

# RENAL CELL CARCINOMA

Effective Date: June, 2017

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.

## **BACKGROUND**

In 2016, it is estimated that 6400 Canadians (4100 men and 2300 women) will be diagnosed with kidney cancer, and that 1850 Canadians will die from kidney cancer. In Alberta, 600 new kidney cancer diagnoses are anticipated in 2016 <sup>1</sup>.

Renal cell carcinoma (RCC), a subtype of adenocarcinoma, accounts for 61.5% of all kidney and renal pelvis cancers and is the focus of this guideline. The most common subtype of renal cell carcinoma is clear cell RCC, followed by papillary and chromophobe tumours. Staging of renal cell carcinoma is currently based on the seventh edition (2010) of the American Joint Committee on Cancer's AJCC Cancer Staging Manual <sup>2</sup>. A detailed description of the staging can be found in the Appendix.

## **GUIDELINE QUESTIONS**

- What are the appropriate diagnostic tests for renal cell carcinoma?
- How should renal cell carcinoma be managed (i.e., surgically)?
- What is the role of systemic therapy and radiotherapy in the management of renal cell carcinoma?
- Are there other therapies that have shown benefit for patients with renal cell carcinoma?
- What are the appropriate follow up strategies for renal cell carcinoma?

## **DEVELOPMENT AND REVISION HISTORY**

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, urologists, 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 Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Unit Handbook](#).

This guideline was originally developed in April, 2005. This guideline was revised in 2009, 2010, 2011, 2012, 2013 and 2017.

## **SEARCH STRATEGY**

Cochrane and National Guidelines Clearinghouse databases, as well as individual guideline developers' websites were searched for evidence relevant to this topic. The MEDLINE and EMBASE databases were searched for evidence relevant to this topic. The search strategy included the term "renal cell carcinoma" and limited the results to clinical trials published in English. Articles were further excluded if they were phase I, included fewer than ten patients, and were non-treatment related (i.e. pathology/staging, imaging, genetics, prevention, etc.), were retrospective without a comparison group, did not include adult patients, or did not look at survival, recurrence or quality of life outcomes.

## RECOMMENDATIONS

### Stage T1-3, N0

Indications include imaging suspicious for primary renal malignancy localized to the kidney or immediate surrounding structures.

#### ***Management***

##### Staging

- History and physical examination (Hx/Px) (lymph node survey)
- CXR
- CT scan of abdomen/pelvis with contrast (or MRI)
- CBC, Creatinine, calcium, liver function tests (LFTs)
- Biopsy is an option as part of active observation or prior to ablative therapy
- Optional Tests:
  - CT chest if T2 or T3
  - Bone scan if T2 or T3 or alkaline phosphatase is elevated

##### First-line Therapy

Active Surveillance is a reasonable option for T1a disease in elderly or medically comprised patients:

- Biopsy an option initially.
- Repeat imaging every 6 months.
- Intervention is indicated if there is progression.

##### Surgical Intervention

- Partial nephrectomy should be considered in all cases where surgery is being considered especially in T1 lesions. This can be done either as an open, laparoscopic, or assisted laparoscopic procedure.
- If a partial nephrectomy is not feasible, consider a laparoscopic/robotic nephrectomy.
- If the laparoscopic or robotic procedures cannot be performed then an open nephrectomy should be done.
- Wherever possible the adrenal gland should not be removed unless involved on imaging.

##### Minimally Invasive Therapy

- Both radiofrequency ablation (RFA) and cryoablation are suitable treatments for primarily T1a RCC with urologic consultation. The treatment decision is only to be made after this consultation. This will ensure appropriate follow up is instituted.
  - Cryoablation: percutaneous (or laparoscopic); T1 size 2-5.5 cm
  - Radiofrequency ablation: peripheral tumors size 2-4 cm (T1a)

#### ***Follow-up***

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<sup>3</sup>, and is stage dependent:

**Months Post-op & Follow-up Recommended:**

	3	6	12	18	24	30	36	48	60	72
<b>pT1</b>										
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 abdomen					X				X	
<b>pT2</b>										
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 abdomen			X				X		X	
<b>pT3</b>										
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 abdomen		X	X	X	X		X	X	X	
<b>pTxN+</b>										
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 abdomen	X	X	X	X	X	X	X	X	X	X

- If relapses are to occur, they may happen early or very late. Therefore, the necessary duration of follow-up beyond these guidelines is unclear and should be directed based on relapse risk.

