Diagnosis advice and treatment options for renal cell carcinoma

Renal cell carcinomas (RCCs), which originate within the renal cortex, are the most common type of renal carcinoma. Transitional cell carcinomas of the renal pelvis are the next most common. Other tumours, such as oncocytomas, Bellini collecting duct tumours, and renal sarcomas, occur infrequently. Smoking, obesity, and hypertension are risk factors associated with an increased incidence of RCC.

The incidence of renal carcinomas in Ireland is 11.2 per cent (per 100,000), making up 2.6 per cent of all invasive carcinomas (excluding non-melanoma skin cancers). It occurs more commonly in males compared to females (15.2 vs 7.5 per cent) and is the 10th most common cause of death in males (16th in females). The most common presenting symptoms in patients are haematuria, abdominal mass, pain, and weight loss. Patients may also present with hypercalcaemia, paraneoplastic syndromes or anaemia. Increasingly, an incidental diagnosis is made due to radiologic investigations performed for other indications.

Staging and diagnosis
Symptomatic patients suggestive of a possible RCC should undergo abdominal ultrasound or CT to assess for the presence of renal pathology. MRI may also be considered to identify the extent of involvement of the collecting system or the inferior vena cava. A bone scan is indicated in patients with bone pain or an elevated serum calcium or alkaline phosphatase. CT of the chest will detect evidence of pulmonary or mediastinal lymph node metastases and a CT brain may be indicated based on symptoms. For patients with isolated renal masses, nephrectomy is preferred to biopsy because it provides both the diagnosis and definitive treatment.

When metastatic disease is suspected at the initial presentation, biopsy or nephrectomy for pathological confirmation is required prior to starting therapy. The tumour node metastasis (TNM) staging system is used to stage RCC. It can be classified as localised disease which includes stages 1 to 3 and advanced disease (stage 4) which includes tumour invading beyond Gerota’s fascia or extending into the ipsilateral adrenal gland (T4) and metastatic disease (M1).

Surgery
Surgery is curative in the majority of patients with localised disease and is the preferred treatment for patients with stages 1, 2, and 3 disease. Surgery can involve either a radical nephrectomy or renal-sparing approaches (partial nephrectomy or ablative techniques) in selected patients. Partial nephrectomy is performed more frequently for small, incidentally discovered, low-stage renal tumours (T1 and T2). This can be carried out through a conventional approach or by minimally-invasive approach such as laparoscopy. In selected patients who present with a resectable primary tumour and a concurrent single metastasis, surgical resection of the metastasis, in conjunction with radical nephrectomy, may be curative. Surgery should also be considered in patients with metastatic disease as trials have demonstrated a survival benefit after surgery with cytoreductive nephrectomy in carefully selected patients who received interferon alpha therapy with metastatic disease. It is unknown if there is a survival benefit in the era of targeted therapy although the ongoing CARMENA trial aims to answer this question.

Subtypes and histology
Clear cell carcinomas, which typically have a deletion of chromosome 3p, are the most common subtype and arise from the proximal tubule. The Fuhrman grading system is the most commonly used pathological staging and has been demonstrated to be an independent predictor of survival. A poor prognosis is associated with higher nuclear grade or the presence of a sarcomatoid pattern. Other less common subtypes include papillary, chromophobe, oncocytic, and Bellini’s collecting duct tumours. Papillary renal cell carcinomas can be multifocal and bilateral, originate from the proximal tubule and commonly present as small, early stage tumours. Chromophobe carcinomas originate from the intercalated cells of the collecting system and may have a lower risk of disease progression and death compared to clear cell carcinomas. Renal oncocytomas are uncommon and also arise from the intercalated cells of the collecting system. Bellini’s collecting duct tumours are rare, tend to occur in younger patients and are frequently aggressive. They commonly present with gross haematuria. Sarcomatoid variants have also been noted. Other rare primary malignancies that can sometimes arise in the kidney include lymphomas, soft tissue sarcomas (e.g., leiomyosarcoma, liposarcoma), and carcinoid tumours.

