Kidney cancer: current management guidelines

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Renal cell carcinoma accounts for 2% of all cancers. Medical progress has improved the outcome of early but not advanced disease. This article highlights the current practice for the management of renal cell carcinoma.

Renal cell carcinoma (RCC) is known as the 'physician's tumour' because of its wide range of presenting characteristics (*Table 1*) and associated systemic disturbances (*Table 2*). Awareness of these features among cross-speciality practitioners will avoid diagnostic delay by prompt investigation and referral, thus improving patient outcome.

EPIDEMIOLOGY

Two per cent of all adult malignancies are RCC, with the highest incidence occurring in the 7th decade of life (median = 66 years). Hellsten et al (1990) reported a 2% incidence of RCC at autopsy from all causes of death in a single institution.

More men are affected than women (2:1 respectively), with RCC being the eighth commonest cancer in men and the fourteenth in women. In 1996, there were 3450 new cases of kidney cancer in men and 2160 cases in women (Office for National Statistics, 1996a,b).

The incidence of RCC increased from 13% to 61% from 1973 to 1998 (Jayson and Sanders, 1998), mainly because of the rising number of incidental tumours detected by either ultrasound or computed tomography (CT) imaging in asymptomatic patients being investigated for other intra-abdominal pathology.

TABLE 1.
Relative frequency of presenting features in patients with renal cell carcinoma

Features	Relative frequency
Pain	1 in 3
Haematuria	1 in 3
Weight loss	1 in 3
Mass	1 in 5
Hypertension	1 in 5
Fever	1 in 5
Classic triad	1 in 10
Hypercalcaemia	1 in 20

From Belldegrun and deKernion (1998)

PATHOLOGY

Each anatomical element in the kidney can give rise to benign and malignant tumours (*Table 3*). RCC is believed to originate from the proximal renal tubular cells, with most being unilateral. Bilateral tumours (either synchronous or metachronous) account for 2% of cases (e.g. von Hippel–Lindau disease, VHLD).

Macroscopically, RCC are usually rounded and have a pseudocapsule composed of compressed renal parenchyma and fibrous tissue. There are areas of yellow or brown tumour interposed between patches of haemorrhage and necrosis. Calcification and cystic areas may be present. The common sites for metastasis are lung, bone, liver, adrenal and brain, occurring via the blood

TABLE 2.
Relative frequency of systemic disturbances in patients with renal cell carcinoma

Systemic disturbance	Relative frequency
Increased erythrocyte sedimentation rate	1 in 2
Hypertension	1 in 3
Anaemia	1 in 3
Weight loss, cachexia	1 in 3
Pyrexia	1 in 10
Deranged hepatic function	1 in 10
Raised alkaline phosphatase	1 in 10
Hypercalcaemia	1 in 20
Polycythaemia	< 1 in 20
Neuromyopathy	< 1 in 20
Amyloidosis	< 1 in 20

From Chisholm (1974)

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and lymphatic stream equally. Histologically, RCC can be divided into subtypes of conventional (clear cell), papillary, chromophobic and multilocular cystic tumour (Storkel et al, 1997). All these tumour types can show cytoplasmic granularity or spindle cell features. Therefore, 'granular' and 'sarcomatoid' RCC no longer exist as distinct entities in the latest classification.

RISK FACTORS

Environmental

Smoking (cigarette, cigar and pipe), obesity, a high protein diet and exposure to petrol, cadmium and lead have been postulated as risk factors (Dhote et al, 2000).

Genetic

Familial forms of papillary and clear cell RCC exist. However, the discovery of the von Hippel–Lindau gene (chromosome 3p) associated with VHLD has improved our understanding of the genetic basis of RCC (Iliopoulos and Eng, 2000). Other oncogenes implicated include *erb*B, *c-myc* and tuberous sclerosis-2 tumour-suppressor genes (Kirkali et al, 2001). In this whole group, 35–40% of patients will die of RCC if early detection and treatment does not occur.

Others

Hypertension, diuretics and renal stones have been suggested as risk factors for RCC (Dhote et al, 2000). Malignant change can also occur within acquired renal cysts secondary to long-term dialysis (Brennan et al, 1991; Sant and Ucci, 1998).

CLINICAL PRESENTATION

The classic triad of haematuria, loin pain and a mass is found in only 10% of patients and is suggestive of advanced disease (*Table 1*). The most common presentation is 'incidental'. However, 25–30% of patients have metastatic disease at the time of presentation (Motzer et al, 1997).

Hypertension can be caused by segmental renal artery occlusion or the production of renin (or renin-like) substance. Polycythaemia and hypercalcaemia (paraneoplastic syndrome) occur as a result of the production of erythropoietin and parathyroid hormone-like substance respectively. Non-metastatic hepatic dysfunction with necrosis and fever can occur (Staufer's syndrome). Persistence or recurrence of this post-nephrectomy is invariably associated with tumour recurrence.

