PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GENITOURINARY

RENAL CELL CARCINOMA
GU Site Group – Renal Cell Carcinoma

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1. **INTRODUCTION**

An estimated 5000 Canadians will be diagnosed with renal cell carcinoma (RCC) in 2012. This comprises of approximately 2-3 % of all cancers and the median age at diagnosis is 65 years. Approximately 90% of Kidney tumors are RCC. Renal pelvic transitional cell carcinoma comprises most of the other 10%. These are managed under urolethial carcinoma guidelines. Of the RCCs approximately 85% are clear cell carcinoma and the rest comprise non-clear cell RCC (papillary, chromophobe and collecting duct (Belini’s tumor or medulary carcinoma)).

Risk factors for RCC include smoking, obesity. Several hereditary syndromes are recognized. The most common in von Hippel-Lindau (VHL) disease which results in a mutation in VHL that predisposes to clear cell RCC. This is also a common mutation in sporadic cases.

Recent estimates of 5 year survival approximate 70%. The most important prognostic determinant of longer term survival is tumor grade, stage (local involvement, nodes and presence of distant metastasis). RCC most commonly metastasizes to pulmonary parenchyma and nodes, abdominal/ pelvic nodes, bone, liver, adrenal, brain. However rarer sites are recognized and include skin, pancreas, thyroid, cervical nodes, oral cavity, sinuses and eye.

2. **PREVENTION**

The most effective prevention strategy for RCC is avoidance of smoking, healthy body weight and familiarity with one’s family history for cancer. Patients and family with a potential hereditary risk (young age at diagnosis and frequent cases among kindred) should be referred for genetic counseling and screening recommendations.

3. **SCREENING AND EARLY DETECTION**

There is no formal screening system for RCC. Incidental findings of small renal masses require a specialist evaluation and radiological follow-up for appropriate management.

4. **DIAGNOSIS**

Patients with RCC generally present with a radiological finding of a kidney mass. Complaints leading to this diagnosis can include flank pain, flank mass, or hematuria. Less commonly RCC is diagnosed with investigations arising from signs or symptoms of the metastatic disease including respiratory symptoms, bone pain, anemia, constitutional problems (weight loss, night sweats, and fatigue) and metabolic derangements such as hypercalcemia. Patients often require multimodality input and/or treatment) at the initial assessment, and should be assessed in a multidisciplinary environment. Full diagnosis and staging requires a tissue biopsy and review with pathologist, radiological
investigations generally consisting of CT thorax, abdo/pelvis, labs including CBC and full chemistry.

**Clinical Evaluation:**
- Complete history in all patients including past medical and drug history
- Record of presenting problems
- Patients ECOG performance status
- Social & personal history (exposure to smoke, carcinogens)
- Co-morbid conditions (previous cancers, heart disease, cerebrovascular disease, liver disease, diabetes, renal dysfunction)
- Family history of cancer
- Prior treatment of cancer, if any
- Complete physical examination in all patients.

**Oncologic Imaging and Laboratory Evaluations:**
Evaluation of local extent of disease - CT abdomen/pelvis with contrast, if renal function permits

**Metastatic Workup:**
As above: Imaging is undertaken for patients to determine the presence of nodal, visceral, skeletal and CNS metastases in high-risk individuals, or in those with signs or symptoms suggestive of metastatic disease.

- A contrast-enhanced CT of the thorax, abdomen and pelvis to detect metastases in chest, pelvic or abdominal lymph-nodes, prior renal bed, or liver. Metastases may be detected in the imaged skeleton, and these should be confirmed with a nuclear medicine bone scan and MRI spine if involving the axial skeleton.

Laboratory Tests:
- CBC, electrolytes, calcium, creatinine, liver function studies, TSH

Other Investigations:
- CT or ultrasound guided aspiration biopsy to confirm malignancy in nodal, visceral or skeletal lesions suspicious on imaging is cases where the diagnosis may be in question. (Other cancers or long interval since primary diagnosis of RCC)

5. **PATHOLOGY**

All patients should have documentation of the tumor histology and its subtype
Pathology reports in RCC cancer should specify histological subtype and grade. Fuhrman grading is preferred in clear cell carcinoma. Mixed populations should be described. Non-clear cell histology should be noted and ideally reviewed by a GU pathology specialist. In resection specimens, reports should include the following information: the
type of specimen, tumor size, extent of local invasion (kidney confined, perinephric fat, renal sinus), lymphovascular space invasion, presence/absence of necrosis, sarcomatoid or rhabdoid features, lymph node status and resection margin status (renal parenchymal margin for partial nephrectomies; renal artery, renal vein, ureteric and peripheral margins for total nephrectomies) so that an accurate pathological staging and risk strafication of the tumor can be rendered.

All current and previous specimens from community hospitals should be obtained for expert uropathology review to accurately document the grade, stage and the patient’s personal natural history of disease.

6. **MANAGEMENT**

**Management of Localized RCC:**

**6.1 Principles of Surgery: (adapted from NCCN guidelines)**

Surgical treatment is generally a radical nephrectomy. Nephron-sparing surgery may be indicated in selected patients, for example

- Multiple primaries
- Uninephric state
- Renal Insufficiency
- Selected patients with small unilateral tumors

Lymph node dissection is optional.

Adrenal gland may be left if uninvolved and tumour is not high risk on the basis of size and location.

Special teams may be required for extensive inferior vena cava involvement.

Observation or local ablative techniques (eg cryosurgery or radiofrequency ablation) may be considered for non-surgical candidates with small tumours.

**6.2 Systemic Therapy:**

Adjuvant or neoadjuvant systemic therapy surrounding curative resection of primary tumour

- No role for drug therapy- either cytokine or targeted agents.
- Suitable patients can be considered for appropriate clinical trials comparing therapy to surveillance.

Pseudoadjuvant systemic therapy:

- No role for systemic agents in absence of evaluable disease

**6.3 Management of Stage IV Disease**

- Goal is prolongation of life and palliation as treatment is not generally curative.
  There have been tremendous improvements to overall survival in recent years
with targeted agents. These new targeted agents have essentially replaced cytokine therapy in this cancer site, with rare exceptions. Best recommendations require a personalised patient plan with input of multidisciplinary care (medical oncology, uro-oncologist, occasional radiation oncologist and neurosurgeons.) Palliative care team should be introduced prior to symptomatic end-stage progression.)

**Surgery:**
- There is a small subset of patients where surgical resection of primary and a synchronous or metacronous solitary site of metastasis is appropriate and may have curative intent.
- Cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a resectable primary and known sites of metastatic disease based on evidence of improved survival in the prior cytokine era. Patient selection is important and includes good PS, low volume metastatic disease, ideally lung only metastasis and good to intermediate prognostic factors. (Flannigan et al). There is a priority for clinical trials to confirm the survival benefit of cytoreductive nephrectomy and the best integration of cytoreductive nephrectomy in the era of targeted agents.
- Pre-op therapy: The rare patient will present with an unresectable primary tumor in the face of metastatic disease but be rendered resectable after a response to systemic therapy. This is a reasonable strategy to consider. Generally targeted therapy should be held a week before planned surgery and resumed once well enough post-op.
- Palliative nephrectomy may be considered in a patient with difficult hematuria or other symptoms related to the primary tumor.

**First-line systemic: (VEGF TKIs)**
- For newly presenting stage IV disease a tissue diagnosis is required. For recurrent and metastatic disease after previously confirmed RCC primary a biopsy is usually not needed if presentation is consistent with mRCC. It is probably of value where tumor banking mechanisms are in place.
- There are a number of drugs currently licensed in Canada for 1st-line mRCC based on level 1 evidence showing improved progression-free survival and overall survival. These include the tyrosine kinase inhibitors (TKIs) sunitinib and pazopamib (both VEGF inhibitors) and temsirolimus (mTOR inhibitor) (Motzer et al, Sternberg et al and Hudes et al.) Currently, Ontario funds 3 drugs through the special access drug program (section 16). These include sunitinib for patients with a good or intermediate prognosis category, pasopamib if intolerant to sunitinib and temsirolimus in patients with poor prognosis group. It is expected that soon there will be data supporting other drugs in the same class as these. The choice will likely be driven by patient specific issues of tolerance, co-morbidity and availability of drug funding,
rather than clear data supporting one drug over another. There appears to be a class effect for benefit of these drugs in mRCC.

- Recommended baseline investigations and follow-up include, history, physical, full staging (CTs chest, abdo, pelvis, bonescan and brain as indicated) routine bloods including CBC and full chemistry. Different drugs have specific monitoring recommendations as well. For sunitinib these include thyroid function and baseline ECG and MUGA scan. Temsirolimus requires baseline and follow-up fasting lipids and glucose a well as close monitoring for non-infectious pneumonitis. Pazopamib requires close monitoring of liver function tests in addition to above recommendations for sunitinib.

- All patients receiving systemic therapy require close follow-up and supportive care for the expected common and rare complications of systemic therapy. This follow-up may range from weekly to q 2 monthly visits as indicated. Frequent BP assessments at home or with general practitioner are strongly encouraged and hypertension should be treated early, especially during the early cycles. Radiological evaluation of drug benefit is generally recommended every 3 months but certainly may vary from q 6 weeks to q 4 months, guided by the clinical scenario.

- **Clinical trials are strongly supported.**
- Expectant management may be appropriate in patients with asymptomatic and/or indolent disease.
- IV Bevacizumab plus sc interferon has also demonstrated improved PFS in randomised phase III trials. This is currently not funded in Canada nor offered at PMH, but occasional patient may pursue this with private means.
- High-dose IL-2 therapy is an alternative approach for very select patients with high performance status and low volume or lung only metastasis. This is based on the observation of durable responses or rare complete responses from non-randomised studies. It can only be recommended when delivered at a center with considerable experience with HD IL-2 and in managing the serious side effects. Recent studies have not shown improved selection criteria. This is not offered at PMH. It is offered in Montreal and Buffalo. Currently the ministry of health in Ontario will not fund the costs of this out of province therapy.
- There is level 2 evidence supporting the use of sorafenib (VEGF inhibitor) in 1st-line patients either intolerant or have strong contraindications to sunitinib or temsirolimus. This is not funded in Ontario but can be covered privately.

**Second-line systemic therapy:**

- With level one evidence supporting more than 1 treatment option (or class of drugs) treatment decision must be guided by patient factors and physician experience with agents.
Everolimus (mTOR inhibitor) is a standard of care in those patients who have failed on at least 1 (2 or more) prior VEGF TKI therapy based on improved PFS vs. placebo. (Motzer et al). This drug is licensed in Canada, funded on the Ontario special access section 16 program.

- Follow-up recommendations are similar to temsirolimus and include baseline and follow-up fasting lipids and glucose as well as close monitoring for non-infectious pneumonitis.

Axitinib (VEGF TKI) is a new potential standard of care in the post 1st-line VEGF TKI setting (generally post sunitinib), Rini B et al. The data does not appear superior to the PFS seen with second line everolimus. It represents an alternative evidence-based approach. Currently no funding decisions have been made in Ontario. It is available thru private means.

- Follow-up, monitoring guidelines are similar to sunitinib. Close monitoring of BP during early cycles is key, and hypertension treated early

**Clinical trials strongly supported**

**Sorafenib** (VEGF inhibitor) is generally recommended in patients who have progressed after prior cytokine therapy based on improved PFS (level 1). This drug is funded through section 16 mechanism for this indication.

- Follow-up and monitoring is similar to sunitinib (as above) although there is little need to monitor cardiac toxicity unless a high risk patient.

**Level 2-3 evidence supports sequencing more than 1 VEGF inhibitor before mTOR inhibitor therapy.** (example sorafenib-> sunitinib or vice versa prior to m-TOR inhibitor)

Expectant management may be appropriate in patients with asymptomatic and/or indolent disease.

Palliative or supportive care alone may be indicated for those not expected to benefit from further systemic therapy.

Post mTOR inhibitors

- **Clinical trials strongly supported**
- Level 3 evidence supports a rechallenge with a VEGF TKI

**Palliative radiotherapy**

- Can be used for relief of symptoms from local and distant disease (primarily bone). If visceral organs or CNS within the fields, targeted therapy should be interrupted during radiation.

- Gamma knife or other focal techniques are strongly supported for limited brain mets. Multiple mets may benefit from whole brain radiation.

**6.4 Non-Clear Cell Histology:**

- No standard of care in Stage IV

**Surgery:**

- no established role for cytoreductive nephrectomy
Systemic therapy

- **Clinical Trials when available**
- Some small series and sub-group analysis of larger trials support mTOR inhibitors and VEGF TKIs in papillary and chromophobe RCC. Ongoing trials will provide further data
- Stage IV collecting duct cancers: level 3 evidence supporting combination platinum based chemotherapy with anecdotal durable responses.

**6.5 Oncology Nursing Practice**

Refer to [general oncology nursing practices](#)

7. **SUPPORTIVE CARE**

7.1 **Patient Education**

Patient education is an integral aspect of cancer management in the GU site group. In addition to one-on-one education specific to the patient situation, written educational materials are provided to patients. The specific educational content is provided depending on the patient's diagnosis and management options. In addition, there is a library with resources available to the patient.

7.2 **Psychosocial Care**

Refer to [general psychosocial oncology care guidelines](#)

7.3 **Symptom Management**

Patients with RCC may have a multitude of physical and emotional symptoms related to their disease, treatment and co-morbid condition. DART and ESAS (Distress Assessment and Response Tool and Edmonton Symptom Assessment System) are the screening tools used to identify the symptoms of most concern to the patient. They add to the clinical assessment of the patient made by the clinician at an individual attendance, but are also recorded serially at each attendance, to observe outcomes of interventions used. Patients answers are reviewed by the nurse and oncologists, symptom management guides are used in response to this screening and patients with significant burden of symptoms can be referred to appropriate services (eg palliative care, social work etc).

7.4 **Clinical Nutrition**

Written materials on nutrition and health and access to a dietician are made available to patients with RCC.

7.5 **Palliative Care**

Refer to [general oncology palliative care guidelines](#)
8. KEY REFERENCES


