Multi-disciplinary Team (MDT) Guidance for Managing Renal Cancer

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Abbreviations

5-FU: 5-fluorouracil

AE: adverse event

BMI: body mass index

CI: confidence interval

CN: cytoreductive nephrectomy

CR: complete response

CSS: cancer-specific survival

CT: computed tomography

DFS: disease-free survival

ECOG: Eastern Co-operative Oncology Group

FDG: fluorodeoxyglucose

GFR: glomerular filtration rate

eGFR: estimated glomerular filtration rate

HR: hazard ratio

IFN: interferon

IL-2: interleukin-2

ITT: intention-to-treat

IV: intravenous

MDT: multi-disciplinary team

MPA: medroxyprogesterone acetate

MRI: magnetic resonance imaging

MSKCC: Memorial Sloan-Kettering Cancer Center

NSS: nephron-sparing surgery

OR: odds ratio

ORR: overall response rate

OS: overall survival

PET: positron emission tomography

PFS: progression-free survival

PN: partial nephrectomy

PR: partial response

PRFA: percutaneous radiofrequency ablation

PS: performance status

RCC: renal cell cancer

RCT: randomised controlled trial

RFS: recurrence-free survival

RN: radical nephrectomy

RR: relative risk

SC: subcutaneous

SD: stable disease

TIL: tumour-infiltrating lymphocyte

TNM: tumour-node-metastasis

TTP: time to progression

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Integrated care and the Multi-disciplinary Team (MDT)

- The concept of integrated care is becoming increasingly accepted as a way to overcome fragmentation of patient management and to provide a consistent treatment strategy across the MDT
    - It also creates an optimal structure that facilitates audit and peer review
- Integration within the MDT is essential for patients with renal cancer because the collaboration between MDT members (Table 1) is central to the treatment strategy, with ongoing support from the wider team to manage pain and the adverse effects of therapy
- By being familiar with the complete spectrum of management strategies, the MDT can assist patients in making treatment decisions that are specific for their individual disease state, co-morbid conditions, age and lifestyle
- It is important that decisions regarding more complex surgical/oncological treatments should only be made if the members of the MDT can deliver these

Table 1: The make-up of the MDT for management of patients with renal cancer

- Urologist(s) with expertise in renal cancer
- Clinical nurse specialist
- Oncologist(s) with expertise in renal cancer
- Radiologist
- Pathologist
- Palliative care specialists
- MDT co-ordinator
- MDT secretary

Approach within the MDT

Key questions for the MDT

- Tumour/Node/Metastasis (TNM) stage?
- Fuhrman grade?
- Histological type?
- Symptoms?
- Risk category (primary or metastatic disease)?
- Age?
- Co-morbidities?
- Life expectancy?
- Renal function?
- Family history of cancer/renal cancer?

- Treatment strategies are influenced by the stage and grade of disease and by an interaction between the risk of disease progression and patient characteristics, such as age and general health. The discussion of these factors is of crucial importance in determining the most appropriate way forward. For example, age and the presence of co-morbidities may be limiting factors when considering surgery.
- The case notes, pathology reports, test results and radiology for each patient must be available to be discussed at the meeting.
- Patient preference should also be discussed within the MDT.
- The case should ideally be presented by a clinician or Clinical Nurse Specialist who knows the patient, and is clear on what question needs to be addressed by the MDT.

Staging

Most of the studies on which this guidance is based used TNM version 6 or earlier. The current TNM staging system is TNM version 7.

Table 2 outlines the differences between TNM 6 and TNM 7.

Table 2: Staging of Renal Cell Cancer (RCC): Comparison of TNM 6 versus TNM 7[1, 2]

Tumour stage	**TNM 6**	**TNM 7**
T1	≤7 cm; limited to the kidney	≤7 cm; limited to the kidney
T1a	≤4 cm	≤4 cm
T1b	>4 cm	>4 cm
T2	>7 cm; limited to the kidney	>7 cm; limited to the kidney
T2a	NA	>7 cm but <10 cm
T2b	NA	>10 cm
T3	Adrenal or perinephric invasion; involvement of major veins	Perinephric invasion; involvement of major veins
T3a	Perinephric fat or ipsilateral adrenal	Renal vein, perinephric fat
T3b	Renal vein ± vena cava involvement below diaphragm	Vena cava below diaphragm
T3c	Vena cava involvement above diaphragm	Vena cava involvement above diaphragm
T4	Beyond Gerota fascia	Beyond Gerota fascia; ipsilateral adrenal
N1	Single regional lymph node	Single regional lymph node
N2	>1 regional lymph node	>1 regional lymph node

Approach to the patient

Key points for discussion with the patient

- Treatment options
- Treatment side-effects
- Impact of treatment on quality of life
- Family history of cancer/renal cancer
- It is essential that the patient and healthcare professionals discuss the likelihood of adverse events (AEs) associated with each treatment option and implications for their future lifestyle when determining management strategies.
- The patient, and with the patient's consent their partner, family and/or other carers should be fully informed about treatment options and the potential effects of these on their lifestyle and quality of life and therefore be able to make appropriate decisions based upon the choices offered by their healthcare professionals.
- Prognosis to be discussed as per patient's requirement for information.

Assessment and diagnosis

Risk factors for renal cancer

The most well-known risk factors for renal cancer are highlighted below.

- Age[3]
    - Peak incidence is at 60–70 years of age
- Gender[3]
    - 1.5:1 predominance for men: women
- Family history[4, 5]
    - Having at least 1 first-degree relative with renal cancer increases an individual's relative risk (RR) of renal cancer by 1 to 5 times
        - The risk is highest if a sibling is affected
    - The risk of RCC may also be increased in association with a family history of prostate cancer (odds ratio [OR] 1.9), leukaemias (OR 2.2) or any cancer (OR 1.5)
- Single gene mutations
    - Currently there are several renal cancer syndromes, several of which are associated with single gene mutations. Many of these patients will have a family history. These syndromes are outlined in Table 3 below.
- Smoking[6, 7]
    - The RR of RCC for ever-smokers is 1.38 times higher than that for never-smokers
    - A strong dose-response relationship between number of cigarettes smoked and increased risk of RCC has been established
        - Smokers with a history of ≥20 pack-years have an increased risk of RCC 1.35 times that of never-smokers
- Obesity[8, 9]
    - Increasing body weight and body mass index (BMI) incrementally increases the risk of developing RCC
        - Being overweight (BMI 25–29.9 kg/m^2) increases the risk of RCC by 1.35 times versus BMI <25 kg/m^2
        - Being obese (BMI 30–34.9 kg/m^2) increases the risk of RCC by 1.7 times versus BMI <25 kg/m^2

        - Being extremely obese (BMI 35–39.9 kg/m^2) increases the risk of RCC by 2.05 times versus BMI <25 kg/m^2
        - Being morbidly obese (BMI ≥40 kg/m^2) increases the risk of RCC by 2.4 times versus BMI <25 kg/m^2

- Hypertension and antihypertensive therapy[10–13]
    - The presence of hypertension is estimated to increase the RR of RCC by 1.4–1.9 times compared with normotensive individuals
        - Systolic blood pressure ≥160 mmHg increases the RR of RCC by 2.5 times versus <120 mmHg
        - Diastolic blood pressure ≥100 mmHg increases the RR of RCC by 2.3 times versus <80 mmHg
    - Treatment with diuretics also increases the risk of RCC (OR 1.43), but this is only significant in women
- End-stage renal disease[14]
    - Patients undergoing dialysis for end-stage renal disease are estimated to have a 3.6 times higher RR of developing renal cancer than healthy individuals

Table 3: Renal cancer syndromes[15, 16]

Disease	**Renal and other tumours**	**Gene mutation**
Von Hippel–Lindau disease	Clear cell RCC: Clear cell renal cysts Retinal and central nervous system haemangioblastomas, phaeochromocytoma, pancreatic cyst and endocrine tumour, endolymphatic sac tumour, epididymal and broad ligament cystadenomas	VHL
Birt-Hogg-Dubé syndrome	Hybrid oncocytic RCC, chromophobe RCC, oncocytoma, clear cell RCC: multiple and bilateral Cutaneous lesions (fibrofolliculoma +++, trichodiscoma, acrochordon), lung cysts, spontaneous pneumothorax, colonic polyps or cancer	Folliculin (FLCN)
Hereditary papillary RCC	Type 1 papillary RCC: multiple and bilateral	MET
Hereditary leiomyomatosis and RCC	Type 2 papillary RCC: solitary and aggressive Uterine leiomyoma and leiomyosarcoma, cutaneous leiomyoma and leiomyosarcoma	Fumarate hydratase
Tuberous sclerosis complex	Angiomyolipoma, clear cell RCC, cyst, oncocytoma: bilateral and multiple Facial angiofibroma, subungual fibroma, hypopigmentation and café au lait spots, cardiac rhabdomyoma, seizure, mental retardation, CNS tubers, lymphangioleiomyomatosis	TSC-1 TSC-2
Familial clear cell RCC	Clear cell RCC	Unknown