STAGING AND PROGNOSIS

Staging is crucial in planning management and providing prognostic information. The tumour, node and metastasis (TNM) system was revised in 1997, reflecting the improved management of the disease and also accounting for the lack of significant survival difference between tumours less then 2.5 cm and those less than 7 cm in size (Guinan et al, 1997). This cut-off size has been controversial, as other dimensions have recently been proposed (e.g. tumours less than 4 cm may be suitable for nephron-sparing surgery; Herr, 1994; Fergany et al, 2000; Lee et al, 2000).

Apart from pathological stage, important prognostic factors include tumour size (an independent factor in its own), nuclear grade and ploidy, and the performance status of the patient (Thrasher and Paulson, 1993). Some patient-related factors have been identified as having a survival impact. These include time from diagnosis to metastasis, location and number of metastases, weight loss and whether nephrectomy has been performed (Maldazys and deKernion, 1986). There are other markers currently under evaluation as potential predictors of outcome, e.g. nuclear morphometry, serum ferritin and molecular markers measuring tumour cell proliferation, growth factors, cell adhesion, apoptosis, telomerase activity and angiogenesis.

The 5-year survival rate for patients with localized (organ-confined), locally advanced (perinephric tissue involvement with intact Gerota's fascia) and metastatic RCC are about 70–90%, 60% and 4% respectively (Chowdhury and Gore, 1999). There is a need for other treatment modalities to improve the poor outcome in metastatic RCC.

TABLE 3.
Pathological classification of some renal tumours

Benign	Simple cyst		
	Angiomyolipoma		
	Oncocytoma		
	Phaeochromocytoma		
	Leiomyoma		
	Haemangioma		
	Fibroma		
	Arteriovenous malformation		
Malignant	Primary	Renal cell carcinoma	
		Liposarcoma	
		Leiomyosarcoma	
		Rhabdomyosarcoma	
	Metastatic	Local	Adrenal
		Distant	Carcinoid
			Leukaemia
			Lymphoma

MANAGEMENT

Investigations

A thorough history will elucidate the risk factors mentioned earlier, and baseline investigations should include a full blood count, urea, creatinine and electrolytes, urine for microscopy, culture, sensitivity and cytology. If haematuria is present, this should be investigated as previously described (Harper et al, 2001). *Figure 1* gives a management algorithm once a renal mass is located.

Treatment

Surgery is the only curative treatment in localized RCC. Radical nephrectomy is still the gold standard in the presence of a normal contralateral kidney. However, evidence suggests that partial nephrectomy is equally safe in organ-confined tumours (≤4 cm in size; Herr, 1994; Fergany et al, 2000; Lee et al, 2000). Thus, it can be offered to patients with a solitary kidney, a functionally compromised contralateral kidney or in bilateral RCC.

At present, there is no cure for advanced RCC. Cytotoxic and hormonal therapies are of limited use. Radiotherapy is only used for the symptomatic treatment of bone or cerebral metastases. Patients with solitary metastasis may be considered for nephrectomy and excision of the metastatic lesion, but limited evidence exists for outcome.

In patients with advanced disease, alpha-interferon has a 15–20% response rate. Recombinant interleukin-2 therapy has shown more success in terms of a higher response rate and a longer remission time. With regard to the role of cytoreductive nephrectomy in conjunction with immunotherapy, two prospective studies have shown a beneficial effect and that nephrectomy before immunotherapy is superior to immunotherapy alone (Flanigan et al, 1999; Mickisch et al, 1999).

Follow-up

There is no consensus or published guidelines at present, but follow-up should be coordinated via a multidisciplinary team. The interval and the performance of physical examination, serum bone profile, chest X-ray and abdominal CT are tailored to the pathological stage, the individual patient's wishes (e.g. regular review for reassurance *vs* 'prefer not to know') and the knowledge that survival may not be prolonged by the early detection of tumour recurrence.

On the horizon

Gene therapy utilizing transformed autologous tumour cells, tumour infiltrating lymphocytes or encoding of the major histocompatibility complex class I molecules has demonstrated a reduction in tumour growth, metastasis and rejection of subsequent tumour challenges in a murine model (Figlin, 1999). Likewise, monoclonal therapy against the carbonic anhydrase IX antigen in clear cell carcinoma of the kidney has shown excellent targeting results in mice (Lampe and Oosterwijk,

