Protocol for Planning and Treatment

The process to be followed in the management of:
LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

Approximately 50% cases of renal cancer are detected incidentally during abdominal imaging for another medical condition.

Otherwise often associated with haematuria or non-specific symptoms such as fatigue, night sweats, weight loss, malaise and fever.

25-30% of patients have metastatic disease at presentation.

30% of patients initially diagnosed with localised disease will go on to develop metastases post-nephrectomy – these will usually be detected during follow-up surveillance (see TUCN risk-stratified post-operative surveillance protocol).

2. STAGING

As per UICC, TNM 7th edition 2009.
Definition of locally advanced/metastatic disease : T4N1M0, any T N2 M0, or any T, any N M1

3. HISTOPATHOLOGY

Conventional clear cell carcinoma (80%), papillary (12%), chromophobe (4%) collecting duct (<1%), unclassified (3-5%).

4. INVESTIGATIONS

History and clinical examination – include family history to assess risk of inherited syndrome and refer to medical genetic service if concerns.

Routine biochemistry, calcium, LFTs, LDH and FBC.

CT chest/abdomen and pelvis.

Bone scan if alkaline phosphatase raised or bone pain.

CT brain for any neurological symptoms or signs

All patients with locally recurrent or metastatic disease either post-nephrectomy or at initial presentation should be discussed at the urology MDT.

Patients fit for systemic therapy without histology from previous nephrectomy and who are not

suitable for cytoreductive nephrectomy, should undergo biopsy of primary or metastasis if safe and technically feasible (to confirm diagnosis and histological type)

5. SURGERY

Resection of a solitary metastasis or oligometastses in a single site

Should be considered for patients of good performance status if patients present with limited synchronous metastatic spread or a long interval between nephrectomy and detection of metachronous metastasis. The metastatic site should be proven to be solitary by adequate restaging.

Palliative nephrectomy

May be required for uncontrolled pain and /or bleeding.

Cytoreductive nephrectomy

In patients of good performance status with non-resectable low volume metastatic disease at initial presentation consider cytoreductive nephrectomy followed by referral to oncology for systemic therapy.

The role of cytoreductive nephrectomy in combination with VEGF receptor inhibitors in currently unknown and is the subject of an on-going Phase 3 trial. However, as the majority of patients recruited into the pivotal RCTs of VEGF receptor inhibitors had previously undergone nephrectomy, cytoreductive nephrectomy is recommended for patients of good performance status, where the bulk of the disease is within the kidney and the kidney can be removed easily

6. SYSTEMIC THERAPY

N.B It may be appropriate in selected asymptomatic patients with unresectable metastatic disease to monitor disease initially with serial CT scanning e.g. every 3 months initially to gauge tempo of disease progression. In some patients disease may remain stable for some time without any systemic therapy. Systemic treatment should be commenced on disease progression. N.B Renal cancer QPI recommends that 70% of patients of PS0-1 should receive systemic therapy within 12 months of diagnosis of advanced disease.

6.1 First line therapy

As per SMC advice options are:

Sunitinib 50mg PO OD for 28 days then 14 day break q42 days (if patients show rapid progression during the 2 week break consider 37.5mg once daily continuously)

or

Pazopanib 800mg PO once daily continuously

Indications
Non-resectable locally advanced or metastatic renal cell carcinoma.

ECOG performance status 0-1

Good-intermediate prognosis disease as per the Memorial-Sloan Kettering prognostic scoring system – see Appendix)

Contraindications
Patients with poor prognosis disease as per the Memorial Sloan Kettering prognostic scoring system

Patients of PS ≥2

Significant cardiovascular disease (including MI within previous 6 months)

Uncontrolled hypertension

Pregnancy/lactation

Severe hepatic impairment (Pazopanib)

Choice of first line agent

Clear cell renal carcinoma

Both pazonpanib and sunitinib are licensed for and approved by the Scottish Medicines Consortium for first line use in the treatment of metastatic renal carcinoma based on evidence including 2 RCTS supporting their efficacy.

A RCT directly comparing the 2 drugs wrt efficacy and toxicity is currently on-going and is not expected to report until 2012.

From the currently available evidence it seems that sunitinib and pazopanib demonstrate similar oncological efficacy and toxicities although there is some evidence that pazopanib may be better tolerated with reduced incidence of hypertension and fatigue but with an increased risk of causing hepatic toxicity.

As there is currently no available evidence to support the use of one agent over the other at the moment in clear cell renal cancer, choice of first line agent should be made on an individual basis after discussion with the patient.

Non-clear cell renal carcinoma

Only patients with conventional clear cell or predominantly clear cell histology were included in the trials that demonstrated a survival advantage with sunitinib versus interferon as first-line therapy in metastatic disease or with pazopanib versus placebo in cytokine refractory disease.

Data from expanded access program for sunitinib suggests a response rate of 5.4% with disease stabilisation in others with an overall clinical benefit in 47% of patients with non-clear

cell histology.

Therefore sunitinib appears active in non-clear cell renal cell carcinoma but less efficacious than in clear cell carcinoma.

There is currently no data to sport the use of pazopanib in non-clear cell metastatic renal carcinoma and sunitinib should be the first line agent of choice in this group.

Monitoring on treatment

Toxicity
Patients should be booked into clinic for review 2 weeks after starting treatment for toxicity assessment and then reviewed every 2 weeks until toxicities adequately controlled (see separate protocols for toxicity management). Once toxicities controlled see in clinic every 6 weeks.

Response
Clinically assessed during each clinic visit

CT chest/abdomen after 10-12 weeks treatment (or sooner if clinically indicated) and then after every 12 weeks.

(Consider metastatectomy if disease is downstaged by systemic therapy and if surgery felt likely to remove all clinically and radiologically detected disease.)

Criteria for discontinuation of therapy

Evidence of disease progression clinically or radiologically (as demonstrated as definite progression on 2 successive CT scans).

CTC Grade 3 or 4 non-haematological toxicity despite switch to alternative first line agent and dose reduction by 2 dose levels.

6.2 Second line-systemic therapy

Axitinib 5mg PO twice daily continuously (dose may be increased if tolerated to a maximum of 10mg twice daily).

Axitinib (Inlyta®) is accepted for use within NHS Scotland for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. Local agreement allows the use of this agent as second line treatment after failure of any tyrosine-kinase inhibitor used as first line treatment e.g post sunitinib or pazopanib.

If available recruit into suitable clinical trial.

6.3 Systemic therapy for poor prognosis disease

There are currently no systemic therapies approved by the Scottish Medicine Consortium for poor prognosis advanced renal cancer.

Consider recruitment to any ongoing clinical trials.

Consider megoxyprogesterone acaetate (Provera) 100mg TDS for palliation of systemic symptoms (anorexia, malaise)

6.4 Bisphosphonates

Indications
Malignant hypercalcaemia
Bone metastases causing severe bone pain which is uncontrolled by analgesia or radiotherapy.

Dose
Pamidronate 90mg IV every 28 days

N.B Reported increased incidence of osteonecrosis of the mandible when sunitinib and bisphosphonates given concurrently – patients with poor oral hygiene and pre-existing dental problems at most risk. Preferably administer bisphosphonate only to those patients who are not suitable for VEGF TKIs or who have had TKI discontinued due to disease progression.

7. RADIOTHERAPY

Adjuvant radiotherapy

Indications
Post-resection of solitary brain metastasis.
No evidence of metastatic disease elsewhere

Dose
30Gy in 10 fractions to whole brain

Palliative radiotherapy

Indications
Symptomatic metastatic disease depending on site (e.g. bone metastases, non-resectable brain metastases, skin metastases, haemorrhage from GI tract metastases). For example:

Bone metastases

Indications
Painful bone metastasis
Malignant spinal cord compression
Post-surgical fixation of pathological fracture

Dose
8Gy single fraction or 20Gy in 5 fractions over 5-7 days

Whole brain radiotherapy

Indications
Radiologically proven brain metastases
Evidence of metastatic disease elsewhere or multiple brain metastases not amenable to surgical resection.
Capable of at least limited self care (i.e. Karnowsky Performance status >70)
Anticipated survival >3 months
Dose
20Gy in 5 fractions over 5-7 days

8. OTHER PALLIATIVE INTERVENTIONS

Tumour embolisation

Indications
Patients with gross haematuria not fit for palliative nephrectomy or with unresectable primary tumour.

Refer to urology team who will liaise with interventional radiology.

Referral to palliative care services

All patients with metastatic disease should be considered for early referral to palliative care services.

Ensure that all patients have been referred to benefits advisor.

9. APPENDIX 1 : Memorial Sloan Kettering prognostic factors for survival after diagnosis of metastatic renal cancer

Poor risk patients must have 3 or more of following poor risk features:

- LDH greater than 1.5 x upper limit of normal
- Haemoglobin < lower limit of normal
- Corrected calcium > upper limit of normal
- Time from diagnosis to first treatment <1year
- Karnowsky performance status <80 i.e. not capable of normal activity or light work.
- Multiple organ sites of metastases.