

Management of Kidney Cancer: Canadian Kidney Cancer Forum Consensus Update 2011

Canadian Kidney Cancer Forum 2011

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This is an update from the 3rd Canadian Kidney Cancer Forum held on January 20 to 22, 2011 in Toronto, Ontario, and the third report from the Kidney Cancer Research Network of Canada (KCRNC).^{1,2}

Kidney cancer, predominantly renal cell carcinoma (RCC), is the most lethal genitourinary malignancy and kills more than 1500 Canadians a year.³ The overall incidence is increasing by 2% per year for unknown reasons. New targeted systemic therapies, which have been integrated into clinical practice with evolving experience, have been available for more than 5 years. Preservation of kidney function with widespread adoption of partial nephrectomy is a focus of treatment of early stage disease. These and other advances have revolutionized care and stimulated research and discovery. There are several guidelines in Canada that address various aspects of patient care in RCC.^{2,4,5}

The two previous forums were held in 2008 and 2009.^{1,2} These meetings were small, by invitation and attended by survivors and caregivers, as well as expert clinicians and researchers in fields relevant to kidney cancer care. The attendees included representatives of Kidney Cancer Canada.⁶

During the conference, prior management consensus statements were reviewed and updated. This report is an update of the complete consensus published in the 2008 format.¹ The Forum again addressed strategies for kidney cancer control in Canada, which included launching the Canadian Kidney Cancer Information System (CKCis), developing a coordinated approach to genetic counselling for patients and families at risk, fostering an increased awareness of cancer survivorship issues and continuing the process of defining quality indicators as part of an overall strategy to define Networks of Excellence. These subjects will be covered in future reports.

Initial evaluation and management of localized kidney cancer

The incidence of early stage kidney cancer is increasing, in part to due to the widespread use of abdominal imaging.

Diagnosis and staging

Diagnosis and staging of RCC should include:

1. History and physical examination
2. Laboratory tests: complete blood count, lactic dehydrogenase, metabolic panel (creatinine, electrolytes, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, international normalized ratios, partial thromboplastin time, calcium, magnesium, phosphate, albumin), urinalysis and urine cytology
3. Imaging
 - a. Primary tumour
 - ii. Abdominal/pelvic computed tomography (CT) without and with intravenous contrast
 - iii. Abdominal MRI, if CT suggests caval thrombus or because of a contrast allergy or renal insufficiency
 - iv. Metastatic evaluation
 - b. Chest X-ray, consider CT chest if \geq stage T2
 - iii. Bone scan, if clinically indicated or elevated alkaline phosphatase
 - iv. Brain magnetic resonance imaging, if clinically indicated

A suspicious renal mass that enhances by CT scanning is usually considered an RCC for treatment planning. Most new tumours are asymptomatic and undetectable on examination, but may be associated with pain, hematuria or a flank mass. Metastases at presentation are not common.

The 2009 TNM staging system should be used.⁷

Role of renal biopsy

Needle biopsy for histologic diagnosis may be considered before treatment of small < 3cm enhancing solid tumours and should be performed prior to or at the time of probe ablation.

There continues to be growing experience with percutaneous needle core biopsy of early stage renal tumours, indicating that it is relatively safe and diagnostic in most cases.⁸ The high rate of benign pathology in tumours managed by surgery or ablation is leading to a paradigm shift to consider biopsy in all small tumours prior to treatment.⁹ However, this has not yet become a standard of care and requires local expertise with image-guided biopsy techniques and pathological interpretation.

Treatment options

Stage T1aN0M0

- **Open partial nephrectomy recommended**
- **Pure or robot-assisted laparoscopic partial nephrectomy (PN) in experienced centres**
- **Laparoscopic radical nephrectomy for tumours not amenable to partial nephrectomy**
- **Probe ablation by radiofrequency or cryotherapy. A biopsy should be obtained before or at the time of ablation.**
- **Active surveillance**

There is increasing concern about nephrectomy as opposed to nephron-sparing surgery for kidney cancer. PN is associated with a lower risk of long-term renal dysfunction.¹⁰⁻¹² There is no evidence that oncological outcomes are adversely affected by PN and there may be overall quality of life benefits. Laparoscopic PN is increasingly available in Canada and experience with robot-assisted laparoscopic PN has been reported from several centres.^{13,14} Probe ablation is becoming more widely accepted and practiced, but it is important to have a biopsy before or at the time of treatment for follow-up planning and outcome analysis.¹⁵

Stage T1bN0M0

- **PN in cases where technically feasible**
- **Laparoscopic radical nephrectomy should be offered if a partial nephrectomy is not feasible.**

PN is rapidly emerging as the treatment of choice where technically feasible (e.g., exophytic tumours) and should be offered. There are several series demonstrating the feasibility, safety and efficacy of PN for tumours of 4 to 7 cm.^{16,17}

There is further evidence to support the benefits of PN and there may be an overall survival benefit.¹⁸ Surgical expertise with this procedure is increasingly available, but it is an advanced renal procedure. If a PN is not feasible, laparoscopic radical nephrectomy is the surgery of choice in this setting and preferred to open radical nephrectomy. Open surgery is recommended for N+ disease. Probe ablation is not recommended for these tumours due to the high rate of incomplete ablation.¹⁹⁻²¹

There was no change from the consensus of 2008 for T2 and higher stage tumours. Similarly, the role for surveillance in localized disease consensus is unchanged.

Stage T2

- **Radical nephrectomy – open or laparoscopic**

Laparoscopic radical nephrectomy can be safely performed selectively for tumours greater than 7 cm.²² Open radical nephrectomy remains the standard for large renal masses.

These recommendations are based on expert opinion that is broadly supported in Canada and elsewhere at the present time.

Active surveillance

The safety of initial active surveillance with delayed treatment for progression is not yet established. However, it is an alternative for managing small renal masses that are asymptomatic and characteristic of RCC on imaging in the elderly and/or infirm. Follow-up must include serial imaging. It is not yet recommended for the young and fit.

Canadian experience with active surveillance has been reported.^{23,24} This is widely practiced for the aforementioned patient population, but reliable prognostic factors for progression to metastatic disease are not presently defined which makes this approach unsafe for the younger and fit patients.

Surveillance schedules after radical or partial nephrectomy

The recommended Canadian Urological Association guidelines have been adopted with the imaging modality modified to include ultrasound as an option for T1-2 tumours (Fig. 1).

Management of locally advanced kidney cancer

Adjuvant and neoadjuvant therapy

There is no indication for adjuvant therapy following complete resection or neoadjuvant therapy prior to resection outside of clinical trials

	3	6	12	Months Post-op		30	36	48	60	72
				18	24					
pT1										
Hx & PE			x		x		x	x	x	x
Blood test			x		x		x	x	x	x
CXR			x		x		x	x	x	x
CT or U/S abd					x				x	
pT2										
Hx & PE		x	x	x	x	x	x	x	x	x
Blood test		x	x	x	x	x	x	x	x	x
CXR		x	x	x	x	x	x	x	x	x
CT or U/S abd			x				x		x	
pT3										
Hx & PE		x	x	x	x	x	x	x	x	x
Blood test		x	x	x	x	x	x	x	x	x
CXR		x	x	x	x	x	x	x	x	x
CT abd		x	x	x	x		x		x	
pTxN+										
Hx & PE	x	x	x	x	x	x	x	x	x	x
Blood test	x	x	x	x	x	x	x	x	x	x
CXR	x	x	x	x	x	x	x	x	x	x
CT abd	x	x	x	x	x	x	x	x	x	x

Hx & PE: history and physical examination
Blood test: include complete blood count, serum chemistries, and liver function tests
CXR: can be alternated with chest CT
CT abd: can be alternated with abdominal ultrasound in pT1-2N0 patients
* -if patient is symptomatic or abnormal blood test, earlier radiologic investigations may be indicated
-follow-up beyond 72 months, refer to text for more details

Fig. 1. Reprinted with permission from the CUA.⁵

Recommendations are based on level I evidence. To date, very few randomized trials are available which have investigated the role of cytokine therapy as adjuvant treatment for patients with completely resected RCC. Adjuvant therapy with cytokines does not improve overall survival after nephrectomy.²⁵ The results of clinical trials with adjuvant and neoadjuvant anti-angiogenic agents (tyrosine kinase inhibitors, vascular endothelial growth factor [VEGF], antibodies or mTOR inhibitors) will not be available for several more years. Patients with high-risk tumors, who have undergone complete resection, should be asked to participate in clinical trials whenever possible.

Role of lymphadenectomy

- **Lymphadenectomy is optional for clinical N0M0 disease**
- **In N+M0 patients undergoing nephrectomy, lymphadenectomy, including all abnormal nodes, should be performed and submitted separately for staging**
- **In N+M+ patients undergoing cytoreductive nephrectomy, lymphadenectomy, including all abnormal nodes, should be considered**

There is little new evidence about the role for lymphadenectomy in N0 patients. If the primary tumour is locally advanced or enlarged nodes are discovered at surgery, it was felt that they should be removed plus nodes in an ipsilateral template. There is no clear evidence for the limits of dissection, but the lymphatics from right sided tumours drain to the interaortic nodes, while those on the left may only drain initially to nodes anterior, posterior and lateral to the aorta. The optimal minimum number of nodes is unknown, but may be about 13.²⁶ High-risk features in the primary tumour appear to correlate with the presence of nodal metastases, even if nodes are grossly normal.²⁷ This may be an additional indication for lymphadenectomy. The morbidity and additional operative time are minimal, but the oncological benefit is undemonstrated.²⁸ In the event that adjuvant therapy is found to be beneficial, the role for lymphadenectomy may change.

Role of adrenalectomy

Routine ipsilateral adrenalectomy at the time of nephrectomy is not recommended if the adrenal gland is normal sized on imaging and direct invasion by a large upper pole tumour is excluded

The incidence of ipsilateral adrenal involvement is 1.9% to 7.5%.²⁹ Current imaging techniques are reported to have excellent specificity (92.1% to 99.6%), sensitivity (88.8% to 89.6%), negative predictive value (99.4%) and positive predictive value (34.7% to 92.8%) to identify adrenal gland involvement.³⁰ Metastatic disease to the ipsilateral adrenal gland as the only site of metastatic spread is low (range: 0.7% to 2%). Only up to 0.4% of these cases are not detected preoperatively. Tumour stage and the presence of adrenal radiographic enlargement have been identified as prognostic factors (evidence level 4). Ipsilateral adrenalectomy may be performed for patients with higher risk tumours, such as stages T3-4, in particular if they are upper pole tumors and/or N1-3 and or M1.

Management of the inferior vena cava and renal vein thrombus

- **In the absence of distant metastases, tumour thrombus should be resected to provide a chance of cure**
- **It is recommended that these patients be performed in, or referred to, a centre with experience as these potentially complex procedures have significant risk of morbidity and mortality**

About 4% to 10% of all RCCs involve the inferior vena cava (IVC) and about 1% extend into the right atrium. RCCs with tumour thrombi tend to have a higher stage and grade. Distant or lymph node metastases are twice as common. At least one metastatic site is present in 30% of patients with vascular involvement. In the absence of distant metastases, surgery provides the only chance of cure for these patients. Retrospective case series have reported 5-year survival rates of up to 65%.³¹ Little prospective data is available regarding the resection of venous thrombi.

Advanced (metastatic) kidney cancer

Enrolling patients in well-designed clinical trials should always be considered as the first option for patients with advanced or metastatic RCC (Table 1).

First-line therapy

- **Targeted therapy is the preferred treatment (Table 1).**
- **Observation can also be considered, as some patients have slow growing asymptomatic disease.**
- **High dose IL-2 can be considered in selected patients.**

Based on phase III data, sunitinib produces higher response rates, improved quality of life, and a longer progression-free survival than interferon in patients with clear cell carcinoma.³² Subsequent survival analysis showed that patients treated with sunitinib had a longer overall survival than those treated with interferon.³³ In addition, population-

based studies from British Columbia and Alberta have shown an almost doubling of overall survival of metastatic RCC (mRCC) since the introduction of sunitinib or sorafenib.^{34,35} Based on phase III data, pazopanib produces an improvement in progression-free survival (PFS) compared to placebo in both cytokine naïve and refractory patients.³⁶ Based on phase III data, temsirolimus produces an improvement in PFS and overall survival in poorer risk patients than interferon alone or the combination of temsirolimus and interferon.³⁷ Poorer risk was defined by at least 3 out of 6 of the following criteria: KPS 60-70, ↑Ca++, ↓Hgb, ↑LDH, <1 year from nephrectomy to treatment, or multiple metastatic sites. Where drug access is limited, everolimus, if available would be a reasonable alternative.³⁸ In patients with intolerance to sunitinib or temsirolimus, sorafenib remains a good option.³⁹

There is phase III data demonstrating the combination of bevacizumab plus interferon improves PFS over interferon alone.^{40,41} At this time, there has been no application submitted regarding bevacizumab for kidney cancer in Canada, and so it is not an option for Canadian patients.

Forum attendees think that observation is a reasonable option in some patients given that no therapies are currently considered curative, that all available treatments can be associated with side effects, and that some patients have slowly growing asymptomatic metastases.

No phase III studies on the use of interleukin-2 (IL-2) have shown an improvement in survival, and thus it is not considered a standard of care, but may be considered for highly selected patients. Based on phase II data, however, a very select group of patients may be considered for high-dose IL-2. High-dose IL-2 must be delivered in specialized and experienced centres and ideally in the context of a clinical trial or investigational setting. Low-dose IL-2 should not be given.^{42,43}

In patients with metastatic or advanced RCC with non-clear cell pathology, clinical trials of new agents should be considered. Other options include sunitinib, based on subgroup analyses from the Expanded Access trial showing safety and activity; sorafenib, based on subgroup analyses from the ARCCS expanded access trial showing safety and activity; and temsirolimus, based on subgroup analysis of phase III data.⁴⁴⁻⁴⁷ In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options include sunitinib, based on prospective, non-randomized data from the Expanded Access Program; sorafenib, based on prospective, non-randomized data from the ARCC expanded access trial; chemotherapy, based on phase II data using agents, such as 5FU, gemcitabine, doxorubicin and combinations of these showing activity; and temsirolimus based on subgroup analysis from the pivotal phase III trial in which these patients were eligible.^{44-46,48}

When prescribing systemic therapy for advanced or mRCC, several key factors must be taken into account. An oncology specialist knowledgeable about the acute and

long-term toxicities, drug interactions, monitoring treatment and response, should prescribe therapy. Patients should be managed in a multidisciplinary environment with adequate nursing care, dietary care, pharmacy support, etc. Patients must be evaluated frequently to ensure toxicities are recognized and managed appropriately. Patients and caregivers should be provided with information concerning potential side effects, prevention and treatment.

Progression on or intolerance to cytokines

Based on phase III data, sorafenib improved progression-free survival compared to best supportive care alone in previously treated patients.³⁹ Overall survival data were confounded by crossover but reached significance when censored for cross-over.⁴⁹ Pazopanib has also been studied in this patient population and produces an improvement in PFS compared to placebo.³⁶ Sunitinib is an alternate treatment. Based on two phase II trials, sunitinib produced significant response rates and increased progression-free survival compared to historical controls.⁵⁰

Progression after first-line therapy

- **Switch to another targeted agent (Table 1)**
- **Clinical trials in this population should be supported, as the optimal sequence of therapies is unknown.**

Based on phase III data, everolimus (oral mTOR inhibitor) produced a significantly longer PFS than placebo, with an acceptable toxicity profile in patients who had failed sunitinib or sorafenib (or both).⁵¹ This represents the best data to date for sequential therapy. Where drug access is limited, temsirolimus is a reasonable alternative given its similar mode of activity.

In patients with advanced or mRCC post-sunitinib or sorafenib failure, other options include switching to another TKI (e.g., from sunitinib to sorafenib or from sorafenib to sunitinib) based on emerging data showing activity with sequential therapy.⁵² The role of interferon post-targeted therapy is not clear; but based on data in older phase III first-line studies pre-targeted therapy, it may be an option.

Role of cytoreductive nephrectomy

Cytoreductive nephrectomy should be considered in appropriately selected patients presenting with mRCC.

Recommendations for this section are based on level I evidence in patients treated with interferon. Appropriately selected patients for cytoreductive nephrectomy include patients with a primary tumour of clear cell histology amenable to surgical extirpation and a low risk of perioperative morbidity; patients with good performance status (ECOG 0 or 1); and patients without evidence of brain metastases.^{42,53,54} Recognizing that most patients will be planned for tyrosine kinase inhibitor (TKI) therapy rather than cytokine therapy, further prospective study on the true benefit of cytoreductive nephrectomy is required and several trials are being conducted. Data from North America show an improved outcome in patients who had cytoreductive nephrectomy, however this is retrospective data.⁵⁵ At this point, there is no randomized data to guide clinical practice and decisions are to be made based on clinical judgement. Nephrectomy likely will not be harmful based on the fact that about 90% of enrolled patients received nephrectomy prior to systemic therapy in both the sunitinib and the sorafenib phase III trials.^{32,39} In patients with response to TKI or targeted therapy, limited metastatic disease and good performance status, it is reasonable that cytoreductive nephrectomy be considered.

In select patients with limited sites of metastatic disease and clinical stability resection of the metastatic disease may be reasonable.

A 5-year survival rate as high as 50% has been reported in patients with resected solitary pulmonary metastasis.⁵² There is little published data regarding resection of minimal residual disease after a response to TKI therapy, but consideration of this approach is reasonable in selected cases.

Radiation therapy may be considered to control bleeding and pain from the primary tumour, palliate symptoms from metastases and stabilize brain metastases.

Table 1. Enrolling patients according to advanced or metastatic RCC

Setting	Patients	Therapy (level 1 evidence)	Other options (<level 1 evidence)
Untreated	Good or intermediate risk	Sunitinib Bevacizumab+IFN Pazopanib	HD IL-2 Sorafenib Observation
	Poor risk	Temsirolimus	Sunitinib
Second-line	Cytokine refractory	Sorafenib Pazopanib	Sunitinib, Bevacizumab+IFN
	Prior VEGF	Everolimus	Targeted therapy not previously used
	Prior mTOR		Sunitinib or Sorafenib

Clinical trials involving radiation should be supported.

Competing interests: None declared.

This paper has been peer-reviewed.

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