Diagnostic tests

Physical examination

- Physical examination has only a limited role in diagnosing RCC, but it may be valuable in cases where any of the following are present:
    - Palpable abdominal mass
    - Palpable cervical lymphadenopathy
    - Non-reducing varicocele
    - Bilateral lower extremity oedema, suggesting venous involvement
    - Bony tenderness

Laboratory tests

- The most commonly assessed laboratory parameters are:[3, 17, 18]
    - Serum creatinine concentration
    - Haemoglobin concentration
    - Serum alkaline phosphatase concentration
    - Serum corrected calcium concentration
    - Plasma C-reactive protein concentration
    - Serum lactate dehydrogenase concentration
- Glomerular filtration rate (GFR) should be measured in patients with:
    - Compromised renal function
        - Serum creatinine concentration is elevated
        - Risk of future renal impairment is increased, e.g. patients with diabetes, chronic pyelonephritis, renovascular, stone or polycystic renal disease

Renal tumour biopsy

- Biopsy should be performed in patients with advanced or metastatic disease who are being considered for systemic treatment
- Biopsy should be considered in atypical lesions where the diagnosis is not clear and nephrectomy is proposed

- Biopsy should be considered in small renal masses where active surveillance or ablative therapy is planned

Ultrasound and computed tomography (CT)

- CT accurately predicts tumour size to within 0.5 cm of the pathological size of the lesion[19]
    - However, CT also demonstrates a false-positive rate of approximately 10% for the identification of lymph node metastases
- In addition, helical CT may identify a requirement for entry into the collecting system for nephron-sparing surgery (NSS)[20]
- CT is the most sensitive investigation for the identification of pulmonary metastases
- Evaluation of inferior vena cava tumour thrombus extension can be performed with multi-slice CT, which can produce good coronal reconstructions
- Ultrasound is often used for initial screening evaluation when renal disease is suspected. It can be useful to discriminate cystic from solid lesions, to monitor growth of a lesion, and to evaluate lesions found on CT that are probably hyperdense cysts.
- Detection of small renal lesions with ultrasonography is limited. Lesions <3 cm in diameter are detected only 67% to 79% of the time by conventional ultrasonography.
- Bone scans are no longer the standard of care to identify bony metastases – whole body magnetic resonance imaging (MRI) is increasingly used, this is not, however, likely to be routinely available in many centres.

Magnetic resonance imaging

- MRI is an option for the evaluation of inferior vena cava tumour thrombus extension and unclassified renal masses [21]

Positron emission tomography (PET)

Currently PET is not a standard investigation in the assessment of renal cancer

- Fluorodeoxyglucose (FDG) PET does not appear to provide additional information over CT scanning for the characterisation of primary renal tumours, but it may be useful in detecting distant metastases[22]
    - In a small study of 15 patients with end-stage renal disease, FDG PET demonstrated a 67% sensitivity and 90% predictive value for urothelial cancers compared with histological findings[23]

- In 20 patients with suspected RCC, ^{11}C-acetate PET identified 14 correctly when compared with CT and histology[24]

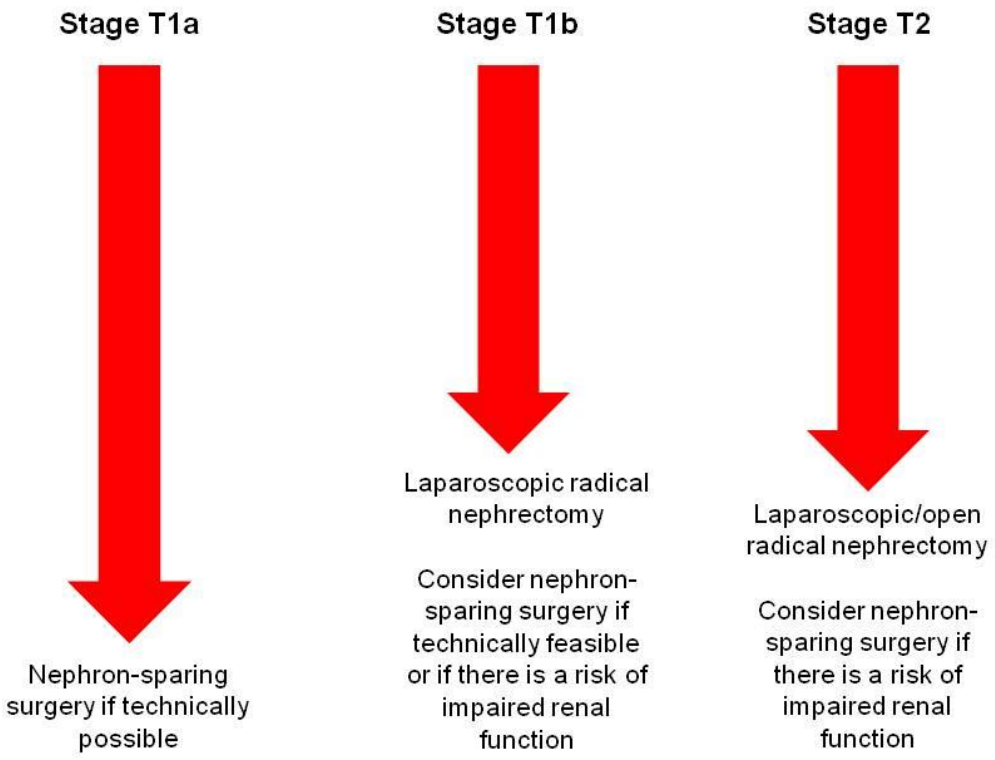
Estimated GFR (eGFR) and imaging

- Parenteral contrast agents used for CT scanning may cause contrast-induced nephropathy
- Those at greatest risk are those with pre-existing renal disease or diabetes
- In these patients consider alternative imaging methods
- If no alternative, then deploy a reno-protective regimen, including pre-hydration, minimal dose and avoiding repeated doses in a short timeframe
- An eGFR of 45 ml/min/1.73m^2 is considered to be the threshold at which renoprotective measures should be implemented[25]

Localised disease: Management options

The following guidance for managing localised renal cancer focuses on patients with T1–T2 disease (Figure 1). In the proposed management algorithms, locally advanced disease is included within the guidance for metastatic disease.

Figure 1: Surgical management of T1 and T2 disease



Personal choice and the presence or absence of co-morbidities is an essential component of management decisions in patients with localised disease. Decisions concerning the choice of radical treatments need to be carefully balanced with the different options available and the impact of such treatments on a patient's co-morbidities.

In this section available evidence for the following management approaches is outlined:

- Radical nephrectomy
- Partial nephrectomy
- Ablative techniques
- Active surveillance

Surgery

Radical nephrectomy (RN)

There are a number of approaches to performing RN: open and laparoscopic, via either transperitoneal or retroperitoneal access.

Overview

- Laparoscopic RN may now be considered a standard of care for patients with T2 and T1b masses not treatable by NSS; but this must ensure:[26]
    - Early control of the renal blood vessels prior to tumour manipulation
    - Wide specimen mobilisation external to Gerota's fascia
    - Avoidance of specimen trauma or rupture
    - Intact specimen extraction
- Routine ipsilateral adrenalectomy is not indicated:[26, 27]
    - Where the adrenal gland appears normal on pre-operative tumour staging (CT, MRI) and intra-operatively where there is no intra-operative suspicion of involvement
- Indications for adrenalectomy include an adrenal nodule or an adrenal gland densely adherent to a large upper pole renal tumour. Routine extended lymphadenectomy should be restricted to dissection of palpable or enlarged lymph nodes[26, 28]

Technique

- Laparoscopic versus open RN
    - There are no randomised controlled trials (RCTs) assessing oncological outcomes
    - A prospective cohort study[29] and a retrospective database review[30] found similar oncological outcomes; there were no statistically significant differences in cancer-specific survival (CSS) and recurrence-free survival (RFS) at 5 years in these studies.
- Transperitoneal versus retroperitoneal laparoscopic
    - Three randomised or quasi-randomised studies compared retroperitoneal and transperitoneal laparoscopic RN.[31–33] Both approaches were found to have similar oncological outcomes, although a low number of metastatic events were reported across the studies.

- Hand-assisted versus transperitoneal or retroperitoneal laparoscopic
    - In a randomised study, there were no reported cancer deaths, positive surgical margins, or recurrences[32]
    - In a non-randomised study, estimated 5-year overall survival (OS), cancer-specific CSS and RFS rates were comparable[34]
- Ipsilateral adrenalectomy
    - In a prospective non-randomised comparative study for partial nephrectomy (PN) with ipsilateral adrenalectomy versus PN without adrenalectomy, only 48 (2.3%) of 2065 patients underwent concurrent ipsilateral adrenalectomy.[27] After a median follow-up of 5.5 years, only 15 patients (0.74%) underwent subsequent ipsilateral adrenalectomy. There was no statistically significant difference in OS at 5 years (82% with adrenalectomy versus 85% without adrenalectomy; p=0.56).
- Lymph node dissection
    - In a Phase III randomised trial which compared RN with and without lymph node dissection in patients with clinical T1–T3/N0/M0 renal tumours, there were no significant differences in OS, or progression-free survival (PFS).[28] The incidence of unsuspected lymph node metastases was low (4%), although the extent of lymphadenectomy was variable. Where nodes were palpable pre-operatively, 16% were pathologically cancerous.

Patient selection

- *S*tage T1–T2 disease
- Normal contralateral kidney
- Fitness for surgery/anaesthesia
- Baseline GFR >60 ml/min/1.73 m^2
    - In an analysis of data from 1479 patients undergoing RN, those with reduced baseline GFR 45–60 ml/min/1.73 m^2 or GFR <45 ml/min/1.73 m^2 demonstrated a significant association with lower OS (hazard ratio [HR]: 1.5; p<0.003 and HR: 2.8; p<0.001, respectively)[35]
- Absence of co-morbidities
    - In patients undergoing surgery for RCC, the presence of co-morbidities was associated with worse OS (HR: 1.37; 95% confidence interval [CI]: 1.16–1.63; p=0.0002)[36]

Adverse effects of treatment

- Impaired renal function/development of chronic kidney disease and requirement for dialysis
- Greater all-cause mortality versus PN

Clinical evidence

- An RCT[37] and a database review[38] both reported significantly lower median creatinine levels at follow-up in the open PN group than in the RN group
- A retrospective matched pair study showed a greater proportion of patients with impaired postoperative renal function in the open RN group[39]
- A database review[40] comparing laparoscopic PN and laparoscopic RN for tumours >4 cm reported a greater decrease in eGFR (decrease of 13 versus 24 ml/min/1.73 m^2; p=0.03) in the laparoscopic RN group and there was a greater proportion of patients with a 2-stage increase in the chronic kidney disease stage in the laparoscopic RN group (0 versus 12%; p<0.001)
- A database review[41] comparing PN and RN (by open or laparoscopic approach) in tumours 4–7 cm in diameter reported that the increase in mean creatinine postoperatively was significantly smaller in the PN group (difference between means at 3 months: 0.23 mg/dL; 95% CI: 0.11–0.34; p<0.0001, and at 6–12 months: 0.21 mg/dL; 95% CI: 0.09–0.34; p<0.0001)
- In a retrospective cohort study involving patients with renal cortical tumours, the 3-year probability of avoidance of GFR falling below 60 ml/min/1.73 m^2 was 80% after open or laparoscopic PN compared with 35% after open or laparoscopic RN[42]
    - Multivariate analysis demonstrated that RN remained an independent risk factor for *de novo* GFR <60 ml/min/1.73 m^2 (HR: 3.82; 95%CI: 2.75–5.32; p<0.0001)
- In 2991 patients with tumours ≤4 cm in diameter and a median follow-up of 4 years, RN was associated with a significantly increased risk of all-cause mortality versus PN (HR: 1.38; p<0.01)[43]
    - In addition, RN demonstrated a significantly increased risk of cardiovascular events after surgery versus PN (HR: 1.4; p<0.05)
- In 9809 patients with T1a disease treated between 1988 and 2004, RN was associated with a significant increase in all-cause mortality relative to PN (HR: 1.23; p=0.001)[44]
- An analysis of data from a patient registry (n=648) has evaluated outcomes for RN versus PN[45]

    - In the total patient population, RN was not associated with a significant increase in all-cause mortality versus PN (RR: 1.12; p=0.52)
    - However, in patients aged <65 years, RN was associated with a significantly increased RR of death from any cause compared with PN (RR: 2.16; p=0.02)
- A Phase III RCT of RN versus PN (n=541 from a recruitment target of 1300) in T1 and T2 tumours showed a survival benefit for RN in an intention-to-treat (ITT) analysis[46]
    - In clinically and pathologically eligible patients (those with T1 or T2 renal cancer) there was no significant difference

Nephron-sparing surgery/partial nephrectomy

Overview

- NSS performed for absolute rather than elective indications has an increased complication rate and higher risk of developing locally recurrent disease, probably due to the larger tumour size
- NSS compared with RN is associated with a reduced risk of impaired renal function
- Even patients with larger tumours (≤7 cm) who have undergone NSS have achieved outcomes comparable to those following RN
    - However, for larger tumours follow-up should be intensified due to an increased risk of intrarenal disease recurrence
- If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood of local recurrence; a minimal tumour-free margin is appropriate to minimise the risk of local recurrence
- Laparoscopic PN is an alternative to open NSS for selected patients – the optimal indication is a relatively small and peripheral renal tumour
- There are currently no large studies to reliably demonstrate long-term equivalence for laparoscopic PN and open NSS
- Potential disadvantages of the laparoscopic approach are the longer warm ischaemia time and increased intraoperative and postoperative complications compared with open surgery

Patient selection

- Stage T1 disease
- Stage T2 disease for absolute indications

- Fitness for surgery/anaesthesia
- Solitary functional kidney or bilateral disease (absolute indication)
- Contralateral kidney with impaired function (relative indication)
- Hereditary RCC, with increased risk of future tumours in the contralateral kidney (relative indication)
- Normal contralateral kidney (elective indication)

Adverse effects of treatment

- Postoperative haemorrhage or urinary leakage
    - In a randomised trial comparing open PN with open RN for small (≤5 cm), solitary renal tumours, perioperative bleeding ($p<0.001$) and urinary fistulae ($p<0.001$) were significantly more common in the PN group.[37] The rate of severe haemorrhage (>1L) was 3.1% after PN and 1.2% after RN. Ten patients (4.4%), all of whom were treated by PN, developed urinary fistulae.
    - The database review[38] and a matched-pair study[30] both reported no differences in the rates of haemorrhage but event rates were very rare
    - In a review of data from 717 patients undergoing open PN in a single centre between 1980 and 2004, postoperative haemorrhage occurred in 19% of patients, urinary fistula in 8% of patients and acute renal failure in 6% of patients[47]
    - In a separate study involving 1048 NSS procedures, tumour size >4 cm was associated with significantly increased risks of blood loss ($p=0.01$), requirement for blood transfusion ($p=0.001$) and urinary fistula development ($p=0.01$)[48]
    - In 223 cases of laparoscopic PN, bleeding occurred in 1.8% of patients and urinary leakage occurred in 1.4% of patients[49]
- Requirement for repeat intervention
    - In a randomised trial, the re-operation rate after open PN was 4.4% compared with 2.4% after open RN[37]
    - In a retrospective analysis of data from 127 patients during 1988–2003, a total of 15.7% of patients required re-intervention following initial NSS (22.6% in absolute and 10.8% in elective indications)[50]

Clinical evidence

- Open PN versus open RN

    - One small randomised trial reported that the two approaches had a median OS of 96 months each[51]
    - A larger randomised study showed no difference in CSS. Only 10% of 117 deaths were due to renal cancer, and death from renal cancer could not account for differences shown in the ITT analysis[46]
    - In two non-randomised studies, the estimated CSS rates at 5 years for RN versus PN respectively were 97% versus 100%[38] and 97.9% versus 100% (p=0.98)[39]
- Laparoscopic PN versus laparoscopic RN
    - In a database review, the estimated OS ,CSS and RFS rates for laparoscopic PN and RN respectively at 80 months were statistically similar (74% versus 72%, 81% versus 77%, and 81% versus 77%[40]
- Laparoscopic or open PN versus laparoscopic or open RN
    - Four non-randomised studies that reported adjusted HRs for CSS showed no statistically significant differences[52–55]
    - One non-randomised study which reported adjusted HR for disease-free survival (DFS) showed no statistically significant difference[41]
- Laparoscopic PN versus open PN
    - In a database review, there were no statistically significant differences in 3-year CSS[56]

