnosis[1] and may present with dyspnoea, persistent cough, haemoptysis, bone pain, pathological fracture or lymphadenopathy. Local tumour spread into the left renal vein may result in a non-reducing varicocoele and extensive tumour involvement within the inferior vena cava may cause bilateral leg oedema.[5,6]

RISK FACTORS

Lifestyle

Recognised risk factors exist for RCC, see table 2, above right. Smoking, obesity and hypertension are common risk factors and all three demonstrate a dose-response relationship with the relative risk of RCC.[7,8,9] These risk factors are potentially modifiable and can be targeted in primary care and through public health promotion. Protective lifestyle factors include physical activity, moderate alcohol intake and consumption of cruciferous (cabbage-like) vegetables.[4]

Environmental

RCC is not a typical occupational disease[10] however exposure to trichloroethylene (metal degreaser) has been implicated. Aniline dyes, used in textile, rubber and plastic industries predispose to renal pelvis transitional cell carcinomas rather than RCCs.

Acquired cystic kidney disease (ACKD) occurs in chronic renal failure from any aetiology. Malignant cyst transformation is a recognised complication of ACKD with a 40-fold increased risk compared with the general population.[11] Thus there should be a higher index of suspicion for RCC in chronic dialysis and renal transplant recipients who are at increased risk of RCC in their native kidneys. Inherited autosomal dominant polycystic kidney disease does not appear to be a risk factor for RCC.

Genetic

Around 2-3% of all RCC are due to a recognised hereditary syndrome. There is a two-fold increase in risk of RCC in those with an affected first-degree relative.[10] Several hereditary renal cancer syndromes exist[12] and those specific to ccRCC include: von Hippel-Lindau syndrome type 1/type 2B (retinal, central nervous system and renal tumours); tuberous sclerosis complex (developmental delay, epilepsy with central nervous system, skin and renal hamartomas); and familial ccRCC for which the genetic mutation is unknown.[6]

These syndromes have an autosomal dominant inheritance pattern and family members at risk should be counselled to consider relevant clinical and genetic testing.[10,12]

Table 2

Risk factors for renal cell carcinoma

- Smoking
- Obesity
- Hypertension
- End-stage renal disease (acquired kidney cyst disease)
- First-degree relative affected
- Genetic cancer syndrome
- Exposure to trichloroethylene, cadmium

INVESTIGATIONS

Ultrasound is a useful initial screening tool when clinical suspicion of RCC is high (e.g. loin pain, flank mass, haematuria or constitutional symptoms). This should be arranged as a red flag investigation. During a consultation other useful simple tests include a urinalysis, full blood picture, ESR, bone profile, liver function tests and an electrolyte profile.

As a test, urinalysis can be of value in unravelling the possible aetiology of visible and non-visible haematuria. Urinary tract infection (UTI) is suggested by the coexistence of leukocytes ± nitrites on dipstick testing. The presence of coexisting proteinuria may suggest an intrinsic renal glomerular pathology. A spot albumin: creatinine ratio will quantify any proteinuria in this setting. However, importantly, haematuria in the absence of co-existing proteinuria suggests a possible underlying structural abnormality in the kidneys, ureters or bladder that may need further evaluation through ultrasound and cystoscopy.

Visible haematuria should trigger suspicion for urological malignancy. Prostate and bladder malignancy are outside the scope of this article. NICE has updated guidance on referral to secondary care for suspected renal and bladder cancers, summarised in table 3, opposite. It is recommended that patients aged 45 years and over with visible haematuria that is unexplained, present in the absence of UTI or persists/recurs after treatment of UTI should be referred urgently for an appointment within two weeks.[13] However, younger patients can have earlier onset of disease. Clinicians should always exercise their own clinical judgement when deciding which patients to refer.

key points

SELECTED BY

Dr Phillip Bland
Former GP, Dalton-in-Furness, UK

Kidney cancer is the seventh most common cancer in the UK, accounting for 3% of all new cases in 2015. Incidence rates for kidney cancer are projected to rise by 26% between 2014 and 2035, to 32 cases per 100,000 people per annum. Renal cell carcinoma (RCC) accounts for 80% of kidney cancers, of which clear cell (ccRCC) is the main subtype. There is a male preponderance in a ratio of 3:2.

Smoking, obesity and hypertension are common risk factors and all three demonstrate a dose-response relationship with the relative risk of RCC. Although RCC is not a typical occupational disease, exposure to trichloroethylene (metal degreaser) has been implicated. Malignant cyst formation may occur in chronic renal failure patients with acquired kidney cyst disease. There is a two-fold increase in risk of RCC in those with an affected first-degree relative, and 2-3% of RCC cases are due to a recognised hereditary syndrome.

More than half of RCCs are detected incidentally on radiological imaging reflecting its often occult presentation. Nevertheless, it is recognised that a GP referral is the most common route to diagnosing kidney cancer. RCC should be suspected in the presence of: localising symptoms such as flank pain, a loin mass or haematuria; constitutional upset including weight loss, pyrexia and/or night sweats; or unexplained test results.

Paraneoplastic syndromes are found in around 30% of patients with symptomatic RCC and are caused by secretion of tumour-derived hormones. These syndromes can be associated with polycythaemia (erythropoietin), hypercalcaemia (parathyroid hormone related peptide) or hypertension (renin). Between 25 and 31% of individuals with kidney cancer will have metastatic disease at diagnosis and may present with dyspnoea, persistent cough, haemoptysis, bone pain, pathological fracture or lymphadenopathy.

