Background

In 2019, it is estimated that 7200 Canadians (4700 men and 2500 women) will be diagnosed with kidney and renal pelvis cancer, and that 1900 Canadians will die from kidney and renal pelvis cancer. In Alberta, 680 new kidney cancer diagnoses are anticipated in 2019.

Renal cell carcinoma (RCC) is the main 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 8th edition (2017) of the American Joint Committee on Cancer’s AJCC Cancer Staging Manual (see Appendix).

Guideline Questions

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

Search Strategy

Phase III trials involving ‘renal cell carcinoma’ that had been published since the last iteration of the guideline were identified and reviewed using the pubmed database. The results of the literature review are available upon request (guru@ahs.ca).

Target Population

Adult patients (≥18 years of age) with a diagnosis, or suspected diagnosis of renal cell carcinoma.

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 contract (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\textsuperscript{1,2}
    - 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\textsuperscript{3-9}. 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 tumours 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\textsuperscript{10}, and is stage dependent:
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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+**

Indications include locally advanced, unresectable cancer or metastatic disease. The International mRCC Database Consortium (IMDC) risk factors (hypercalcemia, neutrophilia, thrombocytosis, anemia, Karnofsky performance status <80%, and time from diagnosis to treatment <1 year) are used to stratify patients into 3 risk groups. Patients with 0 factors vs. 1-2 factors vs. 3 or more factors are deemed favourable-, intermediate-, and poor-risk, respectively. An online calculator is available at [https://www.imdconline.com/](https://www.imdconline.com/)

**Management**

- Staging:
  - CBC, Calcium, LFTs, renal function test
  - CT abdomen, pelvis, thorax and other imaging procedures as clinically indicated
• First-line Therapy: Favourable-Risk
  o Pembrolizumab/Axitinib (Pembro/Axi)
    ▪ Indication: first-line therapy for metastatic RCC based on phase III data
    ▪ Dose and schedule:
      - Pembrolizumab 200mg intravenously once every 3 weeks plus axitinib (5mg) orally twice daily
      - There is no recommended dose changes for pembrolizumab; axitinib dose could be dosed to maximum treatment tolerance (to 7mg, then 10mg, twice daily)
    ▪ Toxicity:
      - Physicians must be aware of the toxicity profile of pembrolizumab and axitinib and the potential overlapping toxicities. As a general rule, axitinib-induced toxicity would be expected to improve quickly with cessation of therapy, whereas an immune mediated adverse event (irAE) would not improve after stopping axitinib.
      - It is extremely important to have early recognition of irAEs that require prompt intervention with high dose steroids. Colitis (diarrhea), pneumonitis, endocrinopathies (hypophysitis, hypothyroidism, adrenal insufficiency), hepatitis and rash are some examples. Patients should be educated about these toxicities and followed every cycle to look for these adverse events. LFTs, cortisol, TSH amongst other bloodwork should be checked regularly. In the Phase III trial, 75.8% of the patients experienced grade 3 or higher toxicities.
      - Guidelines for managing toxicities from immunotherapy are available through ASCO and ESMO.
      - Axitinib dose can be reduced to 3mg, then 2mg, twice daily to manage toxic effects.
  o Sunitinib
    ▪ Indication:
      - First-line therapy for metastatic RCC based on phase III data.
      - 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

  - 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.

- First Line Therapy: Intermediate- and Poor-Risk

  - Ipilimumab and Nivolumab (Ipi/Nivