Kidney Cancer

16

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Clinical Scenario

A 48 year old male with no significant medical history is referred to urology with visible haematuria. A contrast CT reveals bilateral enhancing heterogenous masses; 65 mm in the left upper pole as well as a contralateral 26 mm right upper pole lesion (see CT images below in Fig. 16.1). No other sites of metastases were seen.

What is the most appropriate investigation and management for this patient?

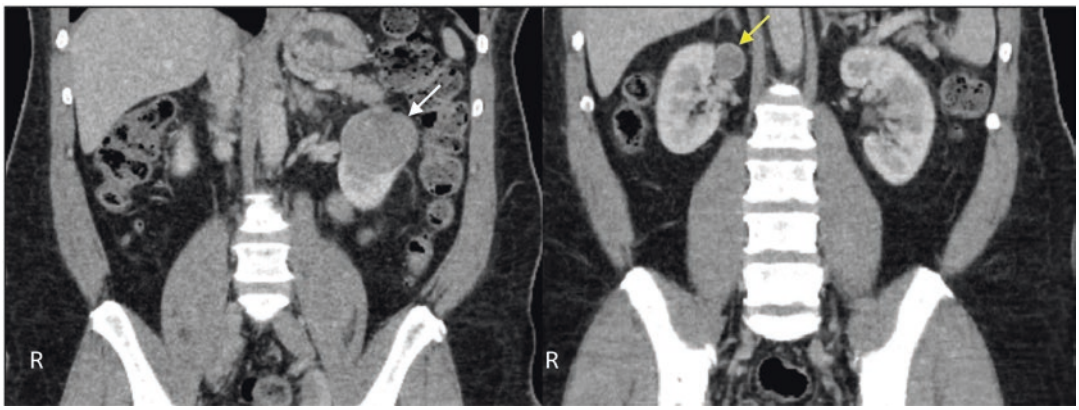

Fig. 16.1 Coronal contrast-enhanced CT scans showing a 65 mm left sided upper pole lesion (white arrow, left) and 23 mm right upper pole lesion (yellow arrow, right)

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Introduction

This chapter will discuss malignancies arising from the renal parenchyma/cortex. These are a heterogenous group of cancers. Renal cell carcinoma (RCC) is the most common solid lesion in the kidney and accounts for the majority of primary renal malignancies (approximately 90%) [1]. It will therefore be our primary focus for the purposes of this chapter (Tables 16.1 and 16.2).

Table 16.1 Principal Subtypes of RCC [1, 2]

	Underlying genetic/histological characteristics	Prognosis
Clear-cell (cc-RCC) *(75% of RCC)*	Loss of chromosome 3p and mutation of the von Hippel-Lindau (*VHL*) gene frequently found.	Worst prognosis of the three subtypes.
Papillary *(15% of RCC)*	Type I—germline mutations of MET Type II—activation of the NRF2-ARE pathway.	Low malignant potential, over 75% can be treated by nephron sparing surgery [1]. Type I has best prognosis.
Chromophobe *(5% of RCC)*	Typical genetic changes include loss of chromosomes Y, 1, 2, 6, 10, 13, 17, 21.	Good prognosis, high 5 and 10 year recurrence free survival [1].

Table 16.2 Other non-RCC renal tumour subtypes [1, 2]

Tumour type	Clinical	Malignant potential	Management
Renal medullary carcinoma	Rare tumour, median age of diagnosis 28 years [1]. Associated with sickle cell disease.	Malignant	Aggressive cancer with most patients presenting with metastatic disease. Radical nephrectomy recommended, even in early disease, along with chemotherapy. Not responsive to targeted anti-angiogenic drugs including tyrosine kinase inhibitors.
Carcinoma associated with ESKD; acquired cystic disease - associated RCC	The lifetime risk of developing RCC is 10 times higher for ESKD patients than the general population [1]. RCCs are generally multifocal and bilateral.	Malignant	RCC associated with ESKD less aggressive than sporadic RCC. Surgical management.
Papillary adenoma	Benign neoplasm arising from renal tubular epithelium. Measure ≤15 mm in diameter. Histologically and genetically indistinguishable from papillary RCC. Estimated prevalence of 20% based on autopsy series [3].	Benign	Surveillance.
Hereditary kidney tumours	5–8% of RCCs are hereditary. Examples of syndromes associated with development of renal tumours include: • Von Hippel-Lindau (VHL) syndrome • Birt-Hogg-Dubé syndrome (BHD) • Hereditary pRCC • Tuberous sclerosis complex (TSC) • Hereditary leiomyomatosis RCC (HLRCC) • Germline succinate dehydrogenase (SDH) mutation	Variable	May require repeated surgeries, nephron sparing approach favoured. • HLRCC and SDH are aggressive and require immediate surgical intervention • Active surveillance for VHL, BHD and HPRCC—monitoring growth, size and location.

Table 16.2 (continued)

Tumour type	Clinical	Malignant potential	Management
Angiomyolipoma (AML)	Benign mesenchymal tumour—occurs sporadically or as part of tuberous sclerosis complex (TSC). Slow growth rate, minimal morbidity. Larger AMLs can cause localised pain and spontaneous bleeding, which can be fatal.	Benign	Active surveillance monitoring risk factors for bleeding—Tumour size, vascularity, and presence of tuberous sclerosis complex [1]. Indications for active treatment include: • Persistent pain • Acute or repeated bleeding • Large size (>4 cm) In patients with tuberous sclerosis complex (TSC), AML size and vascularity may be reduced by mTOR pathway inhibition.
Renal oncocytoma	Benign tumour, representing 18% of solid renal tumours [1]. Slow growing.	Benign	Challenging to diagnose with CT/MRI imaging as similar appearances to RCC. Mainstay of treatment is surveillance; radical/partial nephrectomy is considered if increasing size. Consideration of renal mass biopsy may reduce unnecessary surgical intervention.

Epidemiology and Causes

Kidney cancer is the ninth most commonly occurring cancer in men and the 14th most commonly occurring cancer in women. The age-standardised rate per 100,000 in the US in 2018 was 10.9 per 100,000 [4].

The rate of new kidney cancers has been increasing since the 1990s, though seems to now be plateauing. This rise is thought to be at least partially attributable to the increasing numbers of asymptomatic cancers detected incidentally through CT scanning for other indications.

It is estimated that half of kidney cancers could potentially be prevented by weight loss and tobacco smoking, which are the most potent risk factors [5] (Table 16.3).