NICE recommends that patients aged ≥ 45 years with unexplained visible haematuria in the absence of UTI, or visible haematuria which persists or recurs after successful treatment of UTI should be referred urgently for an appointment within two weeks. For the subtler presentations of RCC, basic blood and urine testing, in conjunction with ultrasound, can guide secondary care referral. The range of treatments, both surgical and systemic, is expanding and requires a coordinated approach between primary and secondary care.
For localised disease, particularly when tumour size is < 7 cm, there has been a move towards nephron sparing surgery in the form of partial nephrectomy. However, radical nephrectomy for more advanced RCC as an attempt at curative therapy remains the best option. Patients with advanced or metastatic RCC may be treated with targeted systemic therapy which modulates molecular pathways that typically promote tumour growth, or immunotherapy which triggers an immune response that destroys cancer cells.

CT or MR imaging will be undertaken in secondary care following an initial abnormal ultrasound. This gives useful information on tumour extension locally, the appearance of the contralateral kidney and aids staging through identification of metastases.[4]

TREATMENT

Surgery

For localised (kidney-limited) disease, particularly when tumour size is < 7 cm, there has been a move toward nephron sparing surgery in the form of partial nephrectomy, however, tumour position in the kidney along with patient choice and consideration of comorbidity will dictate the suitability of such a procedure.[4,6,14]

If feasible, nephron sparing surgery is also preferred for management of hereditary RCC due to increased risk of future tumours. For more advanced RCC staging with localised invasion of adjacent structure (adrenal tissue, vena cava below diaphragm and not beyond Gerota's fascia) radical nephrectomy remains the best option for an attempt at curative therapy. Following surgical resection, 20-30% will experience a relapse often in the form of pulmonary metastases[14] and therefore active interval radiological surveillance is required.

Other options include radiofrequency ablation and cryoablation which may be preferable for renal cortical tumours < 3-5 cm; where there is a solitary kidney or chronic kidney disease; known hereditary/bilateral RCC; or in frail patients unfit for surgery.[3,6]

Sometimes interval surveillance (watchful waiting) may be deemed appropriate if the tumour is small and growing slowly. Embolisation for symptom control (haematuria and/or pain) can be undertaken in those unfit for surgery or with non-resectable cancer.[4]

Targeted systemic therapy and immunotherapy

Targeted systemic therapy modulates molecular pathways that typically promote tumour growth. In ccRCC it is recognised that a mutation results in the production of cytokines stimulating angiogenesis. Tyrosine kinase inhibitors (TKIs) inhibit vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) which in turn prevents tumour cell proliferation and development of tumour blood vessels. The TKIs sunitinib, pazopanib, and sorafenib are currently approved by NICE for treatment of advanced and metastatic RCC.[16,17] In 2015, NICE recommended a multitargeted TKI inhibitor, axitinib, for treatment in advanced RCC after failure of prior systemic treatment.[18] Temsirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors that can be used in the management of advanced RCC. mTOR inhibitors prevent tumour cell division and blood vessel growth in tumours.

Immunotherapy triggers an immune response that destroys the cancer cells. Monoclonal antibodies directed at VEGF are used in the treatment of »

Table 3

Summary of NICE recommendations for referral for suspected renal or bladder cancer (adapted from NG12)[13]

Renal cancer

Refer patients 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 (UTI) or
- Visible haematuria that persists or recurs after successful treatment of UTI

Bladder cancer

Refer patients using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are:
- Aged 45 and over and have:
  - unexplained visible haematuria without UTI or
  - visible haematuria that persists or recurs after successful treatment of UTI 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 UTI

advanced/metastatic RCC. Bevacizumab received NICE approval in 2009[16] but is no longer recommended as a first-line treatment. Nivolumab, a fully human antibody that blocks ligand activation of the programmed death receptor 1 (PD-1) restores cellular immunity and is the only treatment that has shown overall survival benefit in patients who have been previously treated for advanced RCC.[15] NICE published guidance on this therapy in 2016.[19]

Therapeutic options continue to expand and the selection of an appropriate treatment plan is often individualised to the patient taking into account comorbidity, functional status, stage and rate of tumour progression. Patients in receipt of these therapies do experience toxicity and may present to primary care. Common toxicities relating to the TKIs include rash, diarrhoea, mucositis, hand-foot syndrome, thyroid dysfunction, hypertension and left ventricular dysfunction and blood dyscrasias.

CONCLUSION

The incidence of kidney cancer is rising with a lifetime risk of 1 in 52 for men and 1 in 87 for women.[1] GPs will therefore encounter kidney cancer quite frequently and by maintaining a high index of clinical suspicion can help to ensure a prompt diagnosis is made. Improved survival is related to earlier disease recognition and less advanced staging at presentation.

Unexplained visible haematuria in patients over 45 years should trigger referral for suspected renal cancer, as per NICE guidance. For the subtler presentations of RCC, basic blood and urine testing, in conjunction with ultrasound, can provide the necessary information to guide secondary care referral.

The range of treatments, both surgical and systemic, is expanding and requires a coordinated approach between primary and secondary care. Therefore, fundamental knowledge on current treatment options, potential therapy toxicities and indeed where to source information (see Useful information box, right) is essential in supporting patients as they navigate an often uncertain journey following diagnosis.

Competing interests: None

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See also Both visible and non-visible haematuria may herald serious disease, p11.

Useful information

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

Kidney Cancer UK
Understanding kidney cancer booklet and patient helpline
www.kcuk.org.uk/kidneycancer/publications/

Kidney Research UK
Patient information about kidney cancer
www.kidneyresearchuk.org/health-information/kidney-cancer

NHS choices
Patient website
www.nhs.uk/conditions/kidney-cancer/

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