**Stage T4, N1-2, M+<sup>4</sup>**

Indications include locally advanced, unresectable cancer or metastatic disease.

***Management<sup>6</sup>***
Staging

- CBC, Calcium, LFTs, renal function test
- CT abdomen, pelvis, thorax and other imaging procedures as clinically indicated

First-line Therapy
**Sunitinib<sup>6-11</sup>**
**Indication:**

- 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 50 mg/day orally for 4 weeks followed by a 2-week rest period for a 6-week

treatment cycle. Subsequent alternating schedules of 2 weeks on and 1 weeks off or other schedules and dosing that optimize the therapeutic ratio are possible.

- **Toxicity:**  
Physicians must be aware of the toxicity profile of sunitinib and follow patients accordingly with experienced nursing support. Patients should be assessed every cycle for treatment tolerance. Sunitinib should be dosed to maximum treatment tolerance as there is evidence that higher AUC leads to higher response rates.  
Cardio toxicity has become an issue and in patients with pre-existing CAD or CAD risk factors. Monitoring of EF should be considered in high risk or symptomatic patients but routine monitoring in all patients is not indicated.
- **Efficacy Assessment:**  
Imaging of involved sites every 2 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.

#### Pazopanib<sup>12</sup>

- **Indication:**  
First-line therapy for metastatic RCC based on phase III data.
- **Efficacy Assessment:**  
The COMPARZ non-inferiority trial demonstrated that pazopanib is noninferior to sunitinib with respect to progression-free survival, progression of disease or death from any cause. Thus, pazopanib can be used for the first-line treatment of metastatic disease.
- **Dose and schedule:** 800mg PO daily
- **Toxicity:**  
Types of toxicity experienced are similar to other VEGF TKIs but the frequency and grade may be different. Liver function tests should be frequently measured (at least once every two weeks initially) as they are often elevated with this drug. The COMPARZ trial reported safety and quality-of-life profiles may favor pazopanib when compared to sunitinib.
- **Efficacy assessment:**  
Imaging of involved sites every 3 months 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.

#### Temsirolimus<sup>13,14</sup>

- **Indication:**  
First-line therapy for metastatic RCC in poor-prognosis patients.  
Temsirolimus has been shown in a phase III trial of poor-prognosis patients with clear cell and non-clear cell RCC to improve overall survival.
- **Dose and Schedule:**  
Delivered as 25 mg IV weekly.
- **Toxicity:**  
Treatment side effects and laboratory abnormalities should be initially monitored weekly, then every 2 weeks. This follow-up interval may be extended if clinically appropriate.
- **Efficacy Assessment:**  
Efficacy should be assessed every 8 weeks.

## Subsequent Therapies

### Nivolumab<sup>15</sup>

- Indication:
  - Standard of care for metastatic or advanced RCC treated with prior antiangiogenic therapy, based on phase III data demonstrating superior overall survival data compared to everolimus.
- Dose and Schedule:
  - Dose at 3mg/kg IV q 2 weeks
- Efficacy Assessment:
  - Imaging every 12 weeks initially then as clinically indicated. Continue until disease progression or patient intolerance. Rarely, pseudoprogression may occur where tumors may get larger before they shrink due to immune cell infiltration. This occurs in 3-14% of patients and treatment beyond progression can be judiciously used only if the patient is still clinically benefiting. It is important not to over-treat beyond progression: if patients are clinically declining then nivolumab should be stopped.
- Toxicity:
  - Physician must be aware of the toxicity profile of nivolumab and follow patients accordingly with experienced nursing support. Autoimmune toxicities such as colitis (diarrhea), skin rash, and pneumonitis should be treated with steroids as described in the product monograph. Hypothyroidism (TSH), hypophysitis/adrenal insufficiency (cortisol), pancreatitis (glucose, lipase) should be monitored regularly.

### Everolimus

- Indication:

Standard of care as subsequent 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.
- Dose and Schedule:

Starting dose at 10 mg/day orally.
- Efficacy Assessment:

Imaging every 2 cycles (12 weeks) initially then as clinically indicated.  
Continue treatment until disease progression or patient intolerance.
- Toxicity:

Physician must be aware of the toxicity profile of everolimus and follow patients accordingly with experienced nursing support.  
Dose must be modified as per individual's toxicity profile.  
Patient must be assessed every cycle for tolerance; interval may be lengthened after 2 cycles if clinically appropriate.  
Pneumonitis has been reported and should be monitored.

