Renal cell carcinoma

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RCC is the most common solid neoplasm of the kidney . It accounts for around 90% of renal tumours and constitutes 2–5% of all cancers in adult men and 1–3% in adult women. There has been a recent steady increase in the incidence of RCC. It may be sporadic or familial. Familial renal cell carcinoma von Hippel–Lindau (VHL) syndrome is the most common familial syndrome associated with RCC. VHL disease is a rare autosomal dominant disorder that is characterised by multiple pathologies, including clear-cell RCC (ccRCC), phaeochromocytoma, retinal angiomas and haemangioblastomas of the brainstem, cerebellum or spinal cord. Aetiology Cigarette smoking, obesity and hypertension are the major risk factors associated with RCC. Others include diuretics, occupational exposure to petrochemicals and dyes and ARCD in patients on long-term haemodialysis. Clinical presentation The classic triad of flank pain, haematuria and a palpable mass is now uncommon as most renal masses are detected incidentally . Symptoms and signs may be non-specific. The most common presenting symptom is haematuria. Patients may have constitutional symptoms such as fever, malaise and weight loss in advanced disease. Advanced disease can present with bilateral lower limb oedema or recent-onset non-reducing right-sided varicocele owing to thrombus in the IVC. Paraneoplastic syndromes (PNSs) are found in up to one-third of patients with RCC. The most common PNS is an elevated erythrocyte sedimentation ra te (ESR) followed by hypertension, anaemia and hypercalcaemia. Up to a quarter of the patients may have evidence of metastatic disease on pre sentation. The most common site of metastasis is the lung and Eugen von Hippel , 1867–1939, Professor of Ophthalmology , Göttingen, Germany , first described angiomas in the eye in 1904. Arvid Vilhelm Lindau , 1892–1958, Swedish pathologist, described angiomas of the cerebellum and spine in 1927. may occasionally present as pathological fractures. Pathology ccRCC is histologically an adenocarcinoma arising from the - proximal renal tubular epithelium. They are slow growing and bulge out of the renal contour (Figure 82.15). Most are soli - tary , but bilateral and multiple tumours are found in familial RCC. The prognosis of ccRCC varies depending on various - histopathological features, suc h as nuclear grading. Other histological variants are papillary RCC, chromophobe RCC and, rarely , collecting duct carcinoma and renal medullary carcinoma. Table 82.2 summarises the salient features of subtypes of RCC. The tumour can spread directly , invading the perinephric - tissue through the capsule or at times directly extending into the renal vein as a tumour thrombus. V ein wall invasion is asso - ciated with poor prognosis. Diagnosis Laboratory findings Evaluation should include blood count, ESR, serum creatinine, liver function tests, lactate dehydrogenase (LDH), corrected serum calcium, coagulation markers and urine analysis. Increased alkaline phosphatase should prompt further investi - gation to rule out liver and skeletal metastases. LDH is useful in risk stratification of metastatic disease. -

Figure 82.15 Cut surface of a kidney showing a large, well-demarcated clear-cell renal cell carcinoma in the upper pole with foci of yellowish areas signifying the lipid content of the tumour (courtesy of Dr Vikram Raj Gopinathan, Department of Pathology; photo credit: Sekhar, Christian

Medical College, Vellore, India).

/uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Radiological investigations Although US can diagnose the tumour, triphasic CECT is the investigation of choice for diagnosis and staging. RCC typically shows contrast enhancement after contrast injection (a change of >15 /uni00A0 HU is considered significant). The CT also provides additional information on the function of the opposite kidney , primary tumour extension, venous involvement, enlargement Dimitrie D Gerota , 1867–1939, Romanian anatomist, physician and radiologist. and intra-abdominal metastatic disease (Figure 82.16). MRI provides similar information to CT , but can be superior at detecting tumour infiltration into the vein wall and the level of thrombus. A chest radiograph should be obtained in all cases. A bone scan is necessary in a patient with elevated alkaline phospha - tase, bone pain or hypercalcaemia. Tumour staging The treatment and prognosis of RCC depends on its patho - logical staging. The most important factors are the size of the tumour and whether it is confined within the renal capsule and Gerota’s fascia. Involvement of the lymph nodes, renal sinus and vein wall are associated with a poorer prognosis than the presence of tumour thrombus in the renal vein or IVC. Currently the most commonly used system for staging RCC is the TNM classification (Figure 82.17). Prognostic factors Currently , the grading system proposed by the International Society of Urological Pathology (WHO/ISUP) is used for grading renal cancer. Anatomical factors such as tumour size, venous invasion, renal capsular invasion and adrenal involve - ment herald a poorer prognosis. Certain histological types, e.g. sarcomatoid, have a worse prognosis. Management Nephron-sparing surgery Radical nephrectomy remains the gold standard treatment for localised disease. However, with the recent increase in incidental detection of small renal masses (tumours <4 /uni00A0 cm), more nephron-sparing surgery is being performed. Partial nephrectomy should be the treatment of choice in tumours less than 4 /uni00A0 cm, in well-selected tumours between 4 and 7 /uni00A0 cm, in bilateral tumours, in tumours in solitary kidneys and in patients with pre-existing renal dysfunction. Minimally invasive tech - niques by laparoscopy or robots have reduced postoperative morbidity . Because of the limitation of ischaemia time, mini - mally invasive techniques should be reserved for tumours with non-complex anatomy , as predicted by nephrometry scores. Alternative techniques such as surveillance, cryoablation or radiofrequency ablation of small renal tumours may be o ff ered in patients with high surgical risk (e.g. elderly patients, patients with multiple comorbidities). Activ e surveillance is based on the fact that most incidental tumours detected in the elderly grow slowly and have a low chance of local invasion or metas - tasis. Radical nephrectomy Classically , radical nephrectomy involved removal of the entire kidney enclosed in Gerota’s fascia with the ipsilateral adrenal gland and regional lymphadenectomy . Most are now performed laparoscopically and the adrenal is spared if there is no involvement on CT/MRI. Lymphadenectomy is indicated only in high-risk patients with large primary tumours and enlarged lymph nodes.

subtypes of renal cell carcinoma (RCC). RCC subtype Salient features Clear-cell RCC Most common subtype Usually sporadic May be associated with loss of chromosome 3p and a mutated von Hippel–Lindau gene Papillary (type I and Second most common II) RCC Usually sporadic but may be familial Type 1 tumour has a better prognosis than type 2 Chromophobe RCC Usually sporadic but may be familial Good prognosis Collecting duct Uncommon (1–2%) carcinoma Aggressive tumour Arises from the renal medulla, hence centrally located tumour Renal medullary Rare (<0.5%) carcinoma Very aggressive Associated with a younger age and sickle cell trait Centrally located

tumour Figure 82.16 Contrast-enhanced computed tomogram showing a left renal mass with left renal vein thrombus extending into the inferior vena cava (IVC) (hypoattenuated linear area within the IVC) (courtesy of Department of Urology, Christian Medical College, Vellore, India).

Surgical management of inferior vena cava thrombus Renal tumours are associated with IVC tumour thrombus in 5–10% of cases. Tumour thrombus may extend as far as the right atrium. Thrombus extending to the retrohepatic or suprahepatic segment of the IVC requires full mobilisation of the liver, and thrombus extending to the right atrium may require cardiopulmonary bypass and circulatory arrest. Management of metastatic renal cell carcinoma Up to one-third of patients with RCC will present with disseminated disease. The International Metastatic Renal Cell Carcinoma Database Consortium risk stratification classifies a patient with metastases into risk groups based on performance status, time from diagnosis to systemic therapy , haemoglobin levels, calcium levels and platelet and neutrophil counts. The median survival of the good risk group is little more than 3.5 years, compared with just under 2 years in the intermediate-risk group. The expected median survival of the poor risk group is just over 7 months. Tyrosine kinase inhibitors inhibit vascular endothelial growth factor (e.g. sunitinib, pazopanib) and these drugs have improved survival in metastatic ccRCC. RCC is an immu nogenic tumour and responds to immunotherapy . The first generation of agents were interleukins and interferons. More recently , targeted therapy in the form of immune checkpoint inhibitor s and anti-programmed death 1/programmed death ligand-1 inhibitors have been used. Cytoreductive nephrectomy may be beneficial in good and intermediate-risk patients. Palliative nephrectomy may be consider ed for intractable haematuria, pain and symptomatic PNS. Angioembolisation of renal tumour can be performed in medically unfit patients with intractable haematuria.

vena cava Aorta Figure 82.17 Staging of renal cell carcinoma is based on size, position and lymph node involvement: Stage I: tumour <7 cm in the largest dimension, limited to the kidney. Stage II: tumour >7 cm in the largest dimension, limited to the kidney. Stage III: tumour in the major veins or adrenal gland with intact Gerota’s fascia, or regional lymph nodes involved. Stage IV: tumour beyond Gerota’s fascia. Adrenal Lymph gland node Stage I Stage III Stage II Gerota’s fascia Stage IV

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