Renal Cell Carcinoma Care Pathway
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Purpose

This document sets out a care pathway for the management of Renal Cell Carcinoma (RCC). The pathway can be used as a guide to review local RCC pathways for planning and service re-design or improvement projects.

Scope of pathway:
- Presentation, diagnostics, staging, management and treatment of localised and metastatic renal cell carcinoma in adults over 18 years

Out of Scope:
- Renal tumours other than RCC (e.g. transitional cell carcinoma) and renal tumours in patients under the age of 18
- Palliative Care Pathway including End of Life Care – please refer to local pathways/protocols
- Patient Information (e.g. NHS choices Information Prescription Service) – visit www.nhs.uk/ipg

Limitations

Whilst this pathway is aligned with other published pathways, it is meant as a guide to clinicians, service managers and commissioners when planning, reviewing or redesigning services.

Prepared by

This Renal Cell Carcinoma Pathway was commissioned, produced and sponsored by Pfizer Ltd in consultation with a multi-disciplinary group of advisors.

We would like to acknowledge our thanks to members of the Advisory Group for their role in the development of this Renal Cell Carcinoma Pathway:

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Key

Guidelines

Supplementary Information

Pfizer Ltd has taken reasonable care in developing the Resource but excludes responsibility for any loss, liability or costs arising in connection with the outputs of the Resource to the full extent permitted by law.

Pfizer Ltd commissioned and is responsible for the development of the Renal Cancer Service Resource to assist you in the evaluation of your renal cancer service. The Pfizer Specialist Account Manager (SAM) in your area would be happy to assist you if you have any questions about the use of this Resource.
Renal Cell Carcinoma Care Pathway

The Care Pathway

- Initial Presentation
  - GP/A&E/inpatient
- Initial Specialist Consultation and Diagnosis
- Staging and Grading
- Histological Diagnosis
- Multi-Disciplinary Team

Systemic Therapy for Advanced/Metastatic RCC

- Treatment Options (Locally Advanced/Metastatic)
  - Treatment Plan (Metastatic)
  - Treatment Plan (Localised Follow-up)

End of Life Care

Exit Pathway

NHS Timelines
- Urgent Referral
  - 14 days
- 1st Specialist Appointment
  - 62 Days
- Decision to treat
  - 31 days
- Initial Treatment

References:
The NHS England Specialised Urology Clinical Reference Group (CRG)

The NHS England Specialised Urology CRG covers specialised services relating to urological cancer including renal cancer. The CRG have produced a service specification for renal cancer. The service specifications are important in clearly defining what NHS England expects to be in place for providers to offer evidence-based, safe and effective services. They have been developed by specialised clinicians, commissioners, expert patients and public health representatives to describe core and developmental service standards. Core standards are those that any reasonable provider of safe and effective services should be able to demonstrate, with developmental standards being those that really stretch services over time to provide excellence in the field.²

NHS Specialised Urology Service:

Aims

- To deliver high quality holistic care to improve patient survival, functional capability and quality of life
- To ensure ready and timely access to appropriate supportive care for patients, their relatives and carers
- The service will be delivered through a specialist urology multi-disciplinary team (MDT)

Overall objectives

- To provide exemplary and comprehensive care for all referred patients with urological cancers
- To ensure radiological, pathological and diagnostic facilities are available and to use the most up-to-date validated diagnostic tools and knowledge to effectively review, diagnose, classify and stage the cancer prior to planning treatment
- To advise and undertake investigations and to proceed to treatment options if clinically indicated, including high quality surgical treatment of patients
- To carry out effective monitoring of patients to ensure that the treatment is safe and effective
- To provide care that promotes optimal functioning and quality of life for each individual cancer patient
- To provide appropriate follow-up and surveillance after definitive treatment
- To ensure that all aspects of the service are delivered as safely as possible, conform to national standards and published clinical guidelines and are monitored by objective audit
- To provide care with a patient and family centred focus to maximise the patient experience
- To support local healthcare providers whenever it is safe and clinically appropriate within the framework of the Improving Outcomes Guidance (IOG)
- To provide high quality information for patients, families and carers in appropriate and accessible formats and media
- To ensure there is accurate and timely information given to the patient’s General Practitioner
- To ensure that there is involvement of service users and carers in service development and review
- To ensure there is a commitment to continual service improvement
- To comply with Peer Review Cancer Measures and with clinical lines of enquiry when they are developed
- To comply with Care Quality Commission regulations