Table 16.3 Risk factors associated with kidney cancer

Risk Factor	Comments
Smoking	Risk increases proportional to amount smoked. Kidney cancer risk is 33% higher in current smokers compared with non-smokers [5]
Obesity	There is an increased risk of kidney cancer with increasing BMI. Multiple proposed mechanisms include adipokine secretion from adipose tissue promoting tumour growth
Hypertension	Well established risk factor, proportional to the blood pressure [6]
Workplace exposures	Certain occupation exposures such as asbestos, cadmium, trichloroethylene
Male sex	Twice as common in men as women
Advanced kidney disease	Those with ESKD on dialysis have been shown to have a 2.3 times increased risk of kidney cancer [7] this risk increases further in those with ADPKD [8]
Genetic/ hereditary associations	Von Hippel-Lindau (VHL) syndrome, Hereditary papillary renal cell carcinoma (HPRCC), Hereditary leiomyoma-renal cell carcinoma (HLRCC), Birt-Hogg Dube (BHD) syndrome, Familial renal cancer, Cowden syndrome, Tuberous sclerosis complex (TSC)

Genetic Basis of Kidney Cancer

Kidney cancers are heterogenous and there are many associated genetic mutations. These have an important clinical relevance in that they are the basis of the targeted and immunomodulatory therapies which are key to treating advanced kidney cancer. This will be explored later in the chapter.

The *VHL* tumour suppressor gene is the most frequently mutated gene in sporadic RCC, and it is often the first mutation to occur. In normal cells, the VHL-containing complex targets the alpha subunit of hypoxia inducible factor (HIF-a) for degradation. The mutation of *VHL* and subsequent inactivation of VHL leads to accumulation of HIF-a, leading to uncontrolled activation of HIF target genes, including vascular endothelial growth factor (VEGF), which control angiogenesis and cellular proliferation.

The mutation in *VHL* is one of multiple potential genetic mutations which may occur in the development of RCC. Other genetic mutations frequently associated with RCC include *PBRM1, SETD2, BAP1* which, like *VHL,* are all located on the short arm of chromosome 3 (Fig. 16.2).

Other RCCs are characterised by mutations in mammalian target of rapamycin (*mTOR*), a protein kinase involved in the regulation of cell growth and proliferation which has been implicated in the development of kidney cancer.

In recent years, there has been much interest in the immunological factors that allow tumour cells to proliferate. One such focus is the programmed cell death protein 1 (PD-1) receptor and its ligand (PD-L1). PD-1 is a cell surface receptor which regulates T cell activation, promoting apoptosis in antigen specific T cells. PD-1, PD-L1 and PD-L2 have been found to be abnormally expressed by tumour cells and lymphocytes in the tumour microenvironment, where their inhibitory action assists the cancer cells' evasion of the immune response.

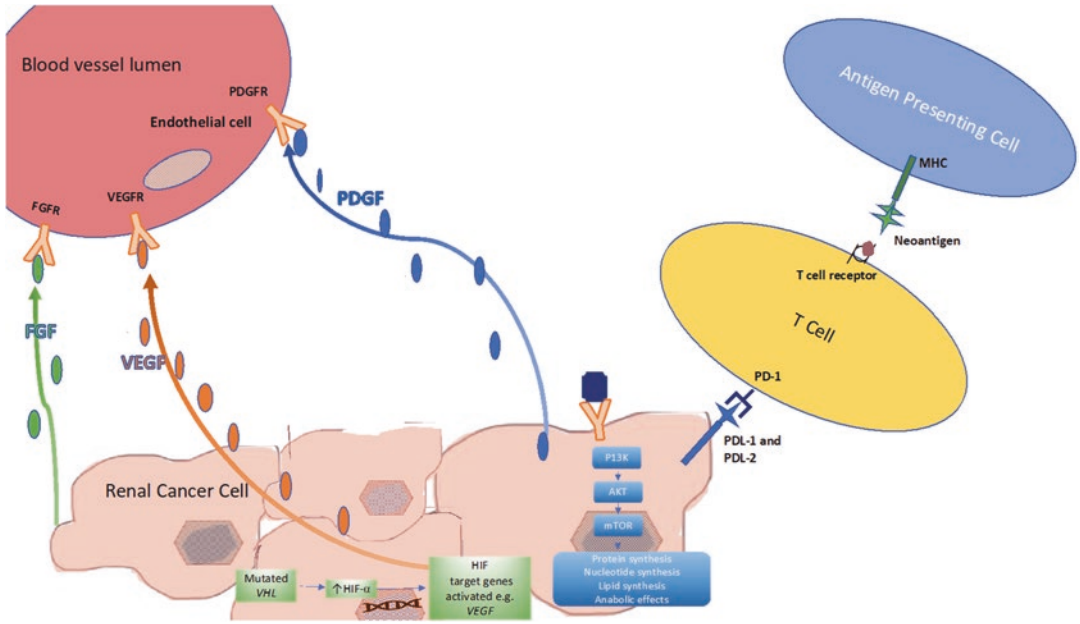


Fig. 16.2 Pathophysiological mechanisms involved in the development of renal cell carcinoma (*Adapted from Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med. 2017 Jan 26;376* (4)*:354–366* [9])
Hypoxia-inducible factor (HIF), VEGF (vascular endothelial growth factor) FGF (fibroblast growth factor), FGFR (FGF receptor), PDGF (platelet-derived growth factor), PDGFR (PDGF receptor) and VEGFR (VEGF receptor), mechanistic target of rapamycin (mTOR), MHC (major histocompatibility complex), PD-1 (programmed cell death protein) PD-L1 (PD-1 ligand, and PI3K (phosphatidylinositol 3-kinase)

Clinical Presentation

More than 50% of RCCs are diagnosed incidentally. The classic presenting triad includes **haematuria, flank pain and a palpable abdominal mass**. Less than 10% of patients present with these symptoms however, and those who do are likely to have locally advanced disease [1] (Fig. 16.3 and Table 16.4).

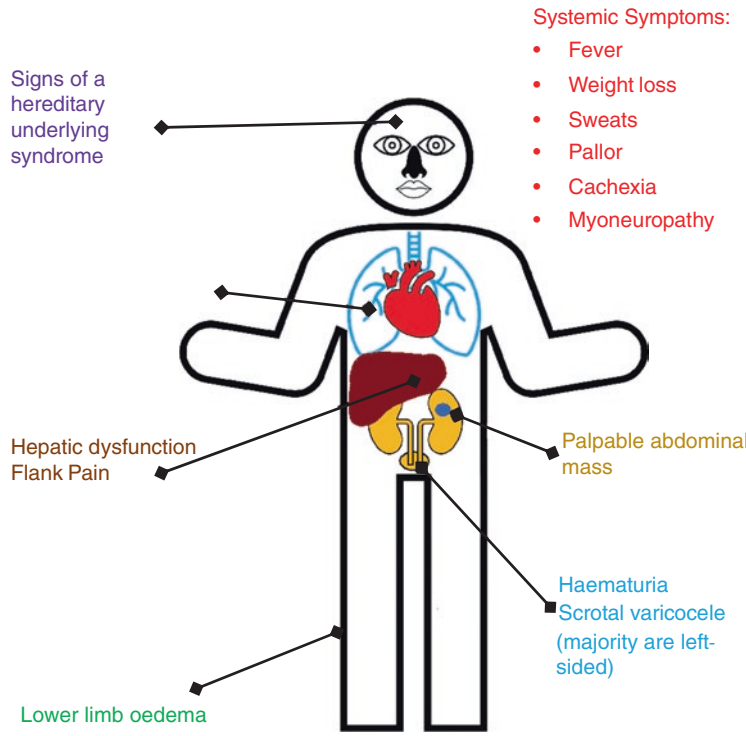


Fig. 16.3 Clinical Presentation of RCC [1]

