The diagnosis of renal cell cancer (RCC) has increased in frequency since the 1990s. This has been attributed to more widespread use of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) that can detect incidental lesions. Lifestyle factors such as obesity, as well as improved life expectancy, may have also contributed to this rise.¹

RCC is more common in men than in women. In their lifetime, 1 in 52 men will be diagnosed with RCC.¹ Its incidence in men in the UK between 2008–2010 was 13–16 per 100,000 persons – an incidence twice that of women.¹ In 2014, RCC was the fifth most common cancer diagnosed in men and the tenth most common in women.¹ Mortality rates in men are also twice as high as in women.²

There are several inherited, autosomal dominant genetic conditions that predispose to RCC development. These include Von Hippel-Lindau (VHL) syndrome, hereditary papillary cancer, hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, and Burt-Hogg-Dubé syndrome, among others. Taking a family history is important, especially in young patients.

CLINICAL PRESENTATION OF RCC
Early-stage RCC may be picked up incidentally on imaging or due to symptoms of the primary tumour, such as back pain, blood in the urine, a palpable mass in the...
abdomen, fever and systemic malaise. Late-stage RCC may also be detected in this manner or due to symptoms of secondary tumours, such as bone pain or cough.

**TYPES OF RENAL CANCER**

There are several histological types of RCC. The most common is clear cell (ccRCC), accounting for up to 90% of cases. The next most frequent type is papillary RCC, with chromophobe RCC and rarer types (e.g., collecting duct, translocational and medullary tumours) comprising the rest. Any histological type may exhibit sarcomatoid features, which are associated with a more aggressive clinical course and poor response to drug therapy.

Clear cell, papillary and chromophobe RCCs all demonstrate different underlying gene mutation profiles that impact multiple growth pathways. Alterations in the VHL gene and loss of the short arm of chromosome 3 define ccRCC, even in non-inherited cases. The UK-based Renal TRACERx program (http://tracerx.co.uk/studies/renal/) is dedicated to studying the genes that drive both sporadic and inherited forms of RCC.

**STAGING AND PROGNOSIS**

As with many other cancers, the extent of RCC is defined according to how large the primary tumour is, whether it has invaded local lymph nodes and whether it has spread to more distant sites. This governs the approach to treatment and, along with other factors, informs the risk of recurrence. Staging according to the ‘tumour, node, metastasis’ (TNM) system is summarised in Table 1. 

The anatomical extent of disease is one of the best prognostic factors for early-stage RCC. Five-year survival rates are included in Table 1. A scoring system derived by Leibovich et al may also be applied to primary ccRCC and incorporates clinical information as well as findings from surgery in Stage I–III disease. The Fuhrman grade is another prognostic measure based on the appearance of the nucleus in the tumour cells (Figure 2).

In Stage IV disease, the overall prognosis is predicted by patients’ risk category and determined by the efficacy of drug therapy. This is further discussed below.

**TREATMENT FOR STAGE I–III CANCER**

Most RCCs are diagnosed at an early stage, enabling definitive treatment of the primary tumour.

**Surgery**

There are several surgical approaches that may be pursued, depending on the location and size of the tumour. ‘Radical’ nephrectomy, where the entire kidney is removed, may be performed laparoscopically (i.e., keyhole surgery) or with an open approach, and is recommended for tumours >7 cm. Partial nephrectomy, often favoured where conserving kidney function is a priority, may require an open procedure. Enlarged local lymph nodes are typically removed at surgery.

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**Table 1. American Joint Committee on Cancer TNM staging system for renal cell cancer and estimated five-year prognosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour</th>
<th>Lymph nodes</th>
<th>Metastases</th>
<th>Estimated 5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0 or N1</td>
<td>M0</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>Tumour ≤7 cm, confined to kidney</td>
<td>None clinically enlarged or pathologically involved</td>
<td>No distant sites of tumour spread</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0 or N1</td>
<td>M0</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt;7 cm, confined to kidney</td>
<td>None clinically enlarged or pathologically involved</td>
<td>No distant sites of tumour spread</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0 or N1</td>
<td>M0</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>Tumour invades major blood vessels or fat around kidney (but not into adrenal gland or beyond Gerota’s fascia)</td>
<td>No involved lymph nodes (N0) OR presence of involved lymph nodes (N1)</td>
<td>No distant sites of tumour spread</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 or T2</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T4</td>
<td>M0 or M1</td>
<td></td>
<td>8%*</td>
</tr>
<tr>
<td></td>
<td>Tumour invades beyond Gerota’s fascia or into adrenal gland</td>
<td>Any N</td>
<td>Tumour spread to distant site(s)</td>
<td></td>
</tr>
</tbody>
</table>

*Probably underestimates current five-year survival rates (see Treatment for Stage IV).
Local therapies for small renal masses
In patients who have renal masses ≤3cm in a peripheral location, ablative therapies using heat (radiofrequency ablation; RFA) or cold (cryo-ablation) may be employed.

Active surveillance
Given that many small primary RCCs are incidentally picked up and can demonstrate an indolent course of growth, active surveillance of such lesions may be the most appropriate course of action in a patient whose risk of anaesthesia may not justify early surgery.

TREATMENT FOR STAGE IV CANCER
When RCC spreads beyond the kidney it typically goes to both local and distant lymph nodes and to the bones, lungs, liver and brain. Surgery to remove the primary tumour, called a cytoreductive nephrectomy (CN), is often undertaken even in the setting of distant secondary tumours, especially if it is causing pain or bleeding. Very occasionally, spontaneous regression of secondary tumours may occur after a CN. Drug treatments are the cornerstone of management in most people with Stage IV disease.

Drug treatments
Much progress has been made in the treatment of advanced (Stage IV) RCC in the last 10 years. Prognostic scoring systems have been developed based on blood test results and the time to development of secondary lesions. These classify patients into favourable, intermediate and poor risk groups that correlate with outcome in patients on targeted therapies.

Oral tyrosine kinase inhibitors (TKIs), such as sunitinib (Sutent) and pazopanib (Votrient), improve survival in patients with Stage IV RCC in comparison to interferon-alpha regimens. They target the vascular endothelial growth factor (VEGF) receptor that allows tumours to perpetuate growth by formation of new blood vessels. There are other anti-VEGF oral therapies, namely axitinib (Inlyta) and cabozantinib (Cometriq), that are effective in patients whose tumours have progressed on sunitinib or pazopanib. Side-effects of the anti-VEGF TKIs include fatigue, diarrhoea, high blood pressure, rash and thyroid dysfunction. Many of these can be managed with supportive medication, dose interruptions or dose reductions. The anti-VEGF TKIs are most effective in ccRCC; responses in other types are inferior.

Temsirolimus (Torisel) and everolimus (Afinitor) are drugs that block the mammalian target of rapamycin (mTOR) pathway, also implicated in RCC development. Temsirolimus has a demonstrated benefit in poor-prognosis RCC compared to interferon-alpha. Everolimus was previously the standard of care for second-line treatment; however, its use in this setting has now been superseded by cabozantinib and nivolumab (Opdivo). Side-effects of the mTOR inhibitor class include lung inflammation, rash, poor wound healing and diabetes.

Nivolumab is an immunotherapy that helps expose RCC to the patient’s immune system. Its use at present is in the second or third line of treatment after progression on an anti-VEGF TKI. The key advantage is that, in a proportion of patients, durable responses may occur beyond cessation of treatment. Nivolumab is well tolerated, although immune-related side-effects such as colitis and hepatitis can occur.

More specific information on the efficacy of these drug treatments is summarised in Table 2.

The median overall survival for metastatic RCC is around 29 months; however, this is likely to increase with the full range of therapies now available. Whether there is a gender difference in outcomes in the metastatic population remains to be explored.

Other treatments for advanced disease
Radiotherapy may be effective to treat bone pain or brain metastases. Occasionally, RFA may also be used in the treatment of lung metastases. In patients with low volume advanced disease who fall into a ‘good’ prognostic category, a ‘watch and wait’ approach may be adopted, with serial monitoring.
imaging to enable early initiation of drug treatments upon any worrying progression.23

Adjuvant therapy
‘Adjuvant’ therapy in oncology aims to reduce any microscopic cancer cells that may remain after definitive treatment (usually surgery) removes all visible disease. Recent studies involving sunitinib have shown conflicting results, and at present there is no standard of care.24,25

Conclusion
RCC is one of the more common types of cancer affecting men and may be silent for a long period of time, leading to late detection. Although drug treatments for the control of advanced disease have improved greatly in the last decade, capturing early tumours amenable to surgical resection gives the greatest chance of long-term cure. Men and their healthcare professionals should be aware that persistent flank pain, blood in the urine and unexplained malaise or weight loss should prompt review, especially in the context of a family history of RCC.

Declaration of interests: none declared.

REFERENCES
11. Motzer RJ, Bacik J, Mazumdar M. Prognostic factors for survival of patients with stage

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<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Proportion of patients with tumour shrinkage by ≥30%</th>
<th>Median duration of therapeutic benefit (months)</th>
</tr>
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<tbody>
<tr>
<td>First</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sunitinib19</td>
<td>Anti-VEGF</td>
<td>24%</td>
<td>9.5</td>
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<tr>
<td></td>
<td>Pazopanib19</td>
<td>Anti-VEGF</td>
<td>31%</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus20 (in poor-prognosis RCC)</td>
<td>mTOR inhibition</td>
<td>9%</td>
<td>5.5</td>
</tr>
<tr>
<td>Second</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Axitinib15</td>
<td>Anti-VEGF</td>
<td>19%</td>
<td>6.7</td>
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<tr>
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<td>Cabozantinib16</td>
<td>Anti-VEGF (with anti-MET activity)</td>
<td>21%</td>
<td>7.4</td>
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<tr>
<td></td>
<td>Nivolumab18</td>
<td>Anti-PD-1</td>
<td>24%</td>
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<td></td>
<td>Lenvatinib with everolimus21</td>
<td>Anti-VEGF with mTOR inhibition</td>
<td>43%</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>Everolimus18</td>
<td>mTOR inhibition</td>
<td>5%</td>
<td>4.4</td>
</tr>
<tr>
<td>Third</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Anti-PD-1</td>
<td>As for second line</td>
<td>As for second line</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib</td>
<td>Anti-VEGF (with anti-MET activity)</td>
<td>As for second line</td>
<td>As for second line</td>
</tr>
</tbody>
</table>

*Given the issues with use of standard response criteria in immunotherapy-treated patients, this figure likely underestimates the true duration of benefit.

Table 2. Drug treatments for advanced renal cell cancer licensed in the UK