References:

The specialist urological cancer MDT will deliver the service in line with the following:

- There is a weekly multidisciplinary team meeting to discuss the needs of each newly referred patient (and other patients as required) in detail and review other non-surgical aspects of their care; patients will be likely to require subsequent additional review at the multidisciplinary team meeting for example after treatment or progression of the cancer.
- Treatment within the specialist multidisciplinary team should be in accordance with locally agreed treatment guidelines which should be consistent with nationally agreed guidelines.
- If surgery is the first planned treatment then efforts should be made to give the patient a date for that surgery at the first visit, and written information provided on that surgery. The timing of surgery is agreed on the basis of evidence based treatment protocols with the local cancer network.
- A written summary of the consultation should be offered to the patient as well as written information on the relevant type of urological cancer.
- Patients should have access to a ‘key worker’ - this is normally the Clinical Nurse Specialist.
- Accurate and timely information should be shared with the patients’ General Practitioner so that they can be in a position to support and advise the patient.
- Patients treated as in-patients are reviewed daily on a ward round supported by a consultant urologist and oncological surgeon with input from the core multidisciplinary team as clinically required.
- Audit should be undertaken as an integral part of improving the delivery of care to provide the evidence to improve and enhance the delivery of the clinical care provided.
- Patients should be actively invited to participate in clinical trials especially those approved by the National Cancer Research Network (NCRN).

### Specialist Urological Cancer Multi-disciplinary Team (MDT)

The specialist urological cancer MDT will deliver the service in line with the following:

- There is a weekly multidisciplinary team meeting to discuss the needs of each newly referred patient (and other patients as required) in detail and review other non-surgical aspects of their care; patients will be likely to require subsequent additional review at the multidisciplinary team meeting for example after treatment or progression of the cancer.
- Treatment within the specialist multidisciplinary team should be in accordance with locally agreed treatment guidelines which should be consistent with nationally agreed guidelines.
- If surgery is the first planned treatment then efforts should be made to give the patient a date for that surgery at the first visit, and written information provided on that surgery. The timing of surgery is agreed on the basis of evidence based treatment protocols with the local cancer network.
- A written summary of the consultation should be offered to the patient as well as written information on the relevant type of urological cancer.
- Patients should have access to a ‘key worker’ - this is normally the Clinical Nurse Specialist.
- Accurate and timely information should be shared with the patients’ General Practitioner so that they can be in a position to support and advise the patient.
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- Audit should be undertaken as an integral part of improving the delivery of care to provide the evidence to improve and enhance the delivery of the clinical care provided.
- Patients should be actively invited to participate in clinical trials especially those approved by the National Cancer Research Network (NCRN).

### Core Members

- Urologist surgeons
- Oncologists (clinical and medical)
- Radiologists
- Histopathologists
- Urological Clinical Nurse Specialist
- Multidisciplinary Team Co-ordinator / Secretary

### Leadership

- There should be a single named lead clinician for the specialist urological cancer service who should also be a core team member. (This is in addition to a single named lead clinician for the local urological cancer service who should also be a core team member)
- A NHS employed member of the core or extended team should be nominated as having specific responsibility for user issues and information for patients and carers.
- A core member must be identified as the individual responsible for recruitment into clinical trials and other well designed studies.

### References:

**Renal Cell Carcinoma Care Pathway**

### Initial Presentation

**Primary Care (GP) - symptomatic**

- History, Examination Symptom Review
  - History of RCC in first degree relative
  - Aetiological factors including lifestyle factors such as:
    - Smoking, obesity, and hypertension