Table 16.4 Paraneoplastic Syndromes associated with RCC [1]

Paraneoplastic phenomena	Cause(s)	Clinical manifestation
Fever	Cytokine production by the tumour cells, particularly IL-1, IL-6 and TNF-β	Fever, night sweats
Anaemia	Inflammation/chronic disease	Fatigue, breathlessness
Erythrocytosis	Excess erythropoietin (EPO)	Occurs in 1–5% of patients with advanced RCC
Hypercalcaemia	Over production of PTH-r protein. Lytic bone lesions.	Clinical signs of hypercalcaemia— Constipation, confusion Bone pain
Hypercortisolism	Excess ACTH	Cushing's syndrome
Hepatic dysfunction	Liver metastases. Stauffer syndrome refers to hepatic dysfunction in the absence of liver metastases	Jaundice, itch, right upper quadrant pain May be asymptomatic
Secondary (AA) amyloidosis	Deposition of fibril proteins.	Clinical presentation depends on organ affected

Given the paraneoplastic presentations of RCC, patients can present with a myriad of symptoms related to this, including:

- Systemic symptoms of fever, weight loss, sweats, pallor, cachexia, myoneuropathy
- Signs of hepatic dysfunction
- Lower limb oedema—may represent inferior vena cava involvement
- Scrotal varicocele
- Signs of an underlying hereditary syndrome

Investigations

Practice point 1
Imaging is key to diagnosis: Most renal masses can be diagnosed accurately by imaging alone

The most important criterion for differentiating malignant lesions is the presence of enhancement, with contrast enhanced CT and MRI being the modalities of choice. For the diagnosis of complex renal cysts, MRI may be preferable: it has higher sensitivity and specificity for small cystic renal masses and tumour thrombi. Contrast enhanced ultrasound also has a high sensitivity and specificity.

The Bosniak Classification is used to stratify cysts by their radiological features on cross-sectional imaging and thus determine a suitable work up and follow up plan (Table 16.5).

Table 16.5 Bosniak Classification of Renal Cysts [1]

Bosniak Category	Features	Clinical implications
I	• Simple cyst • Hairline-thin wall without septa, calcification or solid components • Non-enhancing	Benign, no follow up needed
II	• Minimally complex • May contain a few hairline-thin septa • Fine calcification in wall or septa • Non-enhancing, high attenuation • <3 cm in size	Benign, no follow up needed
IIF	• Minimally complex • May contain more hairline-thin septa with non-measurable enhancement • May contain calcification, nodular or thick	Some are malignant, require US / CT / MRI follow up over 5 years at 6 monthly intervals
III	• Indeterminate cystic mass • Thickened, irregular walls or septa with enhancement	Over 50% are malignant[1] Need active surveillance or surgery
IV	• Clearly malignant • Solid mass with large cystic or a necrotic component	100% malignant Surgical intervention required.

Renal Tumour Biopsy

The vast majority of kidney cancer diagnoses are made on the basis of the radiological findings. In certain situations however, tumour biopsy is indicated (Table 16.6).

Biopsy should be avoided in comorbid and frail patients who, regardless of histology, would not be considered for active management [1].

Percutaneous sampling can be performed with local anaesthesia under US or CT guidance with needle core biopsy. Given concerns regarding tumour seeding along the needle tract, a co-axial technique is recommended. When performed by experienced operators, core biopsy carries a high diagnostic yield, with a metanalysis reporting sensitivity of 99.1% and specificity of 99.7% for the diagnosis of malignancy [10]. In cases where there is a suspicion of malignancy but the biopsy result is non-diagnostic, a repeat biopsy or surgical exploration should be considered [1] (Fig. 16.4).

A larger gauge needle or cannula is advanced into the mass; once adequately positioned a smaller needle is placed through it in order to obtain tissue. This allows for multiple needle biopsies via only 1 point of access, thereby reducing risk of tumour seeding.

Table 16.6 Indications for renal tumour biopsy [1]

Indications for renal tumour biopsy [1]
• Further assessment of radiologically indeterminate masses or in the presence of another primary malignancy
• Prior to ablative treatments (cryotherapy/radiofrequency ablation)
• Where active surveillance is being considered
• To select most suitable treatment strategy in metastatic disease

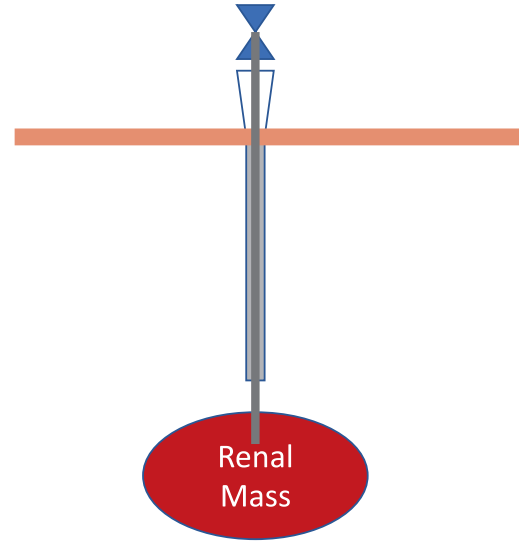


Fig. 16.4 Co-axial technique for biopsy of a kidney mass

Diagnosis and Classification

The approach to classifying renal cell carcinoma involves consideration of both the **stage** (how locally advanced the tumour is) and **grade** (the resemblance of the tumour cells to healthy cells). The TNM classification is universally recognised as the staging tool of choice (Tables 16.7, 16.8, 16.9 and Fig. 16.5).

Table 16.7 TNM Classification [1]

T – Primary Tumour	N – Regional Lymph Nodes	M – Distant metastases
T1 – Tumour ≤ 7 cmin greatest dimension, limited to kidney o **T1a** – Tumour ≤ 4 cm o **T1b** – Tumour >4 cm but ≤ 7cm	**N0** – No regional lymph node metastases	**M0** – No distant metastasis
T2 – Tumour >7 cm in greatest dimension but limited to kidney o **T2a** - Tumour >7 cm but ≤ 10cm o **T2b** – Tumour >10 cm but limited to the kidney	**N1** – Metastasis in regional lymph nodes.	**M1** – Distant metastasis
T3 – Tumour extends into major veins or perinephric tissues but not into ipsilateral adrenal gland and not beyond Gerota's fascia o **T3a** - Tumour extends into renal vein or invades perirenal fat but not beyond Gerota fascia o **T3b** – Tumour extends into vena cava below diaphragm o **T3c** – Tumour extends into vena cava above the diaphragm	**NX** – Regional lymph nodes cannot be assessed	
T4 – Tumour invades beyond Gerota's fascia		