Metastatic disease
Multiple therapies are available for patients with metastatic RCC including anti-vascular endothelial growth factor (VEGF) therapy, mechanistic target of rapamycin (mTOR) inhibitors and immunotherapy.
TKIs
Tyrosine kinase inhibitors (TKI) have clinical activity in blocking the VEGF pathway and are active against RCC. Sunitinib inhibits the VEGF receptor TK, as well as other TKs associated with the PDGF receptor and c-kit oncogene. It is taken orally at 50mg daily for four weeks, followed by a two-week break. A Phase III trial of sunitinib compared to interferon alpha (IF-Na) in patients who had not received prior systemic therapy showed a significantly higher objective response rate (ORR), longer progression-free survival (PFS) and overall survival (OS) (26.4 v 21.8 months, HR 0.82, 95% CI 0.67-1.00). Side effects include hand-foot syndrome, hypertension, and diarrhoea. Pazopanib is an oral agent taken daily (800mg) that inhibits the TKs associated with the VEGF, platelet-derived growth factor (PDGF) receptor, and kit receptors 6 and 7. It has been shown to improve PFS and response rates compared to placebo in both previously cytokine-treated patients and treatment-naïve patients. As both pazopanib and sunitinib improve PFS compared to placebo or to interferon, respectively, both these drugs were compared in head-to-head studies. In a Phase 3 trial, over 1,100 treatment-naïve patients were randomly assigned to treatment with pazopanib or sunitinib. Compared to sunitinib, pazopanib resulted in no difference in PFS or OS. There was a similar rate of drug discontinuation due to toxicity, which was predominantly driven by abnormal liver function tests due to pazopanib. Pazopanib did have better health-related quality-of-life scores, including better mouth and throat symptoms, less fatigue, and less foot soreness. In the PISCES Phase 3 randomised trial, the tolerability of these agents were compared to evaluate if differences in toxicity affected patient preferences. It found that significantly more patients preferred pazopanib over sunitinib (70 v 22 per cent). Pazopanib resulted in a significantly better health-related quality-of-life, with less fatigue and less dysgeusia reported compared to sunitinib. Either drug can be used for first-line management of metastatic renal cell carcinoma.
Sorafenib does not have a clear role in treatment-naïve patients, however, its activity has been demonstrated in previously treated patients. Sorafenib is a potent small molecule inhibitor of multiple TKs including VEGF receptor, platelet-derived growth factor (PDGF) receptor, fibroblast growth factor receptor-1 (FGFR1) and Raf. Compared to placebo, sorafenib (400mg orally twice daily) prolonged the median PFS (5.5 v 2.8 months, HR 0.44, 95% CI 0.35-0.55), however, there was no difference in OS.
Sorafenib is a newer available oral inhibitor of the VEGF receptors 1, 2, and 3. In the first-line setting, axitinib (5mg twice a day) compared to sorafenib resulted in a trend toward improvement in PFS (10 v 6.5 months, HR 0.77, 95% CI 0.56-1.05) and a higher ORR (32 v 15%, p = 0.02). In the second-line setting, patients with previously treated RCC who were treated with axitinib compared to sorafenib resulted in a significant improvement in PFS compared to sorafenib (eight vs six months, HR for PFS, 0.66, 95% CI 0.55-0.78). The benefit in PFS was higher in patients previously treated with either cytokines or sunitinib. There was a significant increase in ORR (23 v 12 per cent), however, no difference in OS was report-

Other less common subtypes include papillary, chromophobe, oncocytic, and Bellini’s collecting duct tumours. Papillary renal cell carcinomas can be multifocal and bilateral, originate from the proximal tubule and commonly present as small, early stage tumours
ed. Axitinib dose can be gradually titrated up to 7mg and 10mg twice daily depending on tolerability.

**mTOR pathway**

Inhibition of the mTOR pathway has the potential to inhibit tumour progression at multiple levels. Temsirolimus, given intravenously, is a treatment option for the first-line treatment of patients with poor-prognostic advanced or metastatic RCC. Everolimus is an orally administered mTOR inhibitor that has shown activity in patients with clear cell RCC whose disease has progressed despite treatment with a VEGF TKI. Though usually well-tolerated, both temsirolimus and everolimus are associated with pneumonitis in 0.5 to 5 per cent of patients.

**Immunotherapy**

Immunotherapy has been used for many years in the management of renal cell carcinoma. High-dose bolus IL-2 can activate an immune response against RCC that results in tumour regression in a minority of patients. Although treatment is associated with severe toxicity, the responses often persist for many years, and complete responders may remain free of relapse long-term. Proving in principle that immunotherapy is active in RCC, both IL-2 and interferon alpha have largely been replaced by the targeted TKIs and newer immunotherapy agents. Nivolumab, given intravenously, is a fully human monoclonal antibody directed against PD-1 (programmed death-1) resulting in the activation of T-cells and cell-mediated immune responses against tumour cells. Compared to everolimus, nivolumab improved overall survival to 25 months versus 19 months for everolimus. Though generally well-tolerated, it is associated with immune-related side effects including pneumonitis, diarrhoea, and hypothyroidism.

**Prognostic model**

Studies have looked at ways of identifying patients who have more aggressive types of disease and may help tailor management plans for these patients. The Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic model has identified five factors that predict shortened survival in patients with advanced RCC. These include a Karnofsky performance status (KPS) of <80 per cent, an elevated serum lactate dehydrogenase (LDH) level, hypercalcaemia, anaemia or the absence of nephrectomy (ie, no disease-free interval). Patients with none of these risk factors versus those with one or two versus those with three or more risk factors had significantly higher survival rates at one year (71 vs 42 and 12 per cent, respectively) and three years (31 vs seven and 0 per cent, respectively). Treatment options may be individualised for patients based on these risk factors.

