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Courtesy of Dr Declan O'Rourke, Consultant Histopathologist, Belfast City Hospital

Kidney divided and opened following nephrectomy. A large renal cell carcinoma has replaced the lower half of the kidney. The upper half has normal anatomy. The kidney is surrounded by visceral fat

How does kidney cancer present?

THE DIAGNOSIS OF KIDNEY CANCER IS OFTEN CHALLENGING BECAUSE OF ITS DIVERSE AND non-specific symptoms, limited or absent physical signs on examination and lack of any specific biomarkers. Many kidney cancers are actually discovered incidentally when abdominal imaging investigations are undertaken for unrelated symptoms or conditions.

Kidney cancers account for 2-3% of all adult malignancies in the UK. The incidence has been increasing which may reflect changing risk factors including a rise in obesity. Men are predominantly affected by renal cancer, a male:female ratio of 3:2, with an average age at diagnosis of 64 years.

What are the risk factors?

Renal (or clear) cell carcinoma (RCC) accounts for 90% of kidney cancers and will be the focus of this article.[1]

Early diagnosis improves survival with five-year survival rates for renal cancer of 70-94% for localised tumours, in the UK, but this survival rate falls to 40-70% when cancer has spread beyond the kidney. A continuing clinical challenge is to recognise the possibility of a kidney cancer so that the patient has appropriate investigations and prompt referral to a uro-oncology clinic if kidney cancer is present. »

How should diagnosis be confirmed?

Table 1

Presentations of kidney cancer

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

CLINICAL FEATURES

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 laboratory tests

Abnormal test results can include anaemia, raised ESR or other inflammatory markers in the absence of infection, or a number of paraneoplastic syndromes arising from secretion of tumour-derived hormones resulting in polycythaemia, hypercalcaemia or hypertension, see table 1, above.

One or several of these symptoms may trigger a patient's initial primary care consultation. Abnormal test results may increase the index of suspicion for underlying malignancy.

Abdominal CT or ultrasound examinations may reveal an incidental renal mass or the patient may request such tests if there is a family history or inherited predisposition to kidney cancer.[2] A new onset right-sided varicocoele has classically been considered an indication to search for an abdominal or renal mass causing venous obstruction.

RISK FACTORS

Lifestyle

Several well characterised risk factors exist for RCC, see table 2, right. Smoking, obesity and hypertension are the most important and most common risk factors. All three demonstrate a dose-response relationship in terms of relative risk of RCC.[3,4] The rising incidence of RCC in many geographical areas parallels the increasing prevalence of these three conditions in the general population, providing further justification for health promotion interventions in primary care.

'Smoking, obesity and hypertension are the most important and most common risk factors'

Environmental

Environmental exposure to asbestos, cadmium and trichloroethylene are recognised, but less common, risk factors for RCC. Aniline dyes, used in the textile, rubber and plastics industry particularly predispose to renal pelvis transitional cell carcinomas.

Patients on chronic dialysis and renal transplant recipients are at increased risk of RCC in their native kidneys. This is likely to be secondary to the acquired cystic kidney disease seen in such individuals with subsequent malignant transformation of the cysts. Interestingly, inherited polycystic kidney disease does not appear to be a demonstrable risk factor for RCC.

Genetic

An inherited susceptibility to RCC is increasingly recognised.[5] In first-degree relatives of those with RCC there is at least a twofold increased risk of RCC, underlining the fact that a family history of either kidney cancer or unusual and early cancers is relevant.