### Axitinib<sup>16</sup>

- Indication:

Standard of care as second-line therapy for metastatic RCC as seen in the phase III AXIS clinical trial.
- Dose and Schedule:

Starting dose at 5mg bid. To be dose escalated to 7mg and then 10mg bid if no side effects. Can be dose reduced for toxicity.
- Efficacy Assessment:

Imaging every every 12 weeks or as indicated. Continue treatment until disease progression or intolerance.
- Toxicity:

Physician must be aware of the toxicity profile of axitinib and follow patients accordingly with

experienced nursing support.

Dose must be modified as per individual's toxicity profile.

Patient must be assessed every cycle for tolerance; interval may be lengthened after 2 cycles if clinically appropriate.

#### Sorafenib<sup>13,17,18</sup>

- 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 twice a day continuously. Each treatment cycle is 6 weeks in duration.
- Toxicity:  
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 can 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.

#### Local Therapy<sup>19-21</sup>

Cytoreductive nephrectomy prior to or following targeted therapy

- There is no prospective data to guide clinical practice in the targeted therapy era at this time. Decisions are to be made based on clinical indications. About 90% of enrolled patients had undergone a nephrectomy prior to systemic therapy in both the sunitinib and the sorafenib phase III trials.
- Nephrectomy has shown overall survival benefit when used in conjunction with interferon.
- Patients who appear to benefit most from nephrectomy are those with:
  - Most of the tumor burden within the kidney ( $\geq 90\%$ )
  - Good performance status
  - No central nervous or liver involvement (with rare exceptions)
  - Patients with 0, 1, 2, 3 (but not 4+) International mRCC Database Consortium criteria so that their prognosis is long enough to benefit from a cytoreductive nephrectomy

Other considerations include:

Surgical resectability taking into consideration possible morbidity to proximal vital structures, encasement of the renal hilum, and other complicating factors<sup>22,23</sup>

- Laparoscopic nephrectomy is the emerging standard surgical procedure whenever technically feasible.
- Patient selection is important and discussion at a multidisciplinary tumor board is recommended.
- If major surgery is planned during targeted therapy, patient should stop their medication 2-7 days prior to surgery and resume their medication no sooner than 4 weeks after (at the discretion/evaluation of treating clinician).

#### Palliative Nephrectomy

Nephrectomy should be offered as a palliative procedure at any time when improvement of clinically meaningful symptoms can be achieved.

#### 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

#### *Oligometastatic Disease*

In patients with limited (e.g. solitary) and resectable metastatic disease, surgical intervention (metastatectomy) can be considered. The clinical decision should be based on ECOG status, size, disease-free interval from time of initial diagnosis) and number of metastases. This can either be offered as the primary modality, or following systemic therapy. Other modalities that can be considered include stereotactic body radiosurgery, radiofrequency ablation, and cryotherapy. These cases should be discussed in a multidisciplinary tumor board.

#### *Palliative Radiation*

For symptomatic lesions, particularly metastases to bone, radiation therapy should be considered.

#### *Bone Metastases*

Bisphosphonates or other inhibitors of bone resorption may be considered as an adjunctive therapy.

### **Follow-up**

- For those not on active treatments, follow-up as clinically indicated.
- If relapses are to occur, they may happen early or very late. Therefore, follow-up should continue for at least five years.

## **DISCUSSION**

### **Early Stage Disease**

For patients with early stage node negative disease, options for first-line therapy include partial nephrectomy, active surveillance or minimally invasive therapy with cryoablation, or radiofrequency ablation. Active surveillance is best suited for individuals with T1a lesions, who are elderly or medically comprised. In these patients, a biopsy should be performed initially, followed by repeat imaging every six months with intervention upon progression. Cryoablation and radiofrequency ablation are also primarily for patients with T1a disease (only after consultation with a urologist, to ensure appropriate follow-up). Both are excellent treatment options for early stage disease, with long-term disease free survival rates ranging from 92 to 98%<sup>24-29</sup>. A retrospective study among patients with renal cell carcinoma who underwent percutaneous CT-guided radiofrequency ablation (n=41) or cryoablation (n=70) demonstrated equivalent imaging (e.g. MRI) recurrence rates (11% vs. 7%, respectively; p=.60)<sup>30</sup>.

In medically fit patients, including those that are elderly, partial nephrectomy is an excellent option. In an analysis of the SEER database, among patients with T1aN0M0 renal cell carcinoma (n=7,280), cancer-specific mortality for partial- and radical-nephrectomy were 1.8% and 2.5%, respectively (p=.5) for all patients and 1.0% and 3.4% (p=0.7), respectively, for patients aged 70 years and over<sup>31</sup>. Van Poppel *et al.* conducted the first prospective randomized study comparing nephron-sparing surgery (NSS) with radical nephrectomy (RN) in a group 541 patients with an average age of 62 years and a renal tumour <=5cm. Their intention-to-treat (ITT) analysis showed 10-yr overall survival rates of 79.4% for RN and 75.2% for NSS among RCC patients, resulting in a non-significant (p=0.07) test of superiority<sup>32</sup>.



## **Advanced Stage Disease**

### ***Systemic Therapy***

For patients with advanced, node positive, and/or unresectable or metastatic disease, systemic is indicated.

### ***First-line Therapy***

Sunitinib is a good option for first-line therapy and should be continued until disease progression or patient intolerance<sup>6-10</sup>. As compared with interferon alpha, sunitinib resulted in significantly better median overall survival (26.4 vs. 21.8 months;  $p=.051$ ) and progression free survival (11 vs. 5 months;  $p<.001$ ) among treatment-naïve patients with metastatic clear cell RCC ( $n=750$ ) in a randomized phase III trial<sup>33</sup>. Sunitinib should be dosed to maximum treatment tolerance as there is evidence that higher AUC leads to higher response rates<sup>10</sup>. The most common grade 3 toxicities include hypertension, fatigue, diarrhea, and hand-foot syndrome<sup>34</sup>. Cardio toxicity has become an issue and in patients with pre-existing coronary artery disease or coronary artery disease risk factors, monitoring of ventricular ejection fraction should be considered<sup>11,34-37</sup>. Routine monitoring in all patients is not indicated<sup>11,34</sup>.

Pazopanib is another option for first-line therapy. A randomized, double-blind phase III trial has shown that, as compared to placebo, pazopanib monotherapy resulted in significantly prolonged progression free survival (9.2 vs. 4.2 months;  $p<.0001$ ), in patients ( $n=435$ ) with advanced disease<sup>38</sup>. In subgroup analyses, treatment-naïve patients ( $n=233$ ) experienced a median progression free survival of 11.1 months (vs. 2.8 months;  $p<.0001$ ) and cytokine-pretreated patients ( $n=202$ ) experienced a median progression free survival of 7.4 months (vs. 4.2 months;  $p<.001$ ). The most common adverse events were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting<sup>38</sup>. The COMPARZ trial compared pazopanib (800 mg/day continuous) to sunitinib (50 mg/day for 4 weeks followed by 2 weeks off treatment) using a noninferiority design ( $N=1110$ ). COMPARZ reported a hazard ratio for progression of disease or death from any cause of 1.05 (95%CI 0.90-1.22) meeting the predefined noninferiority margin. Patients treated with pazopanib, when compared to sunitinib, had a lower incidence of fatigue (53% vs. 55%), hand-foot syndrome (29% vs. 50%), and thrombocytopenia (41% vs. 78%), but higher incidence of increased levels of alanine aminotransferase (60% vs 43%). COMPARZ also reported on 14 health-related quality-of-life domains, of which 11 favored pazopanib (all  $p<0.05$ )<sup>39</sup>.

Temsirolimus is another option for first-line therapy, especially in poor-prognosis patients<sup>13,14</sup>. A multicenter, randomized phase III trial among patients with previously untreated, poor-prognosis metastatic renal-cell carcinoma ( $n=626$ ) demonstrated that intravenous temsirolimus (25 mg weekly) was superior to subcutaneous interferon alfa (3 million units, with an increase to 18 million units, three times per week) or combination therapy with both, in terms of overall survival (hazard ratio for death, 0.73;  $p=.008$ ) and progression-free survival ( $p<.001$ ). Median overall survival times in the temsirolimus and interferon groups were 10.9 and 7.3 months, respectively<sup>14</sup>. The most common toxicities included rash, peripheral edema, hyperglycemia, and hyperlipidemia; however, fewer patients experienced serious adverse events in the temsirolimus group ( $p=.02$ )<sup>14</sup>. Temsirolimus has also been shown in a phase III trial of poor-prognosis patients with clear cell and non-clear cell RCC to improve overall survival<sup>33</sup>. Furthermore, quality-adjusted time without symptoms of progression or toxicity and quality of life were shown to be significantly better with temsirolimus, as compared to interferon alpha<sup>40,41</sup>.

### **After First-line Therapy**

Nivolumab (PD-1 Inhibitor)\*. The CheckMate 025 trial demonstrated an overall survival benefit of nivolumab compared to everolimus with fewer grade 3 or 4 adverse events in patients already treated with one or two targeted therapies<sup>42</sup>. Median overall survival was 25.0 months in the nivolumab arm vs. 19.6 months in the everolimus arm (N=821). Median progression-free survival was 4.6 months with nivolumab and 4.4 months with everolimus. Grade 3/4 treatment-related adverse events occurred in 19% of nivolumab patients and 37% of everolimus patients.

Axitinib is a selective second-generation inhibitor of VEGF receptors. It has shown positive results in a phase III trial compared with sorafenib. The 723 patients included in the study had confirmed renal cell carcinoma that progressed despite first-line therapy containing sunitinib, bevacizumab plus interferon- $\alpha$ , temsirolimus, or cytokines. Median progression-free survival was 6.7 months for axitinib versus 4.7 months in patients receiving sorafenib, with non-significant differences regarding toxicity.<sup>46</sup>

Cabozantinib (VEGF/Met inhibitor)\*. The METEOR trial has reported progression-free survival benefit and an overall survival benefit for cabozantinib when compared to everolimus in patients that progressed after VEGFR-targeted therapy<sup>43</sup>. Median progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus ( $p < 0.001$ ) and the objective response rate was higher with cabozantinib (21% vs 5% with everolimus;  $p < 0.001$ ). Overall survival was longer with cabozantinib when compared to everolimus HR 0.66 (95%CI: 0.53-0.83)<sup>44</sup>. Adverse events were managed with dose reduction; dose reduction occurred in 60% of patients who received cabozantinib (vs. 25% in those on everolimus), and discontinuation of treatment due to adverse events occurred in 9% of patients who received cabozantinib (vs. 10 in those on everolimus). Cabozantinib is not yet Health Canada approved at the time of writing.

Everolimus is indicated for second-line therapy of metastatic renal cell carcinoma, only after progression on sunitinib, sorafenib, or both based on phase III data demonstrating superior progression-free survival to best supportive care<sup>45</sup>. Finally, efficacy results among patients with metastatic renal cell carcinoma treated with either everolimus (10 mg/day; n=277) plus best supportive care or placebo plus best supportive care (n=139) demonstrated an advantage in median progression free survival (4.9 vs. 1.9 months;  $p < .001$ ) but not median overall survival (14.8 vs. 14.4 months;  $p = .162$ ) although it should be noted that this study did allow crossover to everolimus at the time of progression. The toxicity profile for everolimus includes infections, dyspnea, pneumonitis and fatigue<sup>46,47</sup>. Once the newer drugs (e.g. nivolumab) demonstrating superiority against everolimus become reimbursed, the use of everolimus will likely be moved to third or fourth line therapy. At the time of writing this indication is not funded.

Sorafenib is indicated for second-line treatment of renal cell carcinoma, after cytokine failure<sup>18,48,49</sup>. In a randomized phase III trial, sorafenib was shown to be superior to best supportive care (placebo) with regards to median progression-free survival (5.5 vs. 2.8 months;  $p < .01$ ) and survival (hazard ratio for death, 0.72;  $p = .02$ ). Partial responses (as the best response) were seen in 10% of patients receiving sorafenib and in 2% of those receiving placebo ( $p < .001$ )<sup>49</sup>. Physicians should be aware of the toxicity profile of sorafenib (i.e. diarrhea, rash, fatigue, alopecia, and hand-foot skin reactions<sup>49,50</sup>) and follow patients accordingly with experienced nursing support. Doses and treatment intervals should be modified as per the patient's toxicity. Long term efficacy and safety of sorafenib has been established: patients (n=169) who were treated for more than one year with sorafenib achieved a median progression free survival of 10.9 months and a disease control rate of 92% with no unexpected toxicities associated with long-term use<sup>50</sup>. However, overall survival was not significantly different (17.8 vs. 15.2 months;  $p = .146$ ) until post-cross-over placebo survival data were censored (17.8 vs. 14.3 months;  $p = .029$ )<sup>17</sup>. In subgroup analyses, both high-vascular endothelial growth factor (VEGF;  $p < .01$ ) and low-VEGF ( $p < .01$ ) patients benefited from sorafenib<sup>17</sup>.

The appropriate sequencing of these agents after first-line therapy is unknown. Third- and fourth-line regimens would use drugs not previously used in the patient.

### ***Local Therapy***

There is little data to guide clinical practice in relation to cytoreductive nephrectomy in the era of targeted therapy and decisions are made based on clinical indications. In phase III trials, the majority of patients had undergone a nephrectomy prior to systemic therapy<sup>7,48,49</sup>. Nephrectomy has proven overall survival benefit when used in conjunction with interferon<sup>51,52</sup>. Among patients treated with interferon alfa-2a (n=159), univariate and multivariate statistical analyses showed that prior nephrectomy was a significant prognostic factor for survival<sup>52</sup>. A prospective trial also showed that among patients with metastatic renal-cell cancer who were acceptable candidates for nephrectomy (n=120), the addition of interferon alfa-2b resulted in prolonged median survival (11.1 vs. 8.1 months, interferon alone; p=.05)<sup>51,52</sup>. Patients who appear to benefit most from nephrectomy are those with most of the tumor burden within the kidney, good performance status, and no central nervous or liver involvement (with rare exceptions)<sup>51,52</sup>. Other considerations include surgical resectability, including possible morbidity to proximal vital structures, encasement of the renal hilum and other complicating factors<sup>22,23</sup>. Laparoscopic nephrectomy is the emerging standard surgical procedure and should be considered whenever technically feasible<sup>53,54</sup>.

Nephrectomy or renal embolization (when nephrectomy is not possible) can also be offered as palliative procedures at any time when clinically indicated.

### ***Adjuvant Therapy***

Currently, there is no role for adjuvant therapy in localized, resected renal cell carcinoma. The adjuvant ASSURE trial<sup>55</sup> randomized patients between sunitinib, sorafenib and placebo and did not demonstrate any benefit. The S-TRAC trial<sup>56</sup> randomized higher risk clear cell patients to one year of sunitinib versus placebo. There was a difference in disease free survival however the overall survival data were immature and there was no difference. We are awaiting the results of other adjuvant clinical trials before we can recommend adjuvant therapy in this setting. Enrollment of these patients into a clinical trial is encouraged.

## 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
Hx/Px	history, physical examination
IFN	interferon
LFT	liver function tests
RCC	renal cell carcinoma
RFA	radiofrequency ablation
U/S	ultrasound

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

## APPENDIX

### Cancer Staging Manual (American Joint Committee on Cancer, 2016)

#### Primary Tumour (T)

**TX:** The primary tumor cannot be evaluated.

**T1:** The tumor is found only in the kidney and is 7 centimeters (cm) or smaller at its largest area. There has been much discussion among doctors about whether this classification should only include a tumor that is 5 cm or smaller.

- **T1a:** The tumor is found only in the kidney and is 4 cm or smaller at its largest area.
- **T1b:** The tumor is found only in the kidney and is between 4 cm and 7 cm at its largest area.

**T2:** The tumor is found only in the kidney and is larger than 7 cm at its largest area.

- **T2a:** The tumor is only in the kidney and is more than 7 cm but not more than 10 cm at its largest area.
- **T2b:** The tumor is only in the kidney and is more than 10 cm at its largest area.

**T3:** The tumor has grown into major veins within the kidney or perinephric tissue, which is the connective, fatty tissue around the kidneys. However, it has not grown into the adrenal gland on the same side of the body as the tumor. The adrenal glands are located on top of each kidney and produce hormones and adrenaline to help control heart rate, blood pressure, and other bodily functions. In addition, the tumor has not spread beyond Gerota's fascia, an envelope of tissue that surrounds the kidney.

- **T3a:** The tumor has spread to the large vein leading out of the kidney, called the renal vein; the muscular branches of the renal vein; the fat surrounding the kidney; or the fat inside the kidney. The tumor has not grown beyond Gerota's fascia.
- **T3b:** The tumor has grown into the large vein that drains into the heart, called the inferior vena cava, below the diaphragm. The diaphragm is the muscle under the lungs that helps breathing.
- **T3c:** The tumor has spread to the vena cava above the diaphragm and into the right atrium of the heart or to the walls of the vena cava.

#### Regional Lymph Nodes (N)

**NX:** The regional lymph nodes cannot be evaluated.

**N0 (N plus zero):** The cancer has not spread to the regional lymph nodes.

**N1:** The cancer has spread to regional lymph nodes

#### Distant Metastasis (M)

**M0 (M plus zero):** The disease has not metastasized.

**M1:** The cancer has spread to other parts of the body beyond the kidney area.

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