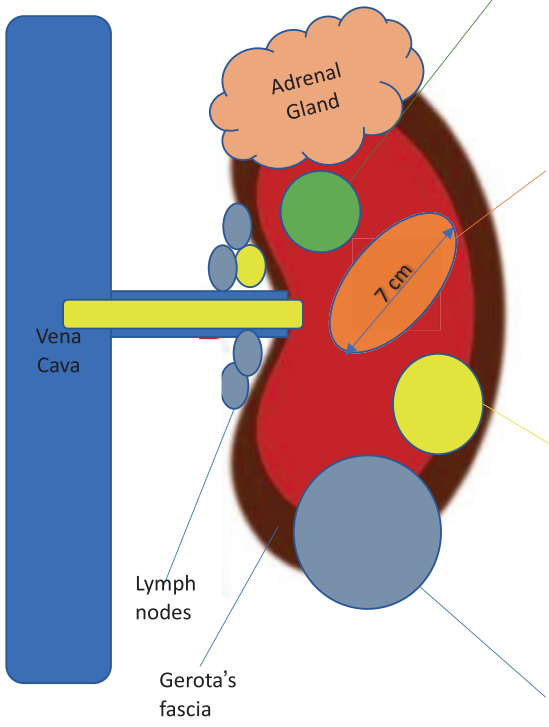
Table 16.8 TNM Stage Grouping [1]

The TNM staging is summarised as RCC Stage 1-4:

Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T3 T1, T2, T3	N0 N1	M0 M0
Stage 4	T4 Any T	Any N Any N	M0 M1

Table 16.9 World Health Organisation (WHO)/ International Society of Urologic Pathology (ISUP) Tumour Grading [1]

Grade 1	Nucleoli absent or inconspicuous and basophilic at 400 x magnification
Grade 2	Nucleoli clearly visible and eosinophilic at 400 x magnification
Grade 3	Nucleoli conspicuous and eosinophilic at 100 x magnification
Grade 4	Extreme nuclear pleomorphism, multinucleate cells, rhabdoid or sarcomatoid differentiation.



T1

Tumour <7 cm in greatest dimension and limited to kidney

T1a – Tumour ≤ 4 cm
T1b – Tumour >4 cm but ≤ 7 cm

T2

Tumour >7 cm in greatest dimension but limited to kidney.

T2a – Tumour >7 cm but ≤ 10 cm
T2b – Tumour >10 cm but limited to kidney

T3

Tumour extends into major veins or perinephric tissues but not into ipsilateral adrenal gland and not beyond Gerota's fascia.

T3a – Tumour extends into renal vein or invades perirenal fat but not beyond Gerota's fascia
T3b – Tumour extends into vena cava below diaphragm
T3c – Tumour extends into vena cava above the diaphragm

T4

Tumour invades beyond Gerota's fascia

Fig. 16.5 Staging of kidney cancer [1]

Management

Surgery

When patients present with localised disease, the mainstay of treatment is surgery, which can be curative. It is therefore the preferred first line treatment for the majority of patients with stage I, II or III disease.

Practice Point 2
Surgery is the first line treatment for localised disease

Surgery can include both partial nephrectomy (PN), also known as "nephron sparing" surgery (NSS) or radical nephrectomy (RN), which involves excision of the entire kidney and Gerota's fascia. Excision of the ureter along with the kidney is a nephroureterectomy and performed for urothelial cell malignancy of the upper tract. Imperative indications for PN include a solitary kidney, bilateral renal tumours or patients with syndromes pre-disposing to renal malignancy.

Patients with advanced or metastatic disease with a favourable prognosis who have a resectable primary tumour may also benefit from surgical resection where this is technically feasible

Table 16.10 Comparison between partial and radical nephrectomy [1]

Partial nephrectomy (PN) "Nephron sparing"	Radical nephrectomy (RN)
Preferred option for all T1a and some T1b/T2 tumours.	Option for larger tumours or more locally invasive disease where PN not possible
• A Cochrane review found that for localised disease, PN was associated with reduced time to death of all-cause mortality. Serious adverse events, CSS and time to recurrence were similar between groups[10] • Several retrospective analyses have suggested a decreased cardiovascular specific mortality with PN versus RN[1] • PN should be surgery of choice, even if it necessitates an open procedure where RN could be minimally invasive • Absolute indications for PN include: o a solitary kidney o bilateral renal tumours o patients with syndromes pre-disposing to renal malignancy • PN is preferred option for patients with pre-existing CKD to limit progression of ESKD requiring kidney replacement therapy (KRT)	• Minimally invasive vs open approach – no RCT has addressed oncological outcomes with either approach though minimally invasive associated with lower morbidity • Less likely to have positive surgical margins with RN vs PN[11]

(Table 16.10). For most patients with metastatic disease further systemic treatment is then warranted which will be discussed in more detail below. When surgical resection is performed in the presence of metastatic disease this is termed a cytoreductive nephrectomy (CN).

Adrenalectomy

Ipsilateral adrenalectomy during PN or RN has not been found to have a survival advantage unless there is clinical evidence of gland invasion (T4 disease) [1].

Lymph Node Dissection (LND)

The only randomised trial to date has not shown a survival advantage of LND in localised disease [13]. Retrospective studies have shown a survival benefit with visible LN disease [14].

Practice Point 3

Despite attempted curative treatment with nephrectomy (either partial or radical), approximately 30% of patients with ccRCC with localised disease will go onto develop metastases [15]

Alternatives to Surgery

Alternatives to surgery include:

- Watchful waiting
- Active Surveillance
- Cryoablation
- Radiofrequency Ablation

Watchful Waiting & Active Surveillance

The increasing incidental detection of small renal masses (SRMs), especially in a predominantly elderly population, has led to the development of active surveillance protocols. In carefully selected patients, this may be an appropriate initial strategy to monitor their renal mass, which could then be treated at a later date if it is seen to progress. Studies suggest that up to 20% of small renal masses are benign, with only 20% having an aggressive phenotype [16].

Active surveillance differs from watchful waiting, which is reserved for those patients who would not be candidates for active treatment, and who therefore do not usually require follow up imaging (Fig. 16.6).

Other less-invasive treatments are also available for those who may not be fit for surgery,

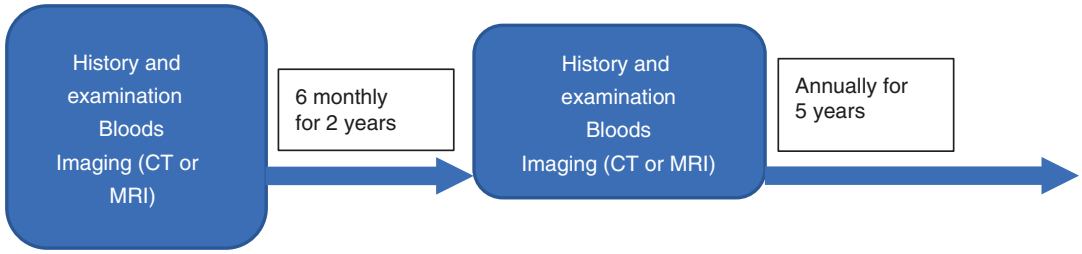


Fig. 16.6 Follow up of patients under active surveillance [1]