**Symptoms:**
- Palpable lump in abdomen
- Unexplained weight loss
- Pain in side
- Loss of appetite

**Additional Symptoms in mRCC:**
- Bone pain
- Persistent cough

**NICE Criteria for urgent referrals for suspected kidney cancer:**
- Patients presenting with painless macroscopic haematuria
- Patients presenting with painless macroscopic haematuria plus symptoms suggestive of UTI. Refer urgently if UTI ruled out on testing
- Patients ≥ 40 years presenting with recurrent or persistent UTI associated with haematuria
- Patients ≥ 50 years presenting with unexplained microscopic haematuria
- Patients with an abdominal mass identified on imaging or clinically that might be arising from the urinary tract
- Patients < 50 years of age with microscopic haematuria, should be tested for proteinuria and serum creatinine levels measured. Those with proteinuria or raised serum creatinine should be referred to a renal physician. If neither is present, a non-urgent referral to an urologist should be made

**A&E - symptomatic**

**Note:**
1. Most RCCs are asymptomatic and non-palpable until the advanced stages of the disease and > half of all RCCs are picked up incidentally.
2. Approx 30% of symptomatic patients have paraneoplastic syndromes.

**In/Outpatient - often asymptomatic, incidental**

**Paraneoplastic Syndromes:**
- Hypertension
- Cachexia
- Weight loss
- Pyrexia
- Neuromyopathy
- Amyloidosis
- Elevated erythrocyte sedimentation rate
- Anaemia
- Abnormal liver function
- Hypercalcaemia
- Polycythaemia

**Note:**
1. Tests should not delay urgent referral if RCC is suspected.

**References:**
Renal Cell Carcinoma Care Pathway

Initial Specialist Consultation and Diagnosis

**History**
- History of RCC in first degree relative
- Symptom Review
- Specifically paraneoplastic syndrome

**Examination**
- Physical examination for:
  - Palpable abdominal mass
  - Palpable cervical lymphadenopathy
  - Non-reducing varicole
  - Bilateral lower extremity oedema

**Imaging Investigations - detection and characterisation of renal masses**
- **Abdominal CT** provides information on:
  - Images performed pre and post IV contrast allow accurate characterisation of renal masses
  - To maximise differential diagnosis and detection, include images from the nephrographic phase
  - Function and morphology of the contralateral kidney
  - Primary tumour extension with extrarenal spread
  - Venous involvement
  - Enlargement of locoregional lymph nodes
  - Condition of adrenal glands and the liver

**MRI**
- If CT results are indeterminate, MRI may provide additional information to:
  - Demonstrate enhancement in renal masses
  - Investigate locally advanced malignancy
  - Investigate venous involvement (if the extent of an inferior cava tumour is poorly defined on CT scan)

**Laboratory Investigations**
- Review results or order tests
  - Complete blood cell count
  - Serum creatinine
  - Glomular filtration rate (GFR)
  - Haemoglobin
  - Erythrocyte sedimentation rate (ESR)
  - Alkaline phosphatase (ALP)
  - Lactate dehydrogenase (LDH)
  - C-reactive protein (CRP)
  - Serum corrected calcium
  - Urinalysis
  - Coagulation study
  - Liver function tests

Total renal function evaluation should be considered to optimise treatment decision e.g. the need to preserve renal function. Estimate split renal function using renal scintigraphy when renal function is compromised or deemed clinically important.

**Note:**
1. According to the EAU Guidelines, physical examination has only a limited role in diagnosing RCC, however, it is important for clinical evaluation
2. In a patient with one or more laboratory or physical findings, the presence of RCC should be suspected and radiological examinations should be initiated
3. About 30% of patients present with symptoms indicative of metastatic disease
4. Central renal masses abutting or invading collecting system: urinary cytology and possibly endoscopic assessment of upper urinary tract to rule out urothelial cancer

**Metastatic RCC**
- Most brain or bone metastases are symptomatic at diagnosis
  - so routine brain scan, brain CT or MRI is not indicated and may be used in presence of specific signs and symptoms
- For chest staging, chest CT is the most accurate investigation but at least a plain chest radiograph should be taken for clinical staging

**MRI is indicated for patients with allergy to intravenous contrast and in pregnancy without renal failure.**

**References:**
Staging and Grading

American Joint Committee on Cancer (AJCC) TNM Classification System (7th ed., 2010)\(^6\)

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour ≤ 4 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour &gt; 4 cm but not &gt; 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour &gt; 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumours &gt; 10 cm limited to the kidney</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour grossly extends into the renal vein or its segmental (muscle containing) branches or tumour invades perirenal and renal sinus (peripelvic) fat but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour grossly extends into the vena cava below the diaphragm</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single regional lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

TNM stage grouping

- **Stage I**: T1 N0 M0
- **Stage II**: T2 N0 M0
- **Stage III**: T1 or T2 N1 M0
- **Stage IV**: T3 N0 or N1 M0
- **Stage IV**: Any T Any N M1

Eastern Cooperative Oncology Group (ECOG) Performance Status at Diagnosis\(^7\)

0 — Fully active, able to carry on all pre-disease performance without restriction
1 — Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 — Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3 — Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 — Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 — Dead

Note:
For renal cystic masses, use the Bosniak classification system

References:
### Renal Tumour Biopsy

**Percutaneous biopsy is:**

- Always required before ablative therapy and systemic therapy without previous pathology
- Recommended in active surveillance strategies in order to stratify the follow-up according to tumour histology

When biopsy is indicated, good-quality needle cores should be obtained with a coaxial technique in order to increase the safety of the procedure and maximise its diagnostic yield.

**Note:**

1. Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes.

### WHO: three major histological subtypes (based on the Heidelberg classification system)

- **Clear cell – (cRCC 80–90%)**
  - Type 1: Low grade with chromophilliac cytoplasm and a favourable prognosis
  - Type 2: Mostly high grade with eosinophilic cytoplasm (great propensity for metastasis)

- **Papillary – (pRCC 10–15%)**
  - Type 1: Low grade with chromophilliac cytoplasm and a favourable prognosis
  - Type 2: Mostly high grade with eosinophilic cytoplasm (great propensity for metastasis)

- **Chromophobe – (chRCC 4–5%)**

### Other rarer types of kidney cancer

- A variety of uncommon, sporadic and familial carcinomas including:
  - Collecting-duct RCC
  - Unclassified

### Nuclear Characteristics used in the Fuhrman System

**Grade 1:**

- Solid arrangement of clear cells which exhibit regular, uniform round nuclei comparable in size to red blood cells seen in the field
- Nucleoli are absent

**Grade 2:**

- Solid sheet of cells with nuclei varying in size, generally larger than in Grade 1 tumours
- Nuclear outlines are slightly irregular
- Nucleoli are frequently visible at high power

**Grade 3:**

- Large nuclei with hyperchromasia with marked variability in size and shape
- Nucleoli are large and conspicuous

**Grade 4:**

- Solid clusters of cells which have large pleomorphic nuclei
- Extremely irregular outlines
- Often multi-lobed and with chromatin clumping and conspicuous nucleoli

### References

## Treatment Options – Localised Disease (T1–2 N0 M0 & T3–4 N0 M0)

### Note:
- Considerations for treatment options – age, VHL, co-morbidity, patient choice, trial options - adjuvant clinical trials (intermediate and high risk)\(^4\)
- Surgical therapy is the only curative therapeutic approach for RCC
- Tumour control rates appear equivalent for T1–2 tumours between laparoscopic and open radical nephrectomy
- Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy
- The data regarding quality of life and perioperative outcomes for laparoscopic nephron-sparing surgery compared with open nephron-sparing surgery remains
- Adrenalectomy is not recommended, provided a pre-operative CT scan shows the adrenal gland is normal and the intra-operative findings do not suggest intra-adrenal metastatic spread or a direct invasion of the adrenal gland
- Extended lymphadenectomy is not recommended since it does not appear to improve survival. It should be restricted to staging purposes with dissection of palpable and/or enlarged lymph nodes

### Tumours: T1 N0 M0

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Approach(^3)</th>
<th>Additional Information(^3)</th>
</tr>
</thead>
</table>
| T1 (T1a,T1b) | Nephron-Sparing Surgery | • Open – recommended standard of care  
• Laparoscopic and robot assisted partial nephrectomy are alternatives to open nephron-sparing surgery (the standard of care) | • Performed whenever possible for T1a/b tumours  
• Standard procedure for solitary tumours < 7cm where technically feasible |
| T1 (T1a,T1b) | Radical Nephrectomy | Laparoscopic – only in patients not suitable for nephron-sparing surgery  
• Open – optional in patients not suitable for nephron-sparing surgery | No longer the standard treatment but may be used where nephron-sparing surgery is not suitable because of: \(^3\)  
• Locally advanced tumour growth  
• Partial resection is not technically feasible because the tumour is in an unfavourable location  
• Significant deterioration of a patient’s general health |
| T1 (T1a,T1b) | Active Surveillance | Active surveillance is a reasonable option for elderly/co-morbid patients with small renal masses and limited life expectancy  
• Cryotherapy and radiofrequency ablation for patients with small renal tumours and/or significant co-morbidity who are unfit for surgery | Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for those tumours that show clinical progression during follow-up  
• Pre-treatment biopsy has to be carried out as standard for ablative therapy and is useful when active surveillance is considered and in order to stratify follow-up based on tumour histology |

### References:
### Treatment Options – Localised Disease (T1–2 N0 M0 & T3–4 N0 M0) – cont’d

**Tumours: T2, T3–4 N0 M0**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Approach</th>
<th>Additional Information</th>
</tr>
</thead>
</table>
| T2                     | Radical Nephrectomy     | • Laparoscopic – recommended standard of care  
                          |                                       | • Open – adequate and recommended but has higher morbidity                             |
| Locally Advanced       | Radical Nephrectomy     | • Open – recommended standard for most patients  
                          |                                       | • Laparoscopic – Feasible in selected patients                                        |
| (T3–4 N0 M0)           | Nephron-Sparing Surgery |                                                                                 | • Recommended in selected patients in experienced centres                               |
|                        |                         |                                                                                 | • There is an increased risk of intrarenal recurrences in larger-size (>7cm) tumours treated with nephron-sparing surgery |

**Note:**
1. Tumour control rates appear equivalent for T1–2 tumours between laparoscopic and open radical nephrectomy.
2. Long-term outcome data indicate that laparoscopic radical nephrectomy has equivalent cancer-free survival rates to those of open radical nephrectomy.
3. The data regarding quality of life and perioperative outcomes for laparoscopic nephron-sparing surgery compared with open nephron-sparing surgery remains.

**References:**
Renal Cell Carcinoma Care Pathway

Treatment Plan Localised – Follow-up/surveillance after treatment of localised RCC

Note:
1. Management Plan agreed by MDT:
   a) Surveillance should also include clinical evaluation of renal function and cardiovascular risk factors
   b) Surveillance should be based on a patient’s risk factors and type of treatment received
   c) There is an increased risk of intrarenal recurrences in larger-size (>7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients

Proposed follow-up according to the EAU Guidelines

There is no consensus on surveillance however follow-up should be performed to identify local recurrence and metastases early
There is controversy over the optimal duration of follow-up and intensive radiological surveillance for all patients is unnecessary
It is reasonable to stratify follow-up according to risk of recurrence or metastases developing and the type of treatment. Scoring systems and nomograms have been designed (notably Kattan, Liebovich, UCLA and Karakiewicz) to quantify the likelihood of patients developing tumour recurrence, metastases and subsequent death.

Follow-up According to Risk

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Surveillance intervals adapted relative to radiation exposure and benefit. MRI can be used to reduce radiation exposure</td>
</tr>
<tr>
<td>Intermediate Risk and High Risk</td>
<td>CT of chest and abdomen is the investigation of choice</td>
</tr>
</tbody>
</table>

EAU proposed algorithm for surveillance following treatment for RCC taking into account patient risk profile and treatment efficacy

<table>
<thead>
<tr>
<th>Risk profile</th>
<th>Treatment</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>1 year</td>
</tr>
<tr>
<td>Low</td>
<td>RN/PN only</td>
<td>US</td>
</tr>
<tr>
<td>Intermediate</td>
<td>RN/PN/cryo/RFA</td>
<td>CT</td>
</tr>
<tr>
<td>High</td>
<td>RN/PN/cryo/RFA</td>
<td>CT</td>
</tr>
</tbody>
</table>

RN = radical nephrectomy; PN = partial nephrectomy; US = ultrasound of kidneys and renal bed; CT = CT of chest and abdomen; cyro = cryotherapy; RFA = radiofrequency ablation.

References:
Renal Cell Carcinoma Care Pathway

Treatment Options – Metastatic (T any, N any, M1)

Note:
1. Usually nephrectomy in setting of metastatic disease is for cytoreductive reasons. (See Treatment Options – Localised for T1–4 surgical options)
2. Radical nephrectomy is only curative if surgery can excise all tumour deposits and for the majority of patients with metastatic disease it is palliative only and other systemic therapies are necessary
3. Nephrectomy is recommended for patients with metastatic disease who are suitable for surgery and have good performance status
4. Involvement of a specialist cardiothoracic centre for invaded vena cava (IVC) involvement (for T3 & T4)
5. Consider role of other specialties e.g.: spinal surgeons for treatment of secondaries and plan care around patient outcomes

Note:
1. In a meta-analysis of two randomised studies comparing nephrectomy combined with immunotherapy versus immunotherapy only, increased long-term survival was found in patients undergoing nephrectomy. The role of nephrectomy in metastatic RCC with targeted therapies is under evaluation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Approach</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic</td>
<td>Metastasectomy</td>
<td></td>
<td>• There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis and therefore the possibility of metastasectomy has to be continuously re-evaluated, especially in combination with a targeted systemic therapy</td>
</tr>
<tr>
<td>T any, N any,</td>
<td></td>
<td></td>
<td>• In patients with metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status</td>
</tr>
<tr>
<td>M1</td>
<td>Radiotherapy</td>
<td>In individual cases, stereotactic radiotherapy for the treatment of bone and brain metastases can induce symptom relief</td>
<td>• Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or other systemic treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain)</td>
</tr>
</tbody>
</table>

References:
Systemic Therapy for Advanced or Metastatic RCC

Memorial Sloan-Kettering Cancer Center (MSKCC)\textsuperscript{3,10}

**Prognostic factors for survival in patients with metastatic renal cell carcinoma**

MSKCC prognostic profiles are derived from the era of cytokine immunotherapy.

**Patients are categorised into one of three risk groups:**
1. Favorable Risk - those with zero risk factors
2. Intermediate Risk - those with one risk factor
3. Poor Risk - those with two or more risk factors

**Where risk factors were identified as:**
- a. Low Karnofsky performance status (< 80%)
- b. Time from diagnosis to treatment with IFN-α < 12 months
- c. Haemoglobin < Lower limit of laboratory’s reference range
- d. Lactate dehydrogenase > 1.5 x the upper limit of laboratory’s range
- e. Corrected serum calcium > 10.0 mg/dL (2.4 mmol/L)

**Database Consortium Model (DCM)\textsuperscript{11,12}

**Prognostic factors for overall survival (OS) in patients with metastatic renal cell carcinoma**

Derived from the era of targeted therapy.

**Patients are categorised into three risk categories:**
1. Favourable-risk group
2. Intermediate-risk group
3. Poor-risk group

**Risk factors:**
- Low Karnofsky performance status (< 80%)
- Time from diagnosis to treatment < 12 months
- Haemoglobin < Lower limit of normal
- Corrected serum calcium > Upper limit of normal
- Neutrophil count > Upper limit of normal

**Median overall survival and percentage of patients surviving 2 years treated in the era of targeted therapy per DCM risk group\textsuperscript{11,12}**

<table>
<thead>
<tr>
<th>DCM risk group</th>
<th>Surveillance</th>
<th>Median OS (months)</th>
<th>2-year OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>157</td>
<td>43.2</td>
<td>75% (65–82%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>440</td>
<td>22.5</td>
<td>53% (46–59%)</td>
</tr>
<tr>
<td>Poor</td>
<td>252</td>
<td>7.8</td>
<td>7% (2–16%)</td>
</tr>
</tbody>
</table>

**Note:**\textsuperscript{11,12}
1. The DCM which has been validated in the era of targeted therapy may yield a more accurate prognosis than the MSKCC risk model. In the DCM, neutrophilia and thrombocytosis are added to the MSKCC risk factors and LDH is omitted.

**References:**
### Systemic Therapy for Advanced or Metastatic RCC – cont’d

#### Systemic Treatments

### Licensed Indications

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>For the treatment of patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine</td>
</tr>
<tr>
<td>Everolimus</td>
<td>For treatment of patients whose disease has progressed on or after treatment with VEGF-targeted therapy</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>For treatment of mRCC patients who have failed prior IFN-alpha or IL2 based therapy or are considered unsuitable for such therapy</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>For treatment of advanced/mRCC in adults</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>For the first line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>In combination with interferon alfa-2a – for first line treatment of patients with advanced and/or mRCC</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>For the first-line treatment of patients with advanced RCC who have at least 3 of 6 prognostic risk factors</td>
</tr>
<tr>
<td>IFN</td>
<td>For treatment of advanced RCC</td>
</tr>
<tr>
<td>IL</td>
<td>For treatment of mRCC</td>
</tr>
</tbody>
</table>

#### National Institute for Health and Clinical Excellence (NICE)

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Line</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Recommended for those who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 (See NICE Guidance)</td>
</tr>
<tr>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>1st Line</td>
<td>Bevacizumab, Sorafenib, Temsirolimus</td>
</tr>
<tr>
<td></td>
<td>Not recommended for treatment of advanced or mRCC</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Sunitinib, Sorafenib, Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Not recommended as 2nd line treatment options</td>
</tr>
<tr>
<td>Prior VEGF-targeted therapy</td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td>Not recommended for the second-line treatment of advanced RCC</td>
</tr>
</tbody>
</table>

#### Scottish Guidance

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Line</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Recommended for those who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 (See NICE Guidance)</td>
</tr>
<tr>
<td>1st Line</td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Recommended in first-line treatment of advanced RCC</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Axitinib</td>
</tr>
<tr>
<td></td>
<td>Recommended for patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine</td>
</tr>
<tr>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>1st Line</td>
<td>Bevacizumab, Sorafenib, Temsirolimus</td>
</tr>
<tr>
<td></td>
<td>Not recommended for treatment of advanced and/or mRCC (See NICE Guidance)</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Sorafenib, Sunitinib, Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Not recommended for treatment of those who have failed with IFN-alpha. (See NICE Guidance for sunitinib and sorafenib)</td>
</tr>
<tr>
<td>Prior VEGF-targeted therapy</td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td>Not recommended for treatment of those whose disease has progressed on or after treatment with VEGF</td>
</tr>
</tbody>
</table>

*where NICE guidance has been referred to, a NICE multiple technology appraisal outcome has been adopted as guidance in Scotland

References: See page 16.
### Systemic Therapy for Advanced or Metastatic RCC – cont’d

**European Society for Medical Oncology**

<table>
<thead>
<tr>
<th>Treatment recommendations (clear cell RCC)</th>
<th>Level and grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line: Good and intermediate risk</strong></td>
<td></td>
</tr>
<tr>
<td>Standard treatment</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>IA</td>
</tr>
<tr>
<td>Bevacizumab + IFN-alpha</td>
<td>IA</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>IIB</td>
</tr>
<tr>
<td>Alternative treatment</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>IIB</td>
</tr>
<tr>
<td>Cytokines (including high dose IL2)</td>
<td>IIIC</td>
</tr>
<tr>
<td><strong>1st line: Poor risk</strong></td>
<td></td>
</tr>
<tr>
<td>Standard treatment</td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>IB</td>
</tr>
<tr>
<td>Alternative treatment</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>IIB</td>
</tr>
<tr>
<td>Best supportive care</td>
<td></td>
</tr>
<tr>
<td><strong>2nd line: Previous treatment with VEGF(R) inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Standard treatment</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>IIA</td>
</tr>
<tr>
<td>Axitinib</td>
<td>IB</td>
</tr>
<tr>
<td>Alternative treatment</td>
<td></td>
</tr>
<tr>
<td>Shifting TKIs</td>
<td>IIIB</td>
</tr>
<tr>
<td>Clinical trial</td>
<td></td>
</tr>
<tr>
<td><strong>2nd line: Previous treatment with cytokines</strong></td>
<td></td>
</tr>
<tr>
<td>Standard treatment</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>IA</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>IIIA</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>IIA</td>
</tr>
<tr>
<td>Axitinib</td>
<td>IA</td>
</tr>
</tbody>
</table>

**Evidence levels and grades**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,..), option</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

**Additional information**

**Immunotherapy**
- 1st Line - Monotherapy with IFN-alpha or high dose bolus IL2 for mRCC for selected patients with clear cell histology and good prognostic factors

**Chemotherapy**
- Chemotherapy as a monotherapy is not effective as a treatment for metastatic RCC and is therefore not recommended

**Clinical Trials** should be considered where appropriate

**References:** See page 16.
Renal Cell Carcinoma Care Pathway

Systemic Therapy for Advanced or Metastatic RCC – cont’d

**Note:**
1. Optimising Systemic Therapy
   a) Pro-active strategies are key to optimising drug therapy
   b) Benefits of optimum side effect management
      – Reduce patient discomfort
      – Avoid the need for dose reductions and discontinuations
      – Improve patient adherence
      – Support optimal clinical outcomes
   c) Education and support
      – Awareness of potential side-effects and how to manage them
      – Self-monitoring and reporting side-effects early to improve the likelihood of continuation of therapy at optimum dose
      – The importance of maintaining dose and optimal duration
      – Specific measures to prevent common side-effects
   d) Reluctance to report side-effects may come from:
      – Embarrassment about symptoms
      – Impression of failure
      – Not wanting to be a nuisance
      – Belief that symptoms are part of the cancer and must be tolerated
      – Concern that treatment dose will be reduced
      – Concern that treatment will be withdrawn.

References:
27. Scottish Medicines Consortium, pazopanib 200mg, 400mg film-coated tablets (Votrient) SMC No.(676/11), February 2011. Available from www.scottishmedicines.org.uk/SMC_Advice/Advice/676_11_pazopanib_Votrient/pazopanib_Votrient
Renal Cell Carcinoma Care Pathway

Treatment Plan - Metastatic

Multi-Disciplinary Management

Note:
1. Considerations
   - Co-morbidities / other care plans
2. Management Plan agreed by MDT
   - Dependent on treatment option
   - Renal Oncologist - Should provide input at all MDT decisions for mRCC patients
3. Shared and agreed with patient
   - Carer involvement if appropriate
4. Monitoring for progression on systemic therapy should include radiological assessment
5. Patient factors
   - Choice / satisfaction
   - Manage patients’ expectations
   - Carer support
   - Mobility
6. Patient Safety
   - Medications full medicine reconciliation to scope for contra-indications & monitoring
   - Adherence issues

Refer to local protocol/End of Life Care Pathway/Palliative Care Pathway for management of patients in these settings

Specialist Management

Acute Oncology Assessment Units
• Support for patients feeling unwell/ requiring help with side-effects management
• Quick access to tests & admissions if required
• Potential to prevent admissions

Renal Oncologist
• Should provide input at all MDT decisions for mRCC patients

Dedicated Renal Radiologist/Pathologist

Key Worker
• Clinical team liaison
• Patient support

Palliative Care Team
• see Palliative Care

Cancer Specialist Dietician
• weight management
• nutrition advice

Specialist Nursing / Pharmacist led clinics (to approved protocol)
• Liaison with primary care to support optimal management of toxicity
• Consistent point of contact for patients seeking advice while on treatment and healthcare professionals requiring specific advice about patient management.
• Streamline drug verification and dispensing
• Pre-treatment and follow-up to include NMP & toxicity monitoring and management telephone, face:face
• Surveillance - post operative, renal function
• Treatment delivery
• Medicines Review
• Managing home delivery

Assessment:
• Screening for adverse toxicities to treatment using the Common Terminology Criteria version 4.03 (National Cancer Institute 2010).
• Assessment of performance status
• Review of thyroid function. (TKIs only)
• Blood pressure monitoring. (TKIs only)
• Monitoring disease response to treatment using computed tomography (CT) scan results

Referral for medical review where:
• Patients reporting persistent or recurrent grade 2 adverse events, or any grade 3 or above toxicities
• Radiological evidence of clinical disease progression, mixed response, or patient-reported suspected new symptoms will also be referred for medical review

References: