

RENAL CELL CARCINOMA

Date Developed: April, 2005

Date Revised: June, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

GUIDELINE GOALS AND OBJECTIVES

To outline management decisions for renal cell carcinoma

GUIDELINE QUESTIONS

What are the appropriate management and follow up strategies for renal cell carcinomas?

DEVELOPMENT PANEL

This **guideline** was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. **Evidence** was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

Entries to Medline (April 2005 to January 2007) and clinical practice guideline databases were searched for updated evidence relevant to this topic.

RECOMMENDATIONS

Stage T_{1, 2, 3}, N₀

Indications	<ul style="list-style-type: none"> Patients presenting with imaging suspicious for primary renal malignancy localized to the kidney or immediate surrounding structures.
Staging	<ul style="list-style-type: none"> History and physical examination (lymph node survey) CXR CT scan of abdomen/pelvis with contrast (or MRI) CBC, Cr, calcium, liver function tests (LFTs) Biopsy is an option as part of active observation or prior to ablative therapy Optional Tests: <ul style="list-style-type: none"> CT chest of T2 or T3 Bone scan of T2 or T3 or alkaline phosphatase is elevated
Management First-line	<ul style="list-style-type: none"> Active Surveillance is a reasonable option for T1a disease in elderly or medically comprised patients <ul style="list-style-type: none"> Biopsy an option initially Repeat imaging q6 months Intervention is indicated if there is progression Minimally Invasive Therapy <ul style="list-style-type: none"> Cryoablation <ul style="list-style-type: none"> Percutaneous (or laparoscopic) T1 size 2 to 5.5 cm Radiofrequency Ablation <ul style="list-style-type: none"> Peripheral tumors size 2 to 4cm (T1a)

	<ul style="list-style-type: none"> Partial nephrectomy is still the best option Both RFA and Cryo are suitable treatments for primarily T1a RCC but only after Urology consultation. The treatment decision is only to be made after this consultation. This will ensure appropriate follow up is instituted after ablation. 																																																																																																																																																																																																																												
F/U	<ul style="list-style-type: none"> Follow up is based on the recommendations of the Canadian Urological Association (CUA) as published on the CUA website (http://www.cua.org/) and the CUA Journal (CUAJ) in 2009,¹ and is stage dependent: <ul style="list-style-type: none"> pT1 <table border="1" data-bbox="363 583 1382 890"> <thead> <tr> <th></th> <th>3mo</th> <th>6</th> <th>12</th> <th>18</th> <th>24</th> <th>30</th> <th>36</th> <th>48</th> <th>60</th> <th>72</th> </tr> </thead> <tbody> <tr> <td>Hx/Px</td> <td></td> <td></td> <td>X</td> <td></td> <td>X</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Blood</td> <td></td> <td></td> <td>X</td> <td></td> <td>X</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CXR</td> <td></td> <td></td> <td>X</td> <td></td> <td>X</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CT or U/S</td> <td></td> <td></td> <td></td> <td></td> <td>X</td> <td></td> <td></td> <td></td> <td>X</td> <td></td> </tr> </tbody> </table> pT2 <table border="1" data-bbox="363 961 1382 1234"> <thead> <tr> <th></th> <th>3mo</th> <th>6</th> <th>12</th> <th>18</th> <th>24</th> <th>30</th> <th>36</th> <th>48</th> <th>60</th> <th>72</th> </tr> </thead> <tbody> <tr> <td>Hx Px</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Blood</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CXR</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CT or U/S</td> <td></td> <td></td> <td>X</td> <td></td> <td></td> <td></td> <td>X</td> <td></td> <td>X</td> <td></td> </tr> </tbody> </table> pT3 <table border="1" data-bbox="363 1306 1382 1558"> <thead> <tr> <th></th> <th>3mo</th> <th>6</th> <th>12</th> <th>18</th> <th>24</th> <th>30</th> <th>36</th> <th>48</th> <th>60</th> <th>72</th> </tr> </thead> <tbody> <tr> <td>Hx Px</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Blood</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CXR</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CT</td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td></td> <td>X</td> <td></td> <td>X</td> <td>X</td> </tr> </tbody> </table> pTxN+ <table border="1" data-bbox="363 1629 1382 1881"> <thead> <tr> <th></th> <th>3mo</th> <th>6</th> <th>12</th> <th>18</th> <th>24</th> <th>30</th> <th>36</th> <th>48</th> <th>60</th> <th>72</th> </tr> </thead> <tbody> <tr> <td>Hx Px</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Blood</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CXR</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>CT</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> </tr> </tbody> </table> 		3mo	6	12	18	24	30	36	48	60	72	Hx/Px			X		X		X	X	X	X	Blood			X		X		X	X	X	X	CXR			X		X		X	X	X	X	CT or U/S					X				X			3mo	6	12	18	24	30	36	48	60	72	Hx Px		X	X	X	X	X	X	X	X	X	Blood		X	X	X	X	X	X	X	X	X	CXR		X	X	X	X	X	X	X	X	X	CT or U/S			X				X		X			3mo	6	12	18	24	30	36	48	60	72	Hx Px		X	X	X	X	X	X	X	X	X	Blood		X	X	X	X	X	X	X	X	X	CXR		X	X	X	X	X	X	X	X	X	CT		X	X	X	X		X		X	X		3mo	6	12	18	24	30	36	48	60	72	Hx Px	X	X	X	X	X	X	X	X	X	X	Blood	X	X	X	X	X	X	X	X	X	X	CXR	X	X	X	X	X	X	X	X	X	X	CT	X	X	X	X	X	X	X	X	X	X
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Duration of F/U	<ul style="list-style-type: none"> If relapses are to occur they may happen early or very late; therefore reasonable follow-up is for five years.
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Stage T₄, N_{1,2}, M⁺ ²

Indications	<ul style="list-style-type: none"> Patients presenting with locally advanced, unresectable cancer or metastatic disease.
Staging	<ul style="list-style-type: none"> As clinically indicated: CT abdomen, pelvis, thorax and other imaging procedures as indicated. CBC and Ca, liver function test, renal function test.
Management³	<p>Sunitinib^{4,5,6,7,8,9}</p> <ul style="list-style-type: none"> Indication: <ol style="list-style-type: none"> 1) first-line therapy for metastatic RCC based on phase III data 2) second-line therapy for metastatic RCC based on phase II data after cytokine failure Dose and Schedule: starting dose at 50mg/day orally for 4 weeks followed by a 2-week rest period to form a 6-week treatment cycle. Patient Management: physician must be aware of the toxicity profile of sunitinib and follow patients accordingly with experienced nursing support. Patient may be assessed every cycle for treatment tolerance and this interval may be lengthened after 2 cycles if clinically appropriate. Sunitinib should be dosed to maximum treatment tolerance as there is evidence that higher AUC leads to higher response rates (Houk et al ASCO 2007). Cardiotoxicity has become an issue and in patients with pre-existing CAD or CAD risk factors, monitoring of EF should be considered. Routine monitoring in all patients is not indicated (Telli et al Ann Oncol 2008). Efficacy assessment: imaging involved sites q2 cycles initially then as clinically indicated. Patients responding with either stable disease or an objective response may continue therapy. Treatment is to be continued until disease progression or patient intolerance. <p>Sorafenib^{10,11,12}</p> <ul style="list-style-type: none"> Indication: second-line therapy after cytokine failure based on superior activity compared to best supportive care in a randomized phase III trial. Dose and schedule: starting dose at 400 mg bid continuously. Each treatment cycle is 6 weeks in duration. Patient management: physician must be aware of the toxicity profile of sorafenib and follow patients accordingly with experienced nursing support. Dose must be modified per individual's toxicity profile. Patient may be assessed every cycle for tolerance. Interval may be lengthened after 2 cycles if clinically appropriate. Efficacy assessment: imaging every 2 cycles initially then as clinically indicated. Treatment is continued until disease progression or patient intolerance. <p>Temsirolimus¹³</p> <ul style="list-style-type: none"> Indication: first-line therapy for metastatic RCC in poor-prognosis patients This has been shown in a phase III trial of poor-prognosis patients with clear cell and non-clear cell RCC to improve overall survival This is delivered at 25mg IV q weekly and can be considered in patients with poor-

prognosis disease

- Treatment side effects and laboratory abnormalities should be monitored initially weekly then every 2 weeks. This follow-up interval may be extended if clinically appropriate.
- Efficacy should be determined every 8 weeks

Everolimus

- Indication: second-line therapy for metastatic RCC after progression on sunitinib, sorafenib or both based on phase III data demonstrating superior progression-free survival than best supportive care.
- This drug has been FDA approved and Health Canada approval is pending
- Referral to a centre with trials or an Expanded Access program) involving everolimus is indicated.

Local Therapy ¹⁴

Cytoreductive nephrectomy prior to or following targeted therapy

- There is no data to guide clinical practices at this time. Decisions are to be made based on clinical indications. About 90% of enrolled patients received nephrectomy prior to systemic therapy in both the sunitinib and the sorafenib phase III trials.
- In patients with response to targeted therapy and limited metastatic disease, nephrectomy may be considered
- Nephrectomy has proven overall survival benefit when used in conjunction with interferon.
- Patients who appear to benefit most from nephrectomy are:
 - Most of the tumor burden is within the kidney
 - Good performance status
 - No central nervous or liver involvement (with rare exceptions)
 - Other considerations include:
 - Surgical resectability including morbidity to proximal vital structures, encasement of the renal hilum, or other complicating factors (Rini, et al. J Urol. 2007, Heng, et al. Curr Oncol. 2009).
 - Laparoscopic nephrectomy is the emerging standard surgical procedure whenever technically feasible.

Palliative Nephrectomy

- Nephrectomy can also be offered as a palliative procedure at any time when clinically indicated.

Renal Embolization

- This approach can be offered as a palliative treatment for those with local symptoms but unable to undergo a nephrectomy.

Treatment to Metastatic Sites

Metastatectomy

- In patients with limited resectable metastatic disease surgical intervention can be considered: the clinical decision should be based on ECOG status, size, and

	<p>number of metastases. This can either be offered as the primary modality, or following systemic therapy. Timing of therapy is based on when metastases occurs post surgery</p> <p><i>Palliative Radiation</i> For symptomatic lesions, particularly metastases to bone, radiation therapy should be considered.</p>
F/U	<ul style="list-style-type: none"> For those not on active treatment follow-up as clinically indicated
Duration of F/U	<ul style="list-style-type: none"> If relapses are to occur, they may happen early or very late; therefore, reasonable follow-up should continue for 5 years.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CBC	complete blood count
Cr	creatinine
CT	computed tomography
CUA	Canadian Urological Association
CXR	chest x-ray
ECOG	Eastern Cooperative Oncology Group
EPA	Expanded Access Program
FDA	Food and Drug Administration
Hx/Px	history, physical examination
IFN	interferon
LFT	liver function tests
RCC	renal cell carcinoma
RFA	radiofrequency ablation
U/S	ultrasound

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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