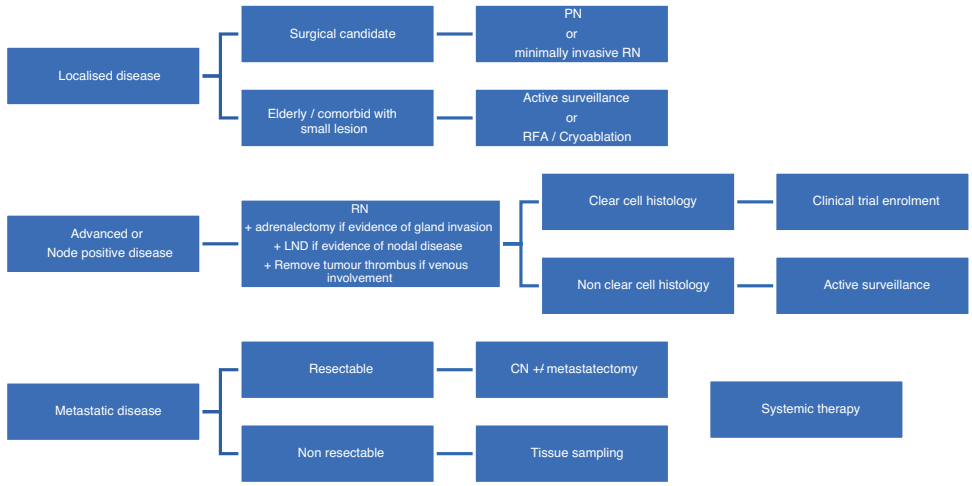


Fig. 16.7 Management of Kidney Cancer [1]
PN Partial nephrectomy, *RN* Radical nephrectomy, *RFA* Radiofrequency ablation, *CN* Cytoreductive nephrectomy, *LND* Lymph node dissection

have small (<4 cm tumours) or those who have multiple and/ or bilateral tumours. These treatments include **cryotherapy** and **radiofrequency ablation**. There are currently no data demonstrating any oncological benefit of these treatments over PN, although benefit has been shown in reduction in loss of kidney function. Increased local recurrence has been seen when compared to partial nephrectomy but cancer specific survival is similar [17].

Cryoablation

Cryoablation can be performed by either the percutaneous or laparoscopic route, with no significant difference in complication between the two routes. Under ultrasound or CT guidance, a probe is inserted into the tumour through which an argon coolant is delivered at subfreezing temperatures. This forms an 'ice ball' around the probe tip, destroying the tumour tissue. Helium is then passed through the probe to induce a slow thaw. In most cases, two freeze-thaw cycles are performed.

Radiofrequency Ablation (RFA)

Percutaneous RFA can be carried out under local anaesthesia and sedation or general anaesthetic. One or more radiofrequency electrodes are inserted percutaneously into the tumour under imaging guidance. Radiofrequency energy is then delivered via the electrode to create high temperatures and destroy the tumour tissue.

Figure 16.7 summarises the approach to management of kidney cancer.

Systemic Therapy

Practice Point 4
Small molecule inhibitors, targeted therapies and immune checkpoint-based immunotherapy form the treatment pathway for advanced or metastatic kidney cancer.
There is no role for chemotherapy [1]

Treatment options are selected based on risk scoring and histology. The most commonly used risk scoring models are the Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model or the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria. Here, we will focus on the IMDC criteria which is most commonly used (Table 16.11 and Fig. 16.8). The MSKCC calculator is based on the older and no longer utilised immunotherapies, IL2/IFN-α. The mechanism of action of systemic therapies are shown in Table 16.12 and Fig. 16.9.

Table 16.11 International Metastatic RCC Database Consortium (IMDC) criteria for predicting survival in patients with metastatic RCC [1]

IMDC criteria: Factors predicting poorer outcome include
• Less than one year from time of diagnosis to systemic therapy • Performance status <80% (Karnofsky performance status (KPS) scale) • Haemoglobin less than lower limit of normal • Calcium greater than upper limit of normal • Neutrophils greater than upper limit of normal • Platelets greater than upper limit of normal
Favourable risk: No prognostic factors **Intermediate risk: 1–2 prognostic factors** **Poor risk: 3 or more prognostic factors**

Table adapted from https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-score-rcc

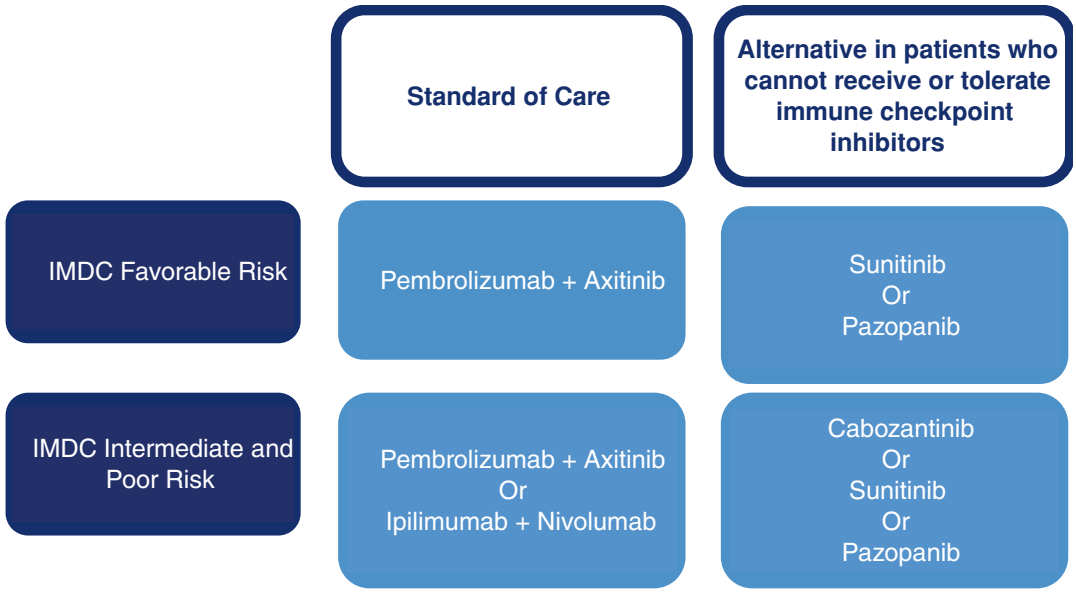


Fig. 16.8 Selection of therapy in metastatic kidney cancer (Adapted from EAU Guidelines [1])

Table 16.12 Systemic therapies used in the treatment of advanced kidney cancer

	Mechanism of Action	Agents
Targeted Therapies	Tyrosine kinase inhibitors	Sorafenib, sunitinib, pazopanib, axitinib, Lenvatinib, cavozantinib
	Monoclonal antibody against circulating VEGF	Bevacizumab
	mTOR inhibitors	Temsirolimus, everolimus
Immunotherapy	PD-1 inhibitors	Pembrolizumab, nivolumab
	PDL-1 inhibitors	Avelumab
	CTLA-4 inhibitors	Ipilimumab

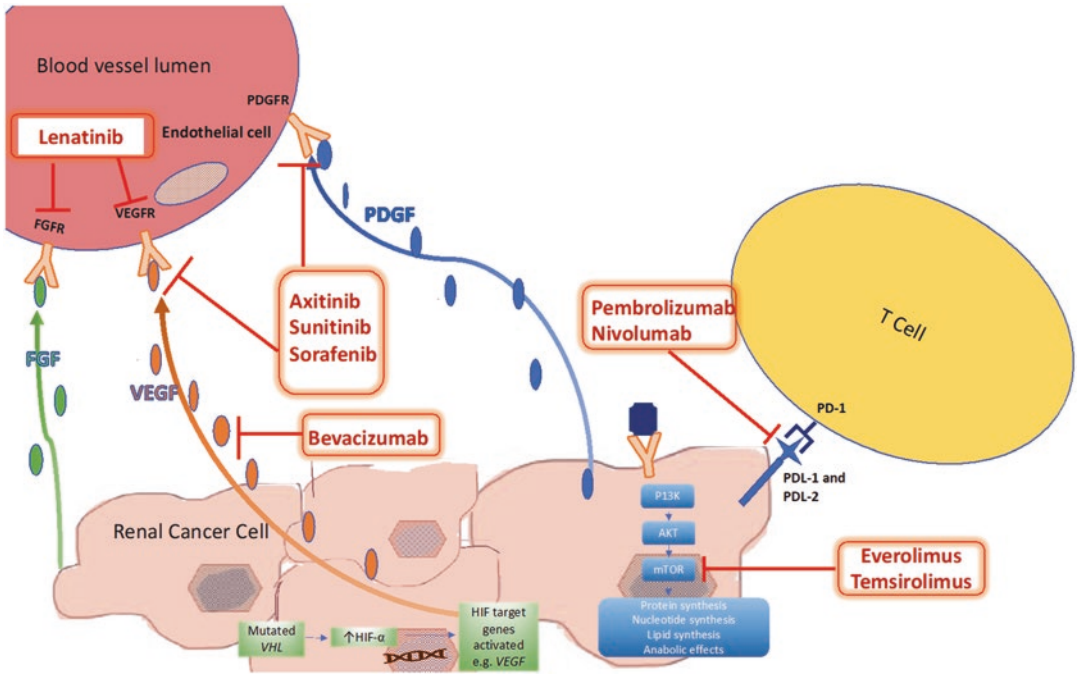


Fig. 16.9 Mechanism of action of targeted and immunological therapies
(*Adapted from Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med. 2017 Jan 26;376* (4)*:354–366* [9])
Hypoxia-inducible factor (HIF), VEGF (vascular endothelial growth factor) FGF (fibroblast growth factor), FGFR (FGF receptor), PDGF (platelet-derived growth factor), PDGFR (PDGF receptor) and VEGFR (VEGF receptor), mechanistic target of rapamycin (mTOR), MHC (major histocompatibility complex), PD-1 (programmed cell death protein) PD-L1 (PD-1 ligand, and PI3K (phosphatidylinositol 3-kinase)

Prognosis

The prognosis depends on stage of the kidney cancer as shown in Fig. 16.10

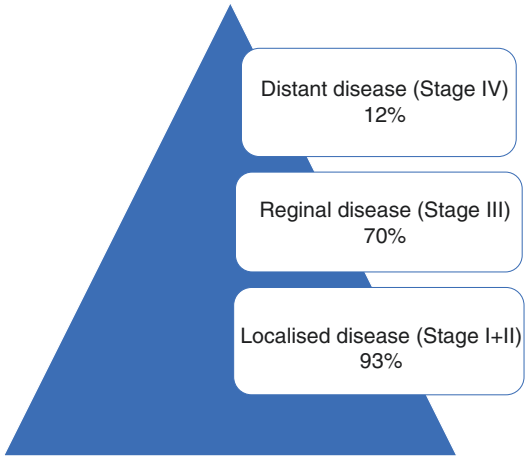


Fig. 16.10 Renal Cell Cancer 5 year percentage survival by stage [18]

Follow up

Surveillance following treatment aims to detect local recurrence or metastatic disease while the patient is still curable. Controversy exists regarding the optimal duration/intervals for follow up of patients who have completed treatment for RCC, and there is no existing evidence base to guide clinicians. The surveillance modality is guided by the individual patient's risk profile. Factors increasing risk include larger tumours (>7 cm), or when there is a positive surgical margin. Follow up following cryoablation or RFA may be more intensive due to the higher recurrence rate (Table 16.13).

Practice Points

1. **Imaging is key to diagnosis:** most renal masses can be diagnosed accurately by imaging alone
2. Surgery is the first line treatment for localised disease
3. Despite attempted curative treatment with nephrectomy (either partial or radical), approximately 30% of patients with ccRCC with localised disease will go onto develop metastases [15]
4. **Small molecule inhibitors, targeted therapies and immune checkpoint-based immunotherapy** form the treatment pathway for advanced or metastatic kidney cancer; **There is no role for chemotherapy** [1]

Table 16.13 Proposed Surveillance Schedule (Adapted from EAU Guidelines [1])

Risk Profile	Surveillance interval							
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	>3 year
Low	-	CT	-	CT	-	CT	-	CT every 2 years
Intermediate	-	CT	CT	-	CT		CT	CT yearly
High	CT	CT	CT	CT	CT	-	CT	CT yearly

(CT should be contrasted if possible, or appropriate imaging schedule agreed with radiologists)

Conclusions

The treatment of kidney cancer has evolved rapidly over the preceding two decades with the advent of targeted and immunotherapies. In future, these treatment modalities are likely to become more individualised with the use of genetic sequencing and biomarkers.

As we reflect on the 48-year-old gentleman with haematuria and two solid kidney lesions identified on CT imaging, whom we met at the start of this chapter, his case was discussed in a urological multidisciplinary meeting. On review of his imaging, the lesions were thought to be radiologically indeterminate: a needle core biopsy was performed on the left, which revealed an ISUP Grade 2 Papillary RCC. A left-sided laparoscopic radical nephrectomy was performed. Histology confirmed papillary RCC, stage T1a. Follow-up using a CT scan was planned 6 months post-operatively for surveillance of the contralateral mass. A fast rate of growth would prompt a biopsy and subsequent partial nephrectomy if this contralateral lesion was also found to be malignant.

