Renal cancer

Synonyms: RCC, hypernephroma, Grawitz' tumour

What is renal cancer?[1]

Renal cell carcinoma (RCC) is the most common of the tumours of the kidney in adults, accounting for over 80% of neoplasms arising from the kidney.[2] In children, Wilms' tumour is the most common. Benign tumours of the kidney are rare.

RCC originates from the proximal renal tubular epithelium. Renal cancer occurs in hereditary and non-hereditary forms, both of which are associated with structural alterations of the short arm of chromosome 3 (3p).

RCC can be further subdivided. Most RCCs are clear cell. Other less common kidney cancers include papillary, chromophobe, and other rare tumours of the nephron and collecting system.[3]

About 15% of renal tumours are benign. The other histological types of renal tumours include:

- Transitional cell carcinoma.
- Renal oncocytoma.
- Wilms' tumour.
- Angiomyolipoma - commonly seen in patients with tuberous sclerosis.
- Leiyomyosarcoma.
- Sarcoma.

- Adenoma - frequently found as an incidental finding at post-mortem; if diagnosed during life, it is treated with partial nephrectomy, due to histological similarity to adenocarcinoma.

How common is renal cancer? (Epidemiology) [2]

- Kidney cancer is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases (2016-2018).
- Incidence rates for kidney cancer in the UK are highest in people aged 85 to 89 (2016-2018). Each year around a third (34%) of all new kidney cancer cases in the UK are diagnosed in people aged 75 and over (2016-2018).
- Kidney cancer incidence rates in England in females are 40% higher in the most deprived quintile compared with the least, and in males are 17% higher in the most deprived quintile compared with the least (2013-2017).
- Incidence rates for kidney cancer are lower in the Asian and Black ethnic groups, and in people of mixed or multiple ethnicity, compared with the White ethnic group, in England (2013-2017).
- Approximately 2-3% of RCCs are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being von Hippel Lindau disease. [4]
- The incidence of renal cell carcinoma in the UK increased by 3.1% annually between 1993 and 2014. [5]
- Kidney cancer incidence rates are projected to rise by 15% in the UK between 2023-2025 and 2038-2040.

Risk factors [6]

- Risk factors include lifestyle, smoking, obesity and hypertension.
- Other risk factors include chronic kidney disease, tuberous sclerosis, renal transplant recipients and acquired renal cystic disease.

Renal cancer symptoms (presentation) [1] [7]

- More than 50% of patients with renal cell carcinoma are asymptomatic and diagnosed incidentally during imaging for unrelated issues. The use of ultrasound and CT scans has increased the detection of asymptomatic renal cell carcinoma.
- Many renal masses remain asymptomatic until late disease stages. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare and correlates with aggressive histology and advanced disease.
- Non-reducing or isolated right-sided varicocele and bilateral lower extremity oedema can also be symptoms of advanced disease through occlusion of the right testicular venous system that drains directly to the inferior vena cava. Bilateral lower-extremity oedema can also occur from tumour occlusion of the inferior vena cava.
- Approximately 30% of patients present with paraneoplastic disease, including neuromyopathy, anaemia, hypertension, polycythaemia, amyloidosis, elevated ESR, hypercalcaemia and abnormal LFTs.
- Fever, weight loss, persistent cough, adenopathy, and bone pain may indicate metastatic disease.

Spread

- Spread is into adjacent structures of the adrenal glands, liver, spleen, colon or pancreas. Local lymph nodes are often involved.
- It may extend into the renal vein and then into the inferior vena cava.
- The lungs are the most common site of metastases. The classical picture of cannon ball secondaries is almost diagnostic.
- It is one of the carcinomas to metastasise to bone where it produces osteolytic lesions.

Differential diagnosis

The differential diagnosis will depend upon the presentation. See the separate articles Abdominal Masses, Loin Pain and Haematuria which discuss the various causes.

Referral[8]

Refer people using a suspected cancer pathway referral (for an appointment within two weeks) for renal cancer if they are aged 45 and over and have:

- Unexplained visible haematuria without urinary tract infection; or
- Visible haematuria that persists or recurs after successful treatment of urinary tract infection.

Editor's note
Dr Krishna Vakharia, 16th October 2023 **Suspected cancer: recognition and referral**[8] The National Institute for Health and Care Excellence (NICE) has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

Investigations[1]

CT imaging, unenhanced, and after intravenous contrast, can verify the diagnosis and provide information on the function and morphology of the contralateral kidney and assess tumour extension, including extra-renal spread, venous involvement, and enlargement of lymph nodes and adrenals.