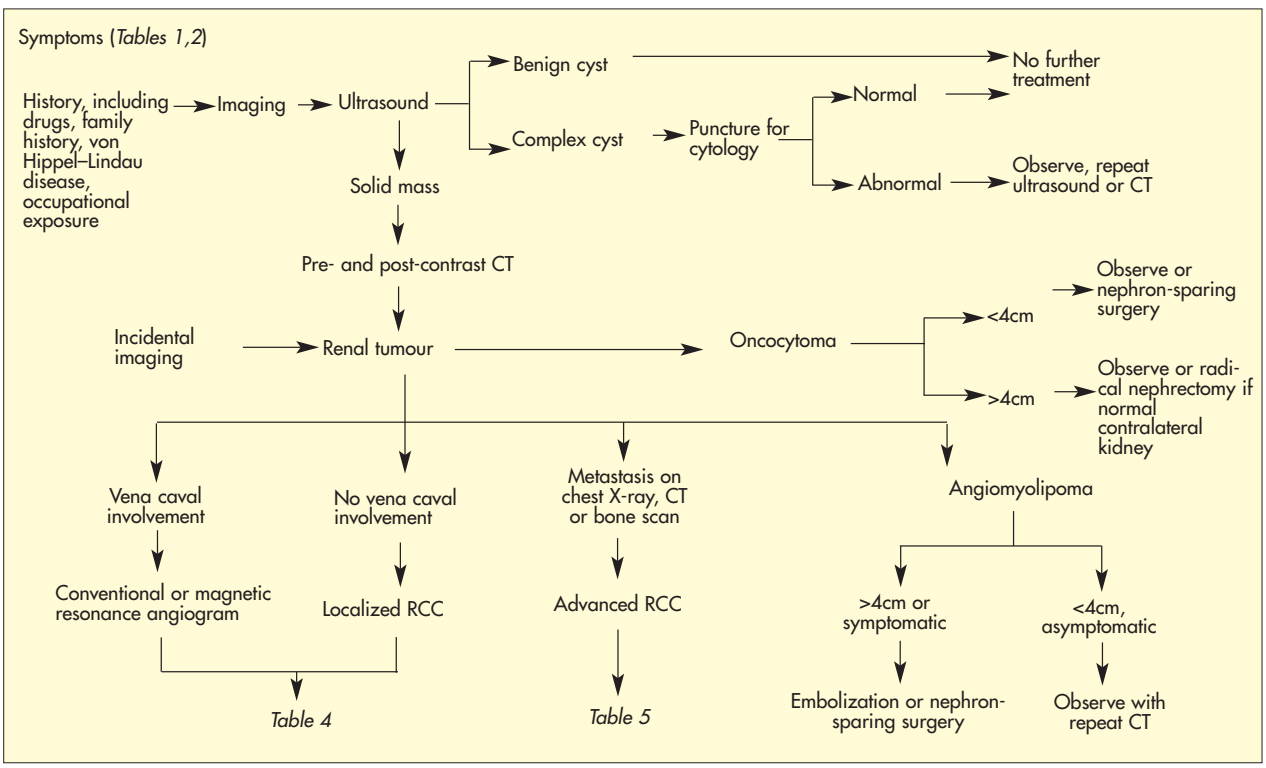

Figure 1. Management pathways for suspected renal masses. If haematuria is present, a different algorithm should be followed (Harper et al, 2001). CT = computed tomography; RCC = renal cell carcinoma.

2000). Thus, tumour cell targeting with cytotoxic agents is possible. Researchers have also demonstrated the possibility of using dendritic cells in a RCC vaccine in patients (Kugler et al, 2000).

CONCLUSIONS

There have been improvements in the diagnosis, staging, management and survival in patients with localized RCC. Unfortunately, the outlook for advanced disease remains poor. A better understanding of RCC tumour biology may help improve the latter. HM

Conflict of interest: none.

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TABLE 4.
Treatment options for localized renal cell carcinoma

Localized	≤4cm or solitary functioning kidney	Radical nephrectomy with subsequent renal substitution therapy, e.g. dialysis
		Nephron sparing surgery (open or laparoscopic)
	>4cm with normal contralateral kidney	Radical nephrectomy
Localized with supra-diaphragmatic caval involvement	Same as management of localized disease but requires cardiothoracic consult and support, e.g. cardiopulmonary bypass	
Locally advanced	Radical nephrectomy	

TABLE 5.
Treatment options for advanced renal cell carcinoma

Solitary metastasis	Radical nephrectomy and excision of metastatic lesion	
	Manage as for multiple metastases	
Multiple metastases	Enter into clinical trial for immunotherapy	
	Palliative, symptomatic treatment of bone pain, cerebral oedema, renal pain, intractable haematuria	Non-steroidal anti-inflammatory, opiate
		Palliative radiotherapy
		Steroids and radiotherapy
		Embolization
		Nephrectomy

KEY POINTS

- Renal cell carcinoma (RCC) is not common but can present to practitioners other than urologists because of its variety of symptoms.
- An increase in abdominal ultrasound and computed tomography has resulted in the detection of more incidental RCC with a smaller size and lower stage.
- Radical nephrectomy offers the best chance of cure in patients with localized RCC.
- There is emerging evidence that nephron-sparing surgery in patients with a localized RCC ≤4cm does not compromise survival.
- The management of oncocytoma and angiomyolipoma is controversial. Those patients who are managed with observation should be monitored carefully, e.g. with regular computed tomography.
- Immunotherapy can provide some survival benefits. A better understanding of RCC tumour biology may bring about a better response rate and duration of survival in the future.
- Improvement in the prognosis of advanced RCC is likely to rely upon future advances in gene therapy, monoclonal therapy and tumour vaccine.