Appendix 1

Table 16.14 Karnofsky Performance Status Score *(adapted from mdcalc.com/karnofsky-performance-status-scale)* [19]

Description	Points Assigned	Description
Normal no complaints; no evidence of disease	100	Able to carry on normal activity and to work; no special care needed
Able to carry on normal activity; minor signs or symptoms of disease	90	
Normal activity with effort; some signs or symptoms of disease	80	
Cares for self; unable to carry on normal activity or to do active work	70	Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
Requires occasional assistance, but is able to care for most personal needs	60	
Required considerable assistance and frequent medical care	50	
Disabled; required special care and assistance	40	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
Severely disabled; hospital admission is indicated although death not imminent	30	
Very sick; hospital admission necessary; active supportive treatment necessary	20	
Moribund; fatal processes progressing rapidly	10	
Dead	0	n/a

Adapted from: Karnofsky DA Burchenal JH. (1949). 'The Clinical Evaluation of Chemotherapeutic Agents in Cancer.' In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196

Questions

1. Which of the following is not a recognised risk factor for the development of kidney cancer?
   A. Smoking
   B. Obesity
   C. Asbestos exposure
   D. Alcohol
   E. Male sex

Answer: D

   A. **Incorrect**—Smoking is a well-established risk factor for kidney cancer.
   B. **Incorrect**—The risk of developing kidney cancer increases with BMI.
   C. **Incorrect**—Asbestos, along with other occupational exposures such as trichloroethylene, increase the risk of kidney cancer
   D. **Correct**—In fact, alcohol has been found to have a protective effect, whereby those who drink up 2 alcoholic drinks per day have a reduced risk of kidney cancer compared with non-drinkers. Alcohol intake is however associated with an increased risk of other diseases and cancers in other solid organs.
   E. **Incorrect**—Kidney cancer is twice as common in men compared to women.

2. As far as the presenting features of kidney cancer are concerned, which of the following statements is true?
   A. Haematuria, flank pain and a palpable abdominal mass is the recognised presenting triad for the majority of patients.
   B. More than half of patients present with a manifestation of a paraneoplastic syndrome rather than symptoms of the RCC itself.
   C. The majority of kidney cancers are diagnosed incidentally
   D. Varicoceles are a common presenting symptom in men.
   E. Absence of haematuria confers a more favourable prognosis**Answer: C**

   A. **Incorrect**—the classical triad of haematuria, flank pain and a palpable abdominal mass is seen in <10% of patients.
   B. **Incorrect**—Most patients are asymptomatic and diagnosed incidentally.
   C. **Correct**—Most kidney cancers are diagnosed incidentally through imaging for other reasons.
   D. **Incorrect**—Scrotal varicoceles are a rare sign of kidney cancer.
   E. **Incorrect**—Absence of haematuria alone does not necessarily confer a more favourable prognosis. However, where patients do present with the classical triad of haematuria, flank pain and a palpable abdominal mass, they are more likely to have locally advanced disease.

3. An 84 year old lady presents to the emergency department with abdominal pain and confusion. She has a known 3 cm lesion on the lower pole of the left kidney (Bosniak IIF) which is under active surveillance by her urologist. On admission her blood tests demonstrate the following: adjusted calcium 3.1 mmol/L, PTH 15 pmol/L, vitamin D 30 nmol/L, creatinine 80 μmol/L (eGFR 64 ml/min/1.73 m [2]). Her other blood tests are unremarkable. What is the most likely cause of her hypercalcaemia?
   A. Production of PTH related peptide
   B. Primary hyperparathyroidism
   C. Metastatic bone disease
   D. Vitamin D deficiency
   E. Secondary hyperparathyroidism.

Answer: B

   A. **Incorrect**—production of PTH related peptide would lead to hypercalcaemia which in turn would cause the PTH to be suppressed, rather than elevated which it is in this case. There is a specific laboratory test for PTHrP. Levels of PTHrP do not cause elevation in native PTH detection.
   B. **Correct**—This patient has primary hyperparathyroidism as evidenced by hypercalcaemia in the setting of a raised

PTH. Given the degree of hypercalcaemia the PTH should be low.

C. **Incorrect**—If the hypercalcaemia was a result of bone metastases, PTH would be suppressed rather than elevated.

D. **Incorrect**—Though the vitamin D is low, this is not responsible for the hypercalcaemia. Low vitamin D is more likely to cause hypocalcaemia.

E. **Incorrect**—Secondary hyperparathyroidism occurs in response to hypocalcaemia where the parathyroid glands hypertrophy and produce excess PTH, commonly seen in chronic kidney disease stage 3 and above.

4. An active 64 year old man with a background of hypertension undergoes a CT scan of the abdomen in his local emergency department after presenting with abdominal pain. He is found to have an 8 cm solid lesion in the upper pole of the right kidney which is staged as T2a N0 M0. Which of the following treatments would be most likely to be recommended?
   A. Active surveillance
   B. Radical nephrectomy with ipsilateral adrenalectomy
   C. Partial nephrectomy
   D. Radical nephrectomy
   E. Radiofrequency ablation

Answer: C

A. **Incorrect**—Given this man's age and lack of significant co-morbidities, a definitive management strategy by way of partial nephrectomy would be recommended.

B. **Incorrect**—Firstly, partial nephrectomy is preferred over radical nephrectomy, secondly, adrenalectomy in only indicated where there is evidence of gland invasion.

C. **Correct**—Surgery is the management of choice for localised kidney cancer and partial nephrectomy is preferred where possible

D. **Incorrect**—Partial nephrectomy is the preferred option for localised tumours where surgically feasible .

E. **Incorrect**—Surgery would be the management of choice given the size of his tumour and the lack of contraindications to surgery.

5. A 94 year old lady with a background of CKD stage G4, ischaemic heart disease, previous stroke, heart failure with reduced ejection fraction and newly diagnosed Alzheimer's dementia is incidentally found to have an indeterminate 4 cm cystic mass in the right kidney (Bosniak III) Which of the following management options is most appropriate?
   A. Renal tumour biopsy
   B. Active surveillance
   C. Radiofrequency ablation
   D. Partial nephrectomy
   E. Watchful waiting**Answer: E**

A. **Incorrect**—though the cystic mass is indeterminate, which is an indication for biopsy, the guidelines are clear that renal tumour biopsy should only be undertaken where it is likely to change management. Given this patient's age and co-morbidities she is unlikely to be a candidate for surgical treatment, regardless of the biopsy findings.

B. **Incorrect**—Active surveillance would involve 6 monthly assessment and imaging for 2 years and annual follow up thereafter. Even if the kidney lesion was found to have grown in size, this lady would not be candidate for treatment.

C. **Incorrect**—Given her co-morbidities and age she is not fit for RFA.

D. **Incorrect**—Given her co-morbidities and age she is not fit for surgery.

E. **Correct**—Watchful waiting differs from active surveillance in that no routine re-imaging or regular assessment is requirement. Given this patient's extensive co-morbidities this would be the most appropriate option.

6. A 64 year old male is found to have an isolated enhancing 3 cm solid kidney mass on CT imaging with no evidence of lymph node involvement or metastatic spread. You are

referring to the urology registrar on the telephone, who wants to know what stage his cancer appears to be.

A. T1a; N0; M0
B. T2b; N1; M0
C. T3; N0; M1
D. T4; N1; M1
E. T1b; N0; M0

Answer: A

A. **Correct**—the isolated enhancing solid kidney mass is <4 cm diameter and is limited to the kidney
B. **Incorrect**—the isolated enhancing solid kidney mass is <4 cm diameter and is limited to the kidney
C. **Incorrect**—the isolated enhancing solid kidney mass is <4 cm diameter and is limited to the kidney
D. **Incorrect**—the isolated enhancing solid kidney mass is <4 cm diameter and is limited to the kidney
E. **Incorrect**—the isolated enhancing solid kidney mass is <4 cm diameter and is limited to the kidney

7. A 48 year old female of normal intellect and no other comorbidity is found to have a cystic lesion on her right kidney—of around 3 cm in diameter. What is the most appropriate next investigation?

A. Contrast enhanced CT
B. Contrast enhanced MRI
C. Non-contrast CT
D. Biopsy of the renal lesion
E. MAG-3 scan

Answer: B

A. **Incorrect**—a contrast-enhanced CT or MRI is advocated, with a preference for MRI in cystic lesions, where MRI has a higher sensitivity and specificity for small cystic renal masses and tumour thrombi.
B. **Correct**—a contrast-enhanced CT or MRI is advocated, with a preference for MRI in cystic lesions, where MRI has a higher sensitivity and specificity for small cystic renal masses and tumour thrombi.
C. **Incorrect**—a contrast-enhanced CT or MRI is advocated, with a preference for MRI in cystic lesions, where MRI has a higher sensitivity and specificity for small cystic renal masses and tumour thrombi. The most important criterion for differentiating malignant lesions is the presence of enhancement so the use of contrast is essential.
D. **Incorrect**—a contrast-enhanced CT or MRI is advocated, with a preference for MRI in cystic lesions, where MRI has a higher sensitivity and specificity for small cystic renal masses and tumour thrombi. Most lesions can be diagnosed on the basis of imaging alone, avoiding the need for an unnecessary invasive procedure.
E. **Incorrect**—a contrast-enhanced CT or MRI is advocated, with a preference for MRI in cystic lesions, where MRI has a higher sensitivity and specificity for small cystic renal masses and tumour thrombi. MAG-3 will give functional information about both kidneys only.

8. A fit, independent 72 year old gentleman has a successful laparoscopic partial left nephrectomy for stage T1a N0 M0 renal cell cancer, with clear tumour margins on resection. His serum creatinine at one month post-procedure is 94 μmol/L (1.06 mg/dL). How should he be followed up?

A. Discharge from follow-up
B. Non-contrast CT at 1 year
C. Non-contrast MRI at 3 months
D. Ultrasound at 6 months
E. Contrasted CT at 6 months

Answer: E

A. **Incorrect**—Whilst this gentleman's 5 year survival with localised stage I disease is around 93%, there is still a significant risk of developing recurrence or metastases of up to 30%
B. **Incorrect**—Non-contrast CT is not appropriate to follow up this patient with normal renal function.
C. **Incorrect**—Non-contrast MRI is not optimal to follow up this patient with

normal renal function. Furthermore, imaging within 3 months is only indicated for patients with a high recurrence risk. The history does not suggest that he falls into this category so repeat imaging within 6 months would be sufficient.

D. **Incorrect**—Ultrasound is of insufficient sensitivity to detect metastatic spread.

E. **Correct**—Contrasted CT of the chest and abdomen is the recommended follow up modality for low-risk localised disease post partial nephrectomy with curative intent

9. A 58 year old female with CKD stage G4 secondary to diabetes mellitus, with concomitant ischaemic heart disease is found to have an incidental 2 cm solid kidney lesion on ultrasound, which is confirmed on CT imaging, with no nodal involvement or metastases. She had a non-ST elevation myocardial infarction 3 months ago. What is the most appropriate management for her?
   A. Immediate partial nephrectomy
   B. Urgent radical nephrectomy
   C. Watchful waiting
   D. Active Surveillance
   E. Start Pembrolizumab and Axitinib

Answer: D

A. **Incorrect**—This lady's recent myocardial event makes immediate surgery risky. Given her localised disease and comorbidity, active surveillance would be more appropriate to allow her medical condition to stabilise, with consideration of definitive surgical therapy in the form of partial nephrectomy or ablative therapy—if appropriate—at a later stage.

B. **Incorrect**—This lady's recent myocardial event makes immediate surgery risky. Given her localised disease and comorbidity, active surveillance would be more appropriate to allow her medical condition to stabilise, with consideration of definitive surgical therapy in the form of partial nephrectomy or ablative therapy—if appropriate—at a later stage.

C. **Incorrect**—Watchful waiting is reserved for patients who are not candidates for active treatment and who therefore do not require follow up imaging. In this case, active surveillance with regular imaging is more appropriate as this patient would be a surgical candidate if her lesion was found to have grown rapidly in size or metastasised.

D. **Correct**—This lady's recent myocardial event makes immediate surgery risky. Given her localised disease and comorbidity, active surveillance is the most appropriate option to allow her medical condition to stabilise, with consideration of definitive surgical therapy in the form of partial nephrectomy or ablative therapy—if appropriate—at a later stage.

E. **Incorrect**—This lady's recent myocardial event makes immediate surgery risky. Given her localised disease and comorbidity, active surveillance would be more appropriate to allow her medical condition to stabilise, with consideration of definitive surgical therapy in the form of partial nephrectomy or ablative therapy—if appropriate—at a later stage. There is no evidence of metastatic spread to warrant systemic therapy.

10. A 45 year old female primary school teacher has been found to have T2aN1M1 renal cell cancer on a delayed follow-up scan, having elected for active surveillance 18 months ago. She has CKD stage G3a (serum creatinine 148 μmol/L (1.67 mg/dL)—eGFR 50 ml/min/1.73 m [2]). All full blood count parameters remain in the normal range, as does her serum calcium level. She otherwise remains well, having prospectively arranged cover for her class to attend the renal clinic with you to follow up her scan results. You rightly refer for her case for consideration urgently in the Uro-Oncology MDT meeting. What is the most likely management for her current disease?

A. Urgent partial nephrectomy
B. Urgent radical nephrectomy and metastasectomy
C. Watchful waiting
D. Active Surveillance
E. Consideration for cytoreductive nephrectomy, metastasectomy and consideration of first line systemic therapy with Pembrolizumab and Axitinib

Answer: E

A. **Incorrect**—This lady has new metastatic renal cell cancer, which warrants cytoreductive nephrectomy, metastasectomy and consideration of first line systemic therapy with Pembrolizumab and Axitinib, since partial nephrectomy alone will not be sufficient to fully treat her disease
B. **Incorrect**—This lady has new metastatic renal cell cancer, which warrants cytoreductive nephrectomy, metastasectomy and consideration of first line systemic therapy with Pembrolizumab and Axitinib, since radical nephrectomy and metastasectomy alone are unlikely to fully treat her disease
C. **Incorrect**—This lady has new metastatic renal cell cancer, which warrants cytoreductive nephrectomy, metastasectomy and consideration of first line systemic therapy with Pembrolizumab and Axitinib – watchful waiting would inevitably lead to further disease spread, and would not be the most appropriate line of management for a young, fit patient.
D. **Incorrect**—This lady has new metastatic renal cell cancer, following delayed re-imaging on active surveillance. Her current disease warrants consideration for cytoreductive nephrectomy, metastasectomy and first line systemic therapy with Pembrolizumab and Axitinib
E. **Correct**—This lady has new metastatic renal cell cancer, which warrants consideration of cytoreductive nephrectomy, metastasectomy and first line systemic therapy with Pembrolizumab and Axitinib

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