Surveillance following radical nephrectomy

Overview

- No RCTs have been published to support specific surveillance measures following RN
- There is no consensus regarding the timing of surveillance
    - Frequency of follow-up is individualised according to the risk of local recurrence or metastasis, assessed using:
        - Tumour size and extension
        - Lymph node status
        - Histological features
        - Performance status (PS)
    - Risk scoring systems are recommended for stratifying patients for follow-up, e.g. the Mayo Scoring system (Table 4)

- In patients considered to be at low risk of relapse (score 0–2), chest X-ray and ultrasound are appropriate assessments
- In patients with intermediate (score 3–5) to high risk (score >6) of relapse, CT of the chest and abdomen is recommended as the optimal assessment tool, performed at regular intervals
- For patients with intermediate and high risk scores there is no established routine adjuvant therapy. Entry into trials such as SORCE should be considered (see section on locally advanced and metastatic disease)

Table 4: Mayo scoring system for prediction of metastases after radical nephrectomy for clear cell carcinoma[57]

Feature	**Score**
Primary tumour	
pT1a	0
pT1b	2
pT2	3
pT3–pT4	4
Tumour size	
<10 cm	0
≥10 cm	1
Regional lymph node status	
pNx/pN0	0
pN1–pN2	2
Nuclear grade	
1–2	0
3	1
4	3
Tumour necrosis	
Absent	0

Present	1

Ablative therapies

Overview

- Possible advantages of these techniques include reduced morbidity, outpatient therapy, and the ability to treat patients unsuitable for surgery (open or laparoscopic), including the elderly[3, 58]

Patient selection

- Stage T1–T2 disease
- Life expectancy ≥1 year
- Small (<5 cm) peripheral (cortical) tumours
- Genetic predisposition to multiple tumours
- A solitary kidney
- Bilateral tumours
- Contraindications: irreversible coagulopathies; severe medical instability, e.g. sepsis

Percutaneous radiofrequency ablation (PRFA)

Overview

- No RCTs evaluating PFRA in renal cancer have been reported
- CT or ultrasound-guided PFRA may be performed under intravenous (IV) sedation and as an outpatient procedure[59, 60]
- Assessment of treatment success is performed using CT scanning or MRI[59, 61]

Patient selection

- Tumours <5.5 cm, in situations where surgery is not feasible[60–62]
- Single functioning kidney[60, 61]
- Normal contralateral kidney[61]
- Multifocal RCC[60]

Adverse effects of treatment

- The most commonly reported complication associated with PRFA is haematoma development
    - The frequency of this has been reported as ranging from 4% to 8% of patients[63–65]
- Haemorrhage has been reported in 6% of patients[60]
- Urinary obstruction has been reported in 4–10% of patients[60, 64, 66]
- In a series of 24 patients, 2 experienced colonic injuries following PFRA[64]

Clinical evidence

- A meta-analysis of data from 99 studies and including 6471 tumours has recently been published[67]
    - When compared with NSS, PFRA was associated with an RR of 18.23 and cryoablation an RR of 7.45 for local disease progression
- A few studies have assessed PRFA in patients with varying tumour sizes
    - In 8 patients with 11 tumours, lesions measuring 1.5–5.5 cm were successfully ablated with a maximum of 2 sessions[61]
        - After a mean of 7.1 months, 7 of 8 patients demonstrated no recurrence
    - In a series of 105 patients with 95 tumours, 12 were >4 cm in diameter[62]
        - For 84 tumours, treatment consisted of a single session of PRFA
        - The majority of these were <3.5 cm in diameter
        - 14 tumours were treated with a second session
        - The overall success rate was 95 of 105 tumours (91%)
    - In 85 patients with 100 tumours (1.1–8.9 cm), 90 tumours in 77 patients were successfully ablated[60]
        - In 7 patients, residual tumour was observed after 1 to 4 PRFA sessions
        - All these tumours were >4 cm in diameter
        - After a mean of 2.3 years of follow-up, 77 patients were alive (23 were >3 years post-PRFA)

- A number of studies have evaluated CT-guided PFRA in patients with tumours <4 cm
    - In a small early study, 12 patients (13 tumours) underwent CT-guided PFRA.[68] At a mean follow-up of 4.9 months, 12 of 13 tumours were successfully ablated
    - A separate study involved 29 patients with 35 lesions undergoing 37 treatments[59]
        - 35 treatments were successfully performed under IV sedation and 32 were successfully performed on an outpatient basis
        - At a mean follow-up of 9 months, 94% of tumours required only a single treatment
        - Of 13 lesions with ≥12-month follow-up, 11 demonstrated no residual enhancement on imaging or growth after PFRA
    - In 32 patients, 26 experienced successful treatment after 1 session of PFRA; of the remaining 6 patients, 5 were successfully treated with a second session[63]
        - Tumours requiring a second treatment session were significantly larger than those successfully ablated after 1 session (3.5 versus 2.4 cm; p=0.0013)
    - CT-guided PFRA performed in 22 patients was successful after a single treatment in 18 patients and a second treatment was successful in an additional 2 patients[69]
        - All tumours ≤3 cm were successfully ablated after 1 treatment session
    - In an updated series from the same institution, 104 patients with 125 tumours were treated with PFRA[70]
        - 109 tumours were completely ablated following a single treatment and another 7 were completely ablated after second treatment
        - All 95 tumours <3.7 cm were completely ablated
        - With each 1 cm increase in tumour diameter over 3.6 cm, the likelihood of tumour-free survival decreased by a factor of 2.2
    - In 23 patients undergoing PFRA under conscious sedation, 16 had a successful ablation following a single treatment; a further 2 experienced successful ablation after a second treatment[65]
        - The overall DFS was 90% at a mean follow-up of 24 months
    - In a series of 29 patients with 30 renal tumours, CT-guided PFRA was performed under general anaesthesia[66]

        - In 24 patients for whom the objective of treatment was tumour ablation, this was achieved in 23 cases
    - A total of 163 tumours in 151 patients were treated with CT-guided PFRA under general anaesthesia[71]
        - At 4–6 weeks post-treatment, the complete ablation rate was 97%
        - Five tumours showed evidence of local recurrence and metastases developed in 2 patients
        - 3-year DFS was 92%
    - In a study comparing outcomes with PFRA (n=82) and laparoscopic cryoablation (n=164), radiological evidence of disease persistence or recurrence was observed in 9 patients receiving PFRA and 3 patients receiving cryoablation[72]
        - At a median follow-up of 1 year, CSS following PFRA was 100%
        - At a median follow-up of 3 years, CSS following cryotherapy was 98%

Cryoablation

Overview

- No RCTs evaluating cryoablation in renal cancer have been reported
- Defining RFS is variable because post-ablation biopsies are not commonly performed and interpretation of post-ablation cross-sectional imaging can be difficult
- Recent changes and advancements in probe technology make percutaneous treatment easier than open or laparoscopic techniques

Adverse effects of treatment

- In a study involving 27 cryoablation treatments, 1 episode of haemorrhage occurred, which required a blood transfusion and 1 patient experienced an abscess[73]

Clinical evidence

- Laparoscopic cryoablation has been evaluated in a number of studies
    - In a database review, time to detection of local recurrence was 5.8 months among those who underwent laparoscopic PN (1/153) and 24.6 months after laparoscopic cryoablation (2/78)[74]

- In a matched pair study, no recurrences were reported in either the laparoscopic PN or laparoscopic cryoablation groups after a mean follow-up of 9.8 and 11.9 months, respectively[75]
- In a matched comparison of laparoscopic cryoablation and open PN, no local recurrences or metastases were reported in either group. However, there were only 20 patients in each arm and follow-up was short, at 27–28 months.[76]
- In 56 patients, 3 years after treatment, only 2 patients experienced recurrent or persistent local disease[77]
    - In the 51 patients with a unilateral, sporadic tumour, 3-year CSS was 98%
- In a study comparing outcomes with PFRA (n=82) and laparoscopic cryoablation (n=164), radiological evidence of disease persistence or recurrence was observed in 9 patients receiving PFRA and 3 patients receiving cryoablation[72]
    - At a median follow-up of 1 year, CSS following PFRA was 100%
    - At a median follow-up of 3 years, CSS following cryotherapy was 98%

- Percutaneous cryoablation has also been assessed
    - In a series of 23 patients with 26 tumours, 24 were successfully ablated, with 23 requiring only a single treatment[73]
    - In an analysis of 48 cases (49 tumours), percutaneous cryoablation was performed under sedation and as an outpatient procedure[78]
        - At a mean follow-up of 1.6 years, for patients with RCC, 11% were considered to be treatment failures
        - Major and minor complications were observed in 3 and 11 procedures, respectively

Surveillance

- Recently it has been recognised that many renal masses do not progress rapidly. This has led to the concept of active surveillance in elderly patients who have small tumours where the aim is to avoid treatment and enable a low risk of progression.
    - A meta-analysis of 880 patients with 936 renal masses demonstrated that only 18 progressed to metastasis at a mean of 40 months[79]
        - A subset of these patients with individual data shows that the mean diameter was small at 2.3 ± 1.3 cm, mean linear growth rate was 0.31 ± 0.38 cm per year at a mean follow-up of 33.5 ± 22.6 months

        - Sixty-five masses (23%) exhibited zero net growth under surveillance, and none of those masses progressed to metastasis
        - A pooled analysis revealed that older age, larger tumour volume and a more rapid growth rate were associated with progression
    - A recent Phase II prospective study in Canada recruited 178 patients, and all were asked to undergo biopsy prior to an active surveillance programme. Ninety-nine patients had a renal biopsy; 12% showed benign disease and 33% were not diagnostic[80]
        - At a median follow up of 28 months, 1.1% developed metastases and 12% had local progression. The mean growth rate was 0.31 cm per year

Locally advanced and metastatic disease: Management options

The following guidance focuses on patients with T3–T4 disease as well as those with distant metastases.

With the availability of several treatment options, each with a slightly different profile of risk and benefit, there are various options for initial treatment. The choice of treatment approach requires appreciation of the risks and benefits of each and knowledge of the limitations of the data currently available, especially for systemic therapies.[58] Fitness for surgery and the presence of co-morbidities and the type and number of metastatic lesions is an essential component of management decisions in patients with advanced disease.

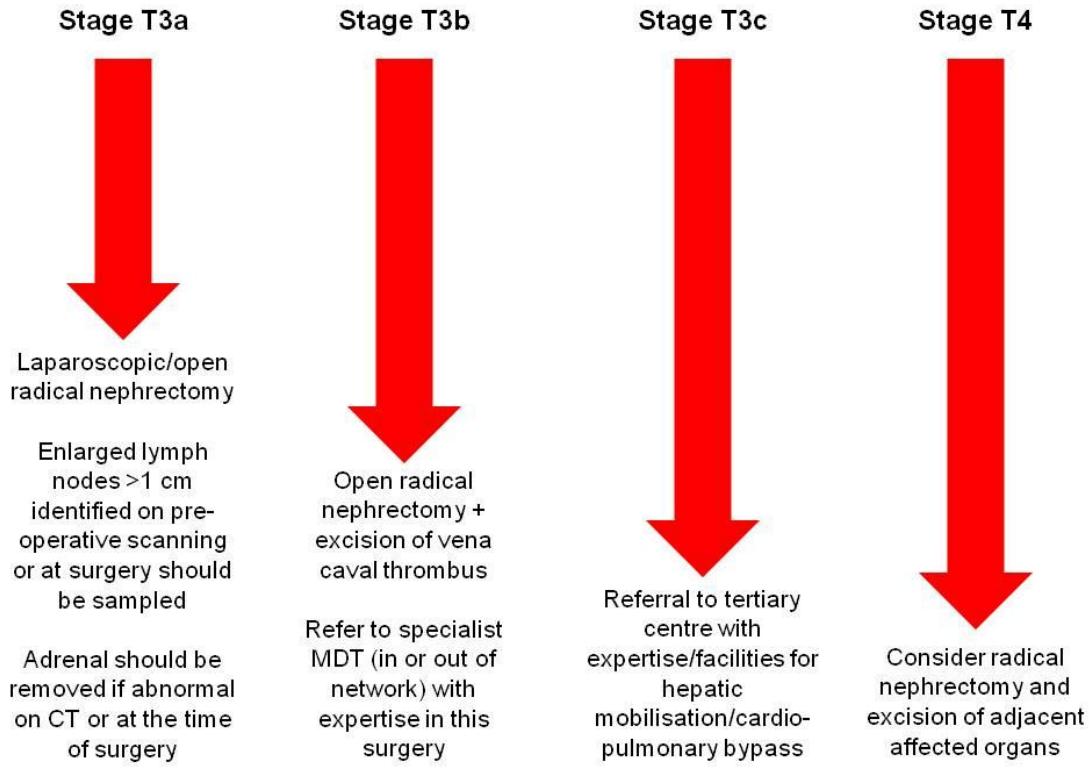
The goal for every patient with metastatic RCC is to maximise overall therapeutic benefit, which means delaying for as long as possible a lethal burden of disease while maximising the patient's quality of life. Treatment is therefore selected according to the best possible risk/benefit ratio for each patient, with the realisation that limited criteria exist for prediction of response to a particular drug and that many sequential treatments are ultimately likely to be pursued for most patients.[58]

In this section available evidence for the following management approaches is outlined:

- RN
- Cytoreductive nephrectomy (CN)
- Resection of metastases
- Immunotherapy
- Angiogenesis inhibitors

Surgery

Figure 2: Surgical management of T3–T4 disease



Radical nephrectomy

Overview

- About 5–10% of RCCs extend into the venous system as tumour thrombi, often ascending the inferior vena cava as high as the right atrium[58]
- RN is strongly indicated for locally advanced RCC[58]
- Total surgical excision should be the objective of surgery, presuming the patient is an appropriate candidate and vital structures are not compromised[58]
- RN will occasionally require *en bloc* resection of adjacent organs, isolation and temporary occlusion of the regional vasculature, and venous thrombectomy[58]

Patient selection

- Stage T3–T4 disease (involvement of adrenal gland and/or renal vasculature) or metastatic disease
- PS 0–1

Clinical evidence

- In 601 patients with T2–T3b RCC, 567 underwent RN and 34 underwent NSS[81]
    - After a mean follow-up of 43.4 months, disease recurred in 28.9% receiving RN and 12.0% of patients receiving NSS
- A retrospective analysis of 38 patients with T3–T4 disease evaluated RN and resection of adjacent organ or structure resection[82]
    - 34 patients (90%) had died from their disease after a median of 11.7 months after surgery
- In an analysis of data from 11,182 patients with metastatic RCC, those who underwent RN experienced a significantly longer median OS than those who did not undergo surgery (11 versus 4 months; $p<0.001$)[83]
    - The survival benefit was similar regardless of age, race and gender
- In a series of 404 patients with metastatic RCC who underwent RN, 3- and 5-year CSS rates were 21% and 13%, respectively[84]
- A retrospective analysis of data gathered between 1970 and 2000 from 540 patients at the Mayo Clinic has evaluated the effect of surgery in renal cancer with renal venous extension[85]
    - Patients with a higher thrombus level had a greater incidence of early surgical complications: Level 0 = 8.6%; Level I = 15.2%; Level II = 14.1%; Level III = 17.9%; Level IV = 30.0% ($p<0.001$ for trend)
    - For patients with clear cell carcinoma, the 5-year CSS rates for thrombus Levels 0 to IV were 49.1%, 31.7%, 26.3%, 39.4% and 37.0% ($p=0.028$ for trend)
- The UK guidelines on systemic treatment of RCC state that there is no standard of care for the adjuvant treatment of RCC and that suitable patients should be referred to centres that can offer entry into the adjuvant therapy clinical trials like SORCE[86]

Cytoreductive nephrectomy

- CN has been suggested to reduce the total burden of disease in patients with metastatic RCC, increasing the time before tumour burden becomes lethal[58]
- However, the benefit of CN is supported by evidence from the era of IFN-α and cannot automatically be extrapolated into the modern era in combination with targeted molecules. Nevertheless, a very high proportion of cases (>90%) had had a nephrectomy in studies of targeted molecules

- This is currently being addressed in the CARMENA trial. There is also a separate EORTC trial addressing optimal timing in this scenario.

Patient selection

- Good PS with adequate cardiac and pulmonary function
- WHO PS 0 or 1
    - In a retrospective analysis of data from 418 patients undergoing CN, those with an Eastern Co-operative Oncology Group (ECOG) PS 2 or 3 experienced a median DSS of 6.6 months compared with 27 months and 13.8 months in patients with ECOG PS 0 and 1, respectively[87]
- Fit for surgery
- >75% of tumour burden in the involved kidney
- Solitary brain or liver metastases
- Patient acceptance of the procedure after full discussion of risks and benefits

Clinical evidence

- In a retrospective analysis of data from 5372 patients with metastatic RCC, CN (n=2447) was compared with no surgery (n=2925)[44]
    - 5-year OS rates were 19.4% for CN versus 2.3% for no surgery
    - 5-year CSS rates were 24.3% for CN versus 4.1% for no surgery
    - Relative to CN, the no-treatment group demonstrated a 2.5-fold greater rate of overall and cancer-specific mortality
- In a separate analysis of data from cancer registries in the US, outcomes for patients with metastatic RCC were compared following CN (n=1997) or PN (n=46)[88]
    - At 5 years of follow-up, CSS rates were 20.9% for patients undergoing CN and 40.3% for patients undergoing PN
    - At 10 years of follow-up, CSS rates were 14.2% for patients undergoing CN and 40.3% for patients undergoing PN
    - CN was associated with a 1.8 fold higher cancer-specific mortality rate than PN (p=0.015)
- A similar analysis in patients with metastases has compared outcomes in 45 patients undergoing PN with 732 patients undergoing CN[89]

- 3-year DSS rates were 75.0% for patients undergoing PN and 52.7% for patients undergoing CN
- The median actuarial survival of the CN versus PN patients was 1.3 versus 5.1 years (rate ratio: 3.0; p<0.001)
- CN was associated with a 1.7 fold higher cancer-specific mortality rate (p=0.1)

- Laparoscopic and open CN were compared in a series of 64 patients with metastatic RCC[90]
  - The estimated 1-year OS rates were 61% in the laparoscopic group and 65% in the open group
- A number of data analyses regarding outcomes of CN in patients with metastatic RCC treated at the MD Anderson Cancer Center have been published
  - In 38 patients who underwent laparoscopic CN between 2001 and 2005, median OS was 18.1 months[91]
  - In 24 elderly patients (aged ≥75 years) undergoing open CN, median OS was 16.6 months, compared with 13.7 months in patients aged <75 years (p=NS)[92]
  - In patients with non-clear cell histology, median DSS was 9.7 months compared with 20.3 months for patients with clear cell carcinoma (p=0.0003)[93]
- In a randomised trial, patients with metastatic renal cancer underwent CN + treatment with IFN-α2b or treatment with IFN-α2b alone[94]
  - Median OS was 13.6 months for CN + IFN-α2b versus 7.8 months for IFN-α2b alone (p=0.002)

Adjuvant tumour cell-derived vaccines

Clinical evidence

- In 89 patients with T3/N0/M0 disease, administration of an autologous tumour cell lysate vaccine following RN was associated with a greater PFS rate than no adjuvant therapy (74.4% versus 65.9%)[95]
- In a separate study, 160 patients with metastatic RCC who had undergone RN were randomised to treatment with $CD8^+$ tumour-infiltrating leukocytes (TILs) + recombinant interleukin-2 (IL-2) or IL-2 alone, administered for 4 days over a 4-week period[96]
  - 1-year OS 55% for $CD8^+$ TILs + IL-2 versus 47% for IL-2 alone
  - The study was terminated early due to lack of efficacy

- In a series of 102 patients with metastatic RCC, 1-year OS was 73% and 2-year OS was 55% following RN and adjuvant IL-2 + TILs[97]

- In patients with T2/N0/M0 or T3/N0/M0 RCC, following RN 148 patients received autologous tumour cell lysate vaccine while 88 patients received no adjuvant therapy[98]

    - In patients with T2 disease, 5-year OS was 86% in the vaccine group versus 71.4% in the control group (p=0.0059), while 5-year PFS was 84.6% and 65.3% for vaccine and control, respectively (p=0.0023)

    - In patients with T3 RCC, 5-year OS was 77.5% in the vaccine group versus 25.0% in the control group (p<0.0001), while 5-year PFS was 68.2% and 19.4% for vaccine and control, respectively (p<0.0001)

- In a German study, 558 patients who had undergone RN were randomised to adjuvant autologous tumour cell vaccine (doses administered at 6-weekly intervals) or no adjuvant treatment[99]

    - At 5 years of follow-up, HR for tumour progression was 1.58 (95%CI: 1.05–2.37; p=0.0204) in favour of the vaccine group

    - 5-year PFS was 77.4% in the treatment arm and 67.8% in the control arm

- A large, randomised Phase III trial evaluated adjuvant autologous tumour-derived heat-shock protein peptide complex vaccine versus observation alone in 818 patients who had undergone RN for locally advanced RCC[100]

    - After a median follow-up of 1.9 years, disease recurrence was reported for 37.7% of patients receiving vaccine and 39.8% of patients under observation only (HR: 0.923; 95%CI: 0.729–1.169; p=0.506)

Adjuvant immunotherapy

Clinical evidence

- 309 patients were randomised to adjuvant IL-2, interferon-alpha (IFN-α) and 5-fluorouracil (5-FU) in patients with a high risk of relapse after nephrectomy for RCC[101]

    - There were no statistically significant differences between the two arms in terms of DFS or OS

    - 35% of patients did not complete the treatment primarily due to toxicity

- 197 patients with metastatic RCC who had undergone RN ≥3 weeks previously were randomised to IFN-γ1b or placebo[102]

    - The overall response rate (ORR) was 4.4% (3.3% complete response [CR] and 1.1% partial response [PR]) in the IFN-γ1b group and 6.6 percent (3.3% CR and 3.3% PR) in the placebo group (p=0.54)

    - Median time to progression (TTP) was 1.9 months in both groups (p=0.49)
    - Median OS was 12.2 months with IFN-γ1b versus 15.7 months with placebo (p=0.52)

- In another randomised study, 83 patients with metastatic RCC received RN + IFN-α or IFN-α alone[103]
    - Median TTP was 5 months for RN + IFN-α versus 3 months for IFN-α alone (HR: 0.60; 95%CI: 0.36–0.97; p=0.04)
    - Median OS for RN + IFN-α versus IFN-α alone was 17 months versus 7 months (HR: 0.54; 95%CI: 0.31–0.94; p=0.03)
    - Five patients in the RN + IFN-α group and 1 in the IFN-α group achieved a CR
- In 247 patients with advanced RCC (Robson stages II and III), treatment with RN followed by IFN-α was compared with RN + observation[104]
    - 5-year OS probabilities were similar for RN + IFN-α and RN alone (0.66 versus 0.67)
    - There were also no differences between groups for 5-year DFS
- In a randomised Phase III trial, 283 patients with T3–T4 and/or node-positive RCC received adjuvant IFN-α (daily for 5 days every 3 weeks; up to a maximum of 12 cycles) or no treatment following RN[105]
    - Median DFS was 2.2 years in the IFN-α arm and 3.0 years in the observation arm (p=0.33)
- In 88 patients who underwent RN for non-metastatic RCC followed by adjuvant IFN-α, OS was 90% at 5 years and 88% at 10 years[106]
    - Median 5-year DFS was 81% and 10-year DFS was 74%
- In 235 patients with metastatic RCC who underwent RN prior to treatment with IL-2, 1- and 2-year OS were 67% and 44%, respectively[97]
- A separate study has evaluated the effects of combined IL-2, IFN-α and 5-FU for 8 weeks compared with observation only, administered after cytoreductive nephrectomy (CN) in 203 patients with locally advanced or metastatic RCC[107]
    - At a median follow-up of 4.3 years, 5-year OS was 58% in the treatment arm and 76% in the observation arm (p=0.02)
    - 5-year RFS for treatment versus observation was 42% versus 49% (p=0.24)

Resection of metastases

- Patients with limited metastatic disease can be considered for metastasectomy[58]

Patient selection

- Good PS
- Resectable, residual metastases following previous response to immunotherapy
- Patients who relapse with oligometastatic disease >1 year are more likely to benefit from metastatectomy than those who relapse <1 year post-nephrectomy
- The decision to proceed with metastatectomy should be taken after a test of time to exclude as far as possible those patients who are rapidly relapsing with metastatic disease appearing at other sites
    - A minimum 3-month period is recommended

Clinical evidence

- In a series of patients with metastatic RCC and pulmonary metastases, 191 underwent pulmonary resection[108]
    - 5-year OS was 41.5% in patients with complete resection and 22.1% in those with incomplete resection
    - In patients with pulmonary or mediastinal lymph node involvement and complete resection, 5-year OS was 24.4%, compared with 42.1% in patients without lymph node metastases
    - OS was significantly longer for patients with <7 pulmonary metastases than those with >7 pulmonary metastases (46.8% versus 14.5%)
- In an analysis of data from 92 patients with metastatic RCC and undergoing resection of pulmonary metastases, median DFS was 3.0 years[109]
- In 64 patients with metastatic RCC and only pulmonary metastases, 5-year OS was 39.9% for those achieving complete resection and 0% for those achieving incomplete resection[110]
    - Median OS was 46.6 months and 13.3 months for complete and incomplete resection, respectively
- In 45 patients undergoing resection of thyroid RCC metastases, 5-year OS was 51%[111]
    - 14 patients subsequently developed pancreatic metastases and 10 underwent pancreatic surgery, with a 5-year OS of 43%

Systemic therapy

- In patients with metastatic RCC for whom no surgical options are advisable, systemic therapy should be considered (Table 5)

Table 5: Treatment algorithm with systemic therapy for locally advanced and metastatic RCC

	Setting	**Phase III**
Treatment-naive	Good or intermediate MSKCC risk status	Sunitinib[112] Bevacizumab + interferon-α[113] Pazopanib[114]
	Poor MSKCC risk status	Temsirolimus[115] Sunitinib[112]
Refractory	Prior cytokine	Sorafenib[116]
	Prior VEGFR-TKI	Everolimus[117]

MSKCC: Memorial Sloan Kettering Cancer Center; VEGFR-TKI: vascular endothelial growth factor receptor-tyrosine kinase inhibitor

- Although several active agents are now available for the treatment of metastatic disease, their general inability to produce durable CRs necessitates chronic treatment in most patients[58]
- The benefits must therefore be weighed against the overall burden of treatment, including acute and chronic toxicity, time and cost[58]

Immunotherapy (interferon-alpha and interleukin-2)

Overview

- IFN-α is a treatment option for selected patients with a good prognosis
- IL-2 is not recommended as a routine treatment as there is a lack of Level 1 evidence proving a survival advantage
    - High-dose IL-2 may be an option for carefully selected patients referred to experienced centres

- Patients should preferably be treated within a clinical trial

Adverse effects of treatment

- The most common AEs associated with IFN-α and IL-2 therapy are hypotension, nausea, vomiting, diarrhoea and anaemia[118]

Patient selection

- Good PS (ECOG 0 or 1)
- Good renal, hepatic and haematological function
- No cardiac or central nervous system disorders
- No active infections

Clinical evidence

- The effect of IFN-α as first-line systemic treatment for metastatic RCC has been assessed in a retrospective analysis of data from 463 patients[119]
  - 12 patients achieved a CR and 41 patients achieved a PR (ORR=11%)
  - Median OS was 13 months
  - Median PFS was 4.7 months
  - 3- and 5-year OS rates were 19% and 10%, respectively
- In a Phase III study, 492 patients with metastatic RCC were randomised to medroxyprogesterone acetate (MPA; 200 mg once-daily), subcutaneous (SC) IFN-α (9 million units 3 times per week), SC IL-2 (9 million units twice-daily for 5 days followed by a 2-day rest, then, during the following 3 weeks, 9 million units twice-daily for 2 days and then 9 million units once-daily for 3 days), or SC IFN-α + SC IL-2[120]
  - Median OS was 14.9 months for MPA, 15.2 months for IFN-α, 15.3 months for IL-2 and 16.8 months for IFN-α + IL-2
  - Median PFS was 3.0 months for MPA, 3.4 months for IFN-α, 3.4 months for IL-2 and 3.8 months for IFN-α + IL-2
- In a separate Phase III trial, 192 patients with metastatic disease who had not received prior systemic therapy were randomised to SC IL-2 (5 million units/m^2 every 8 h for 3 doses, followed by a single 5 million units/m^2 dose once-daily on days 2–5 of week 1 and then for 5 days each week for a further 3 weeks; maximum 6 cycles) + SC IFN-α (5 million units/m^2 3 times per week) for the first 4 weeks of treatment; or IV

IL-2 (600,000 units/kg every 8 h for 5 days, beginning on Day 1 and again on Day 15; maximum 3 cycles)[121]

  - Response rates were 3 CR + 6 PR for IL-2 + IFN-α (ORR=9.9%) and 8 CR + 14 PR for high-dose IL-2 (ORR=23.2%) (p=0.018)
  - Median response duration was 15 months for IL-2 + IFN-α versus 24 months for high-dose IL-2 (p=0.18)
  - Median PFS was 3.1 months for both treatment arms
  - Median OS was 13 months for patients receiving IL-2 + IFN-α and 17 months for patients receiving high-dose IL-2 (p=0.211)

- 425 patients with metastatic RCC and no prior chemotherapy were randomised to SC IFN-α, IV IL-2 or a combination of both treatments[118]
  - At Week 25 of treatment, CR was achieved in 1 patient receiving IFN-α, 2 patients receiving IL-2 and 5 patients receiving IFN-α + IL-2
  - PR was achieved in 3 patients receiving IFN-α, 7 patients receiving IL-2 and 14 patients receiving IFN-α + IL-2
  - At a median follow-up of 39 months, DFS rates were 15%, 12% and 30% for IFN-α, IL-2 and IFN-α + IL-2, respectively (p=0.01 for IFN-α + IL-2 versus IFN-α or IL-2 alone)
  - OS did not differ significantly between treatment and median OS was 12 months for IFN-α, 13 months for IL-2 and 17 months for IFN-α + IL-2
- In the open-label MRC RE04 trial, 1006 patients with metastatic RCC were randomised to IFN-α2a or combination therapy with IFN-α2a, IL-2 and 5-FU[122]
  - OS at 1 year was similar for both treatments (67% in both groups)
  - At 3 years, OS was 30% in the IFN-α2a and 26% in the combination therapy group
  - Median OS was not significantly different between treatment arms (HR: 1.05; 95%CI: 0.90–1.21; p=0.55)
  - There was also no difference between treatments for median PFS

Angiogenesis inhibitors

Overview

- Patients should preferably undergo biopsy prior to the initiation of treatment with these agents

Bevacizumab

Patient selection

- Good and intermediate prognostic groups according to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria
- Clear cell histology
- Adequate cardiac and renal function
- No recent or planned surgery

Adverse effects of treatment

- When administered as monotherapy, the most common AEs associated with bevacizumab 10 mg/kg included proteinuria (25% of patients), hypertension (14%), malaise (13%) and epistaxis (8%)[123]

Clinical evidence

- In a Phase II study, 116 patients with metastatic RCC who had previously received immunotherapy and/or chemotherapy were randomised to bevacizumab 3 mg/kg, bevacizumab 10 mg/kg or placebo, administered every 2 weeks until disease progression[123]
    - Median PFS was 4.8 months for bevacizumab 10 mg/kg versus 2.5 months for placebo ($p<0.001$)
    - Median PFS was 3.0 months for bevacizumab 3 mg/kg versus 2.5 months for placebo ($p=0.041$)
    - Only 4 patients achieved objective responses and these were all in the bevacizumab 10 mg/kg group
- In the Phase III AVOREN trial, 649 patients with previously untreated metastatic RCC were randomised to bevacizumab (10 mg/kg every 2 weeks) + IFN-α (9 million units 3 times weekly) or placebo + IFN-α (9 million units 3 times weekly), with treatment until disease progression[113]
    - ORR was 31% with bevacizumab + IFN-α, compared with 13% for IFN-α alone ($p=0.0001$)
    - Median PFS was 10.2 months for bevacizumab + IFN-α versus 5.4 months for IFN-α alone (HR: 0.63; 95% CI: 0.52–0.75; $p=0.0001$)
    - Median TTP was 10.2 months for bevacizumab + IFN-α versus 5.5 months for IFN-α alone (HR: 0.61; 95% CI: 0.51–0.73; $p=0.0001$)

- The CALGB 90206 study randomised patients with previously untreated metastatic RCC to bevacizumab (10 mg/kg every 2 weeks) + IFN-α (9 million units 3 times weekly) or IFN-α monotherapy (9 million units 3 times weekly)[124]
    - Median OS was 18.3 months with bevacizumab + IFN-α (95% CI: 16.5–22.5) versus 17.4 months for IFN-α monotherapy (95% CI: 14.4–20.0) (p=0.097)
    - Median PFS was 8.4 months for bevacizumab + IFN-α compared with 4.9 months for IFN-α alone (p<0.0001)

Sunitinib

Patient selection

- Good and intermediate prognostic groups according to MSKCC criteria[125]
- Clear cell histology
- Adequate cardiac and renal function
- No recent or planned surgery

Adverse effects of treatment

- In the Phase III study, the most common AEs reported in the sunitinib group included leukopenia (78% of patients), neutropenia (72%), anaemia (71%), increased serum creatinine concentration (66%), thrombocytopenia (65%), diarrhoea (53%) and fatigue (51%)[112]

Clinical evidence

- In a Phase II study, 63 patients with metastatic RCC that had progressed following first-line cytokine therapy received sunitinib (50–75 mg once-daily for 4 weeks, followed by 2 weeks off) until disease progression[126]
    - 25 patients achieved PR and stable disease (SD) for ≥3 months was achieved by an additional 17 patients
    - Median TTP was 8.7 months
    - Median OS was 16.4 months
- In the subsequent Phase III trial, 750 patients with previously untreated metastatic RCC were randomised to 6-week cycles of oral sunitinib (50 mg once-daily for 4 weeks, followed by 2 weeks off) or SC IFN-α (9 million units 3 times per week)[112]
    - ORR was 31% with sunitinib versus 6% with IFN-α (p<0.001)

- Median PFS was 11 months in patients receiving sunitinib and 5 months in patients receiving IFN-α (HR: 0.42; 95%CI: 0.32–0.54; p<0.001)

Pazopanib

Patient selection

- Good and intermediate prognostic groups according to MSKCC criteria[125]
- Clear cell histology
- Adequate cardiac and renal function
- No recent or planned surgery

Adverse effects of treatment

- In the Phase III trial, AEs of mucositis/stomatitis, hypothyroidism and hand-foot syndrome were mostly grade 1 or 2[114]
- 4% pts had arterial thromboembolic events in the pazopanib arm compared to none in the placebo arm
- 10% of patients randomized to pazopanib had grade 3 elevation of alanine aminotransferase and 7% had grade 3 elevation of aspartate aminotransferase. There was no demonstrable haematological toxicity, although 4% pts had arterial thromboembolic events in the pazopanib arm compared to none in the placebo arm

Clinical evidence

- In the Phase III trial of Pazopanib versus placebo, the PFS in treatment-naïve groups was 11.1 months and in pre-treated patients 7.4 months (p<0.001)[114]
    - The final OS result was not significant as the analysis was confounded by early, frequent, and prolonged treatment with pazopanib and other therapies following crossover

Temsirolimus

Patient selection

- Good PS (Karnofsky score ≥60)
- Good renal, hepatic and haematological function
- At least 3 of 6 predictors of short survival

Adverse effects of treatment

- In the Phase III ARCC trial, the most frequently-reported AEs in the temsirolimus group included rash (47% of patients), anaemia (45%), nausea (37%), anorexia (32%), pain (28%) and dyspnoea (28%)[115]

Clinical evidence

- In the ARCC Phase III trial, 626 patients with metastatic RCC who had received no prior systemic therapy were randomised to SC IFN-α2a (9–18 million units 3 times per week), IV temsirolimus (25 mg once-weekly) or SC IFN-α2a (6 million units 3 times per week) + temsirolimus (15 mg once-weekly), until disease progression[115]
    - In the temsirolimus group, mortality was reduced compared with IFN-α2a alone (HR: 0.73; 95% CI: 0.58–0.92; p=0.008)
    - For temsirolimus + IFN-α2a, mortality was similar to that with IFN-α2a alone (HR: 0.96; 95% CI: 0.76–1.20; p=0.70)
    - Median OS was 7.3 months for IFN-α2a alone, 10.9 months for temsirolimus alone and 8.4 months for combination therapy
    - Median PFS was 3.1 months, 5.5 months and 4.7 months for IFN-α2a, temsirolimus and IFN-α2a + temsirolimus, respectively
    - There were no significant differences between treatment groups for ORR but the proportion of patients achieving SD for 6 months or objective response was significantly higher in the temsirolimus group (32.1%; p<0.001) and the combination therapy group (28.1%; p=0.002) than in the IFN-α2a group (15.5%)

Sorafenib

Patient selection

- Good PS (ECOG 0 or 1)
- Life expectancy >3 months
- Low- or intermediate-risk according to MSKCC criteria
- Clear cell histology
- Good renal, hepatic and haematological function
- No cardiac or central nervous system disorders

Adverse effects

- In Phase III studies, the most common AEs following sorafenib therapy included diarrhoea (43% of patients), rash (40%), fatigue (37%), hand-foot syndrome (30%), alopecia (27%) and nausea (23%)[116]

Clinical evidence

- In a Phase III, double-blind trial, patients with advanced clear cell carcinoma that had progressed following one previous systemic therapy were randomised to oral sorafenib (400 mg twice-daily) or placebo, continued until disease progression[116]
    - Median OS was 19.3 months for sorafenib and 15.9 months for placebo (HR: 0.77; 95% CI: 0.63–0.95; p=0.02)
    - Median PFS was 5.5 months for sorafenib and 2.8 months for placebo (HR: 0.51; 95% CI: 0.43–0.60; p<0.001)
    - ORR was 11% for sorafenib versus 8% for placebo
    - SD was achieved for 74% of patients receiving sorafenib and 53% of patients receiving placebo (p<0.001)

Everolimus

Patient selection

- Good PS (Karnofsky score ≥70%)
- Good renal, hepatic and haematological function
- No cardiac or central nervous system disorders
- Prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy

Adverse effects of treatment

- In the Phase III RECORD-1 study, the most common AEs associated with everolimus treatment included anaemia (91% of patients), hypercholesterolaemia (76%), hypertriglyceridaemia (71%), hyperglycaemia (50%), elevated creatinine concentrations (46%) and stomatitis (40%)[117]

Clinical evidence

- In the Phase III RECORD-1 study, 410 patients with metastatic RCC that had progressed during treatment with sorafenib, sunitinib, or both, were randomised to treatment with everolimus (10 mg once-daily) or placebo, both in conjunction with best supportive care, until disease progression[117]
    - 3 patients receiving everolimus achieved a PR versus none in the placebo group
    - SD was achieved by 63% of patients in the everolimus group compared with 32% of patients in the placebo group
    - Median PFS was 4.0 months with everolimus and 1.9 months with placebo (HR: 0.30; 95% CI: 0.22–0.40; p<0.0001)
    - The probability of being progression-free at 6 months was 26% for everolimus versus 2% for placebo

National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidance

- NICE has reviewed a number of systemic therapies for the treatment of advanced/metastatic RCC

First-line therapy

- Sunitinib is recommended as first-line therapy in patients with metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1[127]
- Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma:[128]
    - Who have not received prior cytokine therapy and have an ECOG PS of 0 or 1 and
    - If the manufacturer provides pazopanib with a 12.5% discount on the list price, and provides a possible future rebate linked to the outcome of the head-to-head COMPARZ trial, as agreed under the terms of the patient access scheme and to be confirmed when the COMPARZ trial data are made available
- Bevacuzimab, sorafenib and temsirolimus are not recommended as first-line treatment options for patients with metastatic RCC[129]

Second-line therapy

- Sorafenib and sunitinib are not recommended as second-line treatment options for patients with metastatic RCC[129]

Palliative care

Surgery

Overview

- Nephrectomy may be used to resolve symptoms such as pain and bleeding arising from the primary tumour[130]

Tumour embolisation

Overview

- This approach may be considered in patients with large tumours that cannot be resected and that are causing overt symptoms
- Common side effects include fever and transient pain, but these can usually be managed with non-steroidal anti inflammatory drugs

Clinical evidence

- A small number of studies have assessed embolisation in renal cancer
    - In 14 patients with Stage I–III RCC who underwent transarterial embolisation with ethanol, at a median follow-up of 39 months 11 patients remained alive[131]
    - In a series of 36 elderly patients (56–91 years) with a median tumour size of 6 cm, at a median follow-up of 24 months 13 had died (8 of an unrelated illness and 5 of unknown cause)[132]
        - The median time to death after diagnosis was 9 months

Palliative radiotherapy

Overview

- This is an option for patients with large tumours with bleeding where no other options are feasible or available
- In addition, radiotherapy of bone metastases from RCC can provide short-term pain relief[133–135]

Ongoing support

The MDT should ensure regular communication with the primary care team.

This may mean:

- Timely provision of detailed discharge or outpatient summaries
- Explanation of why a treatment route has been decided upon
- The patient's response to the chosen treatment
- Sharing of protocols
- Online educational resources
- Agreement on prescribing policies
- Provision of contact numbers for requests for information

The local patient support network, e.g. with the patients permission partner/family, should be included in the information/education process through the use of:

- Patient information materials
- Audio visual materials such as videos, DVDs and Web-based information

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