Abdominal US and MRI are supplementary to CT. Contrast-enhanced US can be helpful in specific cases. MRI is an alternative to abdominal CT and is useful in patients with allergy to intravenous contrast. It can also be used for the work-up of patients with possible venous involvement.

Chest CT is the most accurate for chest staging and is recommended in the primary work-up of patients with suspected renal cell carcinoma. In younger patients MRI may be offered as an alternative for follow-up imaging.

Percutaneous renal tumour biopsies are used:

- To obtain histology of radiologically indeterminate renal masses.

- To select patients with small renal masses for active surveillance.
- To obtain histology before (advantageous), or simultaneously with ablative treatments.
- To select the most suitable form of medical and surgical strategy in the setting of metastatic disease.

In patients with any sign of impaired renal function, a renal scan and total renal function evaluation using eGFR should always be undertaken. Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management regardless of biopsy results.

A genetic evaluation is recommended for patients aged ≤46 years, with bilateral or multifocal tumours and/or a first-degree or second-degree relative with renal cell carcinoma and/or a close blood relative with a known pathogenic variant and/or specific histological characteristics which suggest the presence of a hereditary form of renal cell carcinoma.

Staging[1]

The current consensus is to use the tumour, node and metastasis (TNM) 2017 system, as recommended by the European guidelines:

- T: primary tumour:
    - TX: primary tumour cannot be assessed.
    - T0: no evidence of primary tumour.
    - T1: tumour 7 cm or less in greatest dimension, limited to the kidney.
        - T1a: tumour 4 cm or less in greatest dimension, limited to the kidney.
        - T1b: tumour >4 cm but not more than 7 cm in greatest dimension.
    - T2: tumour >7 cm in greatest dimension, limited to the kidney:
        - T2a: tumour >7 cm in greatest dimension but not more than 10 cm.
        - T2b: tumours >10 cm limited to the kidney.
    - T3: tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota fascia:
        - T3a: tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades peri-renal and/or renal sinus fat, but not beyond Gerota fascia.
        - T3b: tumour grossly extends into the vena cava below the diaphragm.
        - T3c: tumour grossly extends into vena cava or its wall above the diaphragm or invades the wall of the vena cava.
    - T4: tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).

- N: regional lymph nodes:
    - NX: regional lymph nodes cannot be assessed.
    - N0: no regional lymph node metastasis.
    - N1: metastasis in regional lymph nodes.
- M: distant metastasis:
    - M0: no distant metastasis.
    - M1: distant metastasis.

TNM stage grouping

- Stage I: T1 N0 M0.
- Stage II: T2 N0 M0.
- Stage III:
    - T3 N0 M0.
    - T1/2/3 N1 M0.
- Stage IV:
    - T4 Any N M0.
    - Any T Any N M1.

Renal cancer treatment and management[1] [4]

Nephron-sparing surgery is a selective technique to maintain kidneys in patients while radical nephrectomy and partial nephrectomy are used to remove small tumours. In addition to surgical approaches, adjuvant therapy and targeted therapy are included in the treatment of metastatic renal cell carcinoma.[9]

Localised disease

Localised RCCs are best managed with partial/nephron-sparing nephrectomy rather than radical nephrectomy. Partial nephrectomy is unsuitable in some patients with localised RCC due to locally advanced tumour growth, unfavourable tumour location or significant health deterioration.

Lymphadenectomy should be restricted to staging as the survival benefit of extended LN dissection is unclear in patients with localised disease. In patients who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.

Partial nephrectomy can be performed, either by open, laparoscopic, or robot-assisted approach. Robot-assisted and laparoscopic partial nephrectomy are associated with shorter length of hospital stay and lower blood loss compared to open partial nephrectomy.

Alternatives to surgery:

- Active surveillance and watchful waiting: in selected patients (eg, elderly and comorbidities) initial monitoring of small renal masses (active surveillance), followed, if required, by treatment for progression is appropriate.
- Watchful waiting is reserved for patients whose comorbidities contra-indicate any subsequent active treatment and who do not require follow-up imaging, unless clinically indicated).
- Cryoablation or radiofrequency ablation are associated with less morbidity as compared to partial nephrectomy, at the cost of higher recurrence rates.

NICE has recommended that both laparoscopic nephrectomy and laparoscopic partial nephrectomy are safe and effective when undertaken by surgeons with special expertise in this technique.[10] [11]

NICE has also recommended that percutaneous RF ablation, laparoscopic cryotherapy, percutaneous cryotherapy and irreversible electroporation may be used as options in the treatment of kidney cancer.[12] [13] [14] [15]

Locally advanced disease

- In the presence of clinically positive lymph nodes, lymph node dissection is always justified but the extent of lymph node dissection is controversial.
- Low level data suggest that tumour thrombus in the setting of non-metastatic disease should be excised.
- Adjunctive procedures such as tumour embolisation or inferior vena cava filter do not appear to offer any benefits in the treatment of tumour thrombus.
- In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain.

Advanced/metastatic disease

Tumour nephrectomy is recommended in otherwise fit patients with metastatic disease. Tumour nephrectomy is curative only if all tumour deposits are excised. For most patients with metastatic disease, cytoreductive nephrectomy is palliative and systemic treatments are necessary.

Standard chemotherapy is considered ineffective in patients with RCC. However:

- Immunotherapy - IFN-α or interleukin 2 (ILN-2) can be considered in selected patients with a clear cell subtype histology. Aldesleukin (recombinant ILN-2) is licensed for metastatic RCC but not for patients with poor performance status **and** more than one organ with metastatic disease sites, **and** a period of less than 24 months between initial diagnosis of a primary tumour and date of evaluation of treatment.
- Some drugs with specific molecular targets have shown benefits in the treatment of advanced RCC.[16] [17]
- Sunitinib (a tyrosine kinase inhibitor) is recommended by NICE as first-line treatment for advanced or metastatic RCC in patients who are suitable for immunotherapy (eg, IFN-α 2a), are mobile and are fit enough for light work. Sunitinib inhibits the growth of cancer cells by blocking a group of closely related tyrosine kinase receptors.[18]

- Pazopanib (a tyrosine kinase inhibitor) is recommended by NICE as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy.[19]
- Everolimus is recommended as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy.[20]
- Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor thereby potentiating an immune response to tumour cells. Ipilimumab is a monoclonal antibody which causes T-cell activation resulting in tumour cell death. Nivolumab with ipilimumab is recommended by NICE as an option for untreated advanced renal cell carcinoma in adults whose disease is intermediate or poor risk.[21]

Metastasectomy and other local treatment strategies including whole-brain radiotherapy, conventional radiotherapy, stereotactic radiosurgery, stereotactic body radiotherapy (SBRT), CyberKnife® radiotherapy and hypofractionated radiotherapy can be considered and carried out for selected patients.

In widespread bone metastases, bisphosphonate therapy with zoledronic acid has been shown to reduce skeletal-related events in patients significantly and increase the time to the first skeletal-related event.

Complications

Paraneoplastic syndromes may develop and include:[4]

- Polycythaemia due to erythropoietin production.
- Hypercalcaemia due to production of a parathormone-like hormone.

Prognosis[2]

- 79.3% of people diagnosed with kidney cancer in England survive their disease for one year or more (2013-2017).
- 63.8% of people diagnosed with kidney cancer in England survive their disease for five years or more (2013-2017).

- It is predicted that 51.8% of people diagnosed with kidney cancer in England survive their disease for ten years or more (2013-2017).
- Kidney cancer survival in England is highest for people diagnosed aged under 50 years (2009-2013).
- Around three quarters of people aged 15-45 in England diagnosed with kidney cancer survive their disease for five years or more, compared with more than a third of people diagnosed aged 80 and over (2009-2013).
- Kidney cancer survival is improving and has increased in the last 40 years in the UK.
- When diagnosed at its earliest stage, 96% people with kidney cancer will survive their disease for one year or more, compared with 39% of people when the disease is diagnosed at the latest stage.
- When diagnosed at its earliest stage, 87% of people with kidney cancer will survive their disease for five years or more, compared with 12% of people when the disease is diagnosed at the latest stage.
- Five-year relative survival for kidney cancer in men and women is below the European average in England, Scotland, Wales and Northern Ireland.

Renal cancer prevention

- Cigarette smoking remains the major culprit but the incidence of smoking is not rising in parallel with the number of cases of RCC.[1]
- Obesity is increasing in Europe and the USA. Morbid obesity doubles the risk. People who are overweight but not obese are 35% more likely to develop RCC.
- Screening is currently confined to patients who have been identified as having one of the known genetic lineages linked with specific RCC subtypes.[22]

Further reading

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma; NICE Technology appraisal guidance, August 2009
- Macmillan Cancer Support
- Guidelines on Urothelial Carcinomas of the Upper Urinary Tract; European Association of Urology (2016)

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