Studies of rare genetic diseases such as the von Hippel-Lindau syndrome (retinal, cerebellar, spinal and renal tumours) and tuberous sclerosis (developmental delay, epilepsy with central nervous system, skin and renal hamartomas) have helped unravel many of the underlying genetic and molecular pathways that promote the development of RCC leading

Table 2

Risk factors for renal cell carcinoma

- Smoking
- Obesity
- Hypertension
- Chronic dialysis
- First-degree relative affected
- Genetic syndrome
- Cadmium, asbestos, trichloroethylene

Table 3

Summary of NICE recommendations for referral for suspected cancer

The following patients should be referred urgently:

- Painless macroscopic haematuria at any age
- Macroscopic haematuria with UTI symptoms but UTI not confirmed
- ≥ 40 years with recurrent or persistent UTI and haematuria
- ≥ 50 years with unexplained microscopic haematuria
- Abdominal mass found clinically or radiologically and thought to arise from kidney or urinary tract

Non-urgent referral:

- < 50 years with microscopic haematuria
  - ▶ Test for proteinuria and creatinine:
    If normal, non-urgent referral to urology
    If raised, refer to renal physician

Adapted from NICE. CG27. Referral guidelines for suspected cancer. NICE. London. 2005

key points

SELECTED BY

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Kidney cancers account for 2-3% of all adult malignancies in the UK. Men are predominantly affected by renal cancer with an average age at diagnosis of 64 years. Renal (or clear) cell carcinoma (RCC) accounts for 90% of kidney cancers. Early diagnosis improves survival with five-year survival rates for renal cancer of 70-94% for localised tumours in the UK. 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 with unexplained laboratory tests.

Smoking, obesity and hypertension are the most important and most common risk factors. Environmental exposure to asbestos, cadmium and trichloroethylene are recognised, but less common, risk factors. Patients on chronic dialysis and renal transplant recipients are at increased risk of RCC in their native kidneys. Inherited polycystic kidney disease does not appear to be a demonstrable risk factor for RCC.

If kidney cancer is suspected on history, physical examination or initial screening tests then a red flag ultrasound examination of the renal tracts should be requested. Dipstick urinalysis is of great value as asymptomatic haematuria may be the only abnormal test in the presence of non-specific symptoms such as weight loss or loin pain. Visible or non-visible haematuria, in the absence of proteinuria, suggests an underlying structural abnormality is present in the kidneys, ureters or bladder.

Surgical removal of RCCs, where feasible, may result in cure in up to 40-60% of cases. Individuals too frail for major surgery may benefit from evolving surgical approaches such as thermal ablation and cryotherapy. RCCs tend to be relatively resistant to chemotherapy or radiotherapy and this limits the usefulness of such treatments. Agents that target the VEGF (vascular endothelial growth factor) and mTOR (mammalian target of rapamycin) pathways are considered first line in the treatment of metastatic RCC. Sunitinib, now recommended by NICE, is administered orally and acts by inhibiting the VEGF receptor. Common toxicities of sunitinib include fatigue, diarrhoea, nausea, altered taste sensation, mucositis, hypothyroidism and hand-foot syndrome. More serious side effects include blood dyscrasias such as anaemia and neutropaenia, and bleeding diatheses.

to more rational treatments.

Protective factors such as physical activity, a diet rich in fruit and vegetables and moderate alcohol intake have all been suggested by epidemiological studies and healthy lifestyle advice seems just as relevant for prevention of kidney cancers as for many other chronic diseases.

INVESTIGATIONS

If kidney cancer is suspected on history, physical examination or initial screening tests then a red flag ultrasound examination of the renal tracts should be requested.

Some simple tests such as urinalysis, full blood picture, ESR, urea and electrolytes, liver function tests and bone profile can be organised. Dipstick urinalysis is of great value as asymptomatic haematuria may be the only abnormal test in the presence of non-specific symptoms such as weight loss or loin pain.

‘If kidney cancer is suspected on history, physical examination or initial screening tests a red flag ultrasound … should be requested’

Persistent painless haematuria should trigger urgent referral to secondary care. A urine spot test to measure the albumin:creatinine ratio will quantify any proteinuria. Visible or non-visible haematuria, in the absence of proteinuria, suggests an underlying structural abnormality is present in the kidneys, ureters or bladder.

Ultrasound is helpful in detecting renal masses while a CT scan with contrast can help differentiate between benign and malignant kidney lesions and simultaneously stage any tumours found. Some patients will require a cystoscopy to exclude co-existing bladder pathology.

The recommendations from the 2005 NICE guidelines on referral for suspected cancer are summarised in table 3, opposite. [6]

TREATMENT

Surgery

As up to 85% of suspicious lesions on CT scanning are found to be carcinomas at nephrectomy many surgeons will proceed to excise a part of, or the entire, affected kidney without performing a preliminary biopsy. Surgical removal of RCCs, where feasible, may result in cure in up to 40-60% of cases. [7]

There is also a role for cytoreductive surgery followed by drug therapy in improving patient survival in cases where distant metastatic spread has already occurred. [8] The timing of, and decision to perform, such debulking surgery is still controversial. Individuals too frail for major surgery may benefit from evolving surgical approaches such as thermal ablation and cryotherapy, often employed in combination with active surveillance aiming to reduce interventional morbidity. An advantage is that repeat interventions can be performed but disadvantages include the inability to treat tumours larger than 3.5 cm in diameter effectively and the long-term outcomes compared with more conventional surgical treatment remain unknown.

In cases where surgical excision is not clearly curative, treatment of RCC can be challenging. [9] RCC tends to be relatively resistant to chemotherapy or radiotherapy and this limits the usefulness of such treatments. These difficulties, however, have promoted the development of both the surgical techniques discussed previously and targeted immunotherapy with agents designed to modulate the molecular pathways that promote tumour growth.

Immunotherapy

Patients for whom surgery would not be curative or who have advanced disease at presentation historically received interferon or aldesleukin immunotherapy. However, the standard care has now changed with the introduction of agents that target the VEGF (vascular endothelial growth factor) and mTOR (mammalian target of rapamycin) pathways. These drugs are considered first line in the treatment of metastatic RCC. Sunitinib, now recommended by NICE,[10] is administered orally and acts by inhibiting the VEGF receptor. There is robust trial data supporting its efficacy and it has an acceptable side effect profile. [11,12]

Other drugs such as sorafenib, bevacizumab and temsirolimus are not yet endorsed by NICE but are used in clinical practice in other countries.

Opportunities exist, however, for »

individuals to be enrolled in one of several trials evaluating these newer agents (see Useful information box, below).

PRIMARY CARE

Patients receiving chronic treatment with drugs for RCC will require ongoing monitoring and may present to GPs with troubling side effects. Common toxicities of sunitinib include fatigue, diarrhoea, nausea, altered taste sensation, mucositis, hypothyroidism and hand-foot syndrome. More serious side effects include blood dyscrasias such as anaemia and neutropaenia, and bleeding diatheses. In some cases, hypertension and left ventricular failure develop and may necessitate dose reduction or drug discontinuation. The frequency of these adverse effects and guidance in managing them has recently been comprehensively reviewed.[13]

'The repertoire of treatments is expanding with the introduction of novel targeted therapies'

CONCLUSIONS

Kidney cancer affects at least 1 in 50 adults so GPs will see patients with a new kidney cancer diagnosis quite frequently. A high index of suspicion is required when patients present with non-specific symptoms and signs which may indicate a renal tract malignancy. The clinical features may be quite subtle until advanced stage malignancy is present.

Modifiable risk factors such as smoking, hypertension and obesity provide scope for intervening at an early stage during routine visits. Basic blood and urine tests, in conjunction with an ultrasound scan, can provide the necessary information needed before following guidelines on referral to a surgeon or oncologist.

The repertoire of treatments is expanding with the introduction of novel targeted therapies. Allied to traditional surgical techniques these drug treatments, and their side effects, require the co-ordinated follow-up of patients by both primary and secondary care teams.

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Useful information

Cancer Research UK
Provides a searchable database of trials including those relevant to kidney cancer. Search under 'renal cell cancer' in the 'find a clinical trial' dialogue box
cancerhelp.cancerresearchuk.org/trials/

NHS Choices
Patient-oriented website with useful and straightforward explanations
www.nhs.uk/Conditions/Cancer-of-the-kidney/Pages/Introduction.aspx

Patient support and advocacy sites
www.jameswhalefund.org/
www.kidneycancersupportnetwork.co.uk/

We welcome your feedback

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