**Adjuvant therapy**

TKIs and immunotherapy can induce objective tumour responses in patients with advanced RCC and this has led to further investigation of various agents as adjuvant therapy following surgical resection. Data is still awaited from these trials, including the PROTECT trial which evaluated pazopanib and S-TRAC which evaluated sunitinib as adjuvant treatment for resected localised RCC. Until final data is reported, adjuvant therapy in renal cell cancer is currently not indicated. Careful surveillance following surgical resection is important to allow early diagnosis of recurrence.

**Screening**

Screening of asymptomatic individuals is not recommended because of the low prevalence of RCC in the general population. However, individuals at high risk for the development of RCC should undergo periodic monitoring with abdominal ultrasound, CT, or magnetic resonance imaging (MRI) to detect early disease. Candidates for screening include patients with inherited conditions associated with an increased incidence of RCC including von Hippel-Lindau syndrome and tuberous sclerosis, end-stage renal disease or a strong family history of RCC.

**Conclusion**

Renal cell carcinoma is an important cause of morbidity and mortality in patients. Surgery is curative in patients with localised disease, however, there is still a significant risk of recurrence and a number of patients will present with advanced disease at diagnosis. Clearly there may be a role for adjuvant treatments in patients with high risk disease and data from clinical trials evaluating this is eagerly awaited. Multiple therapies are available for patients with advanced disease including newer immunotherapy agents with proven efficacy in patients with advanced RCC.

**References on request**

Dr John Greene SpR in Medical Oncology, and Prof Ray McDermott, Consultant Medical Oncologist, Tallaght Hospital, Dublin and St Vincent’s University Hospital, Dublin.
Update on the treatment of renal cell carcinoma – Online module pre-assessment questions

Test your knowledge on the diagnosis and management of renal cell carcinoma with the following true/false questions

TRUE/FALSE QUESTIONS

Q1 Obesity is a known risk factor for the development of renal cell carcinomas?
Q2 Patients who present with a suspected renal cancer should always have a diagnostic biopsy prior to surgical removal?
Q3 Surgery for renal cell cancers always involves a total nephrectomy?
Q4 Clear cell carcinoma is the most common subtype of renal cell carcinomas?
Q5 Pazopanib is superior to sunitinib in first-line treatment for metastatic RCC?
Q6 Axitinib is a treatment option for second-line therapy of advanced renal cell carcinoma?
Q7 Temsirolimus is preferable to a TKI for first-line management of good risk metastatic RCC?
Q8 Newer immunotherapy agents that target PD-1 have largely replaced the use of interferon alpha and IL-2?
Q9 Hypercalcaemia at presentation is associated with a poorer prognosis in metastatic RCC?
Q10 Adjuvant therapy is indicated for all resected stage I, II and III renal cell carcinomas?

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Case report

A sixty-three-year-old male presents to his GP with a three-month history of haematuria, right flank pain and weight loss. An MSU performed showed the presence of red cells and he was found to be anaemic with a haemoglobin of 7.9. He was referred to the ED where an ultrasound abdomen was performed. The report identified an 11cm mass at the right renal angle, suggestive of a possible renal cell carcinoma. After a blood transfusion, he was subsequently referred to urology. A CT TAP was performed, which showed no evidence of metastatic disease. After MDT discussion, a decision was made to perform a radical nephrectomy. He underwent a right radical nephrectomy and made a quick postoperative recovery. Histology confirmed an 11cm mass with clear cell carcinoma, Fuhrman grade III differentiation and negative resection margins. The TNM staging was T3NoMX (stage 3). No further adjuvant treatment was required and a surveillance programme with CTs, blood tests, and physical examinations every six months was initiated.

At a follow up visit approximately one year after his initial surgery, his CT TAP reported multiple new pulmonary nodules measuring more than 1cm throughout both lungs consistent with metastatic recurrence. On further questioning, he had noticed some weight loss and a persistent dry cough over the preceding months. A biopsy was performed and confirmed metastatic renal cell cancer. Blood tests identified a low haemoglobin, hypercalcaemia and an elevated LDH consistent with poor risk disease according to MSKCC prognostic criteria.

He was referred to medical oncology with metastatic renal cell carcinoma (stage 4). He was commenced on pazopanib orally 800mg daily. After initiation he was seen on a monthly basis on the dayward. His LFTs started to worsen and he was dose-reduced to 600mg daily, which he tolerated better. After nine months of treatment, a repeat restaging CT TAP showed progressive disease with an increased number and size of pulmonary nodules and multiple new bone metastases including his right scapula. He was complaining of pain in his right shoulder and had a course of palliative radiation, which relieved his symptoms.

He was commenced on axitinib 5mg bd and bisphosphonate therapy. CT TAP after three months showed stable disease and his dose was gradually increased over the following six months to 70mg bd. Unfortunately, subsequent imaging showed progressive disease. He was commenced on nivolumab intravenously every two weeks and remains on this treatment with minimal toxicity and stable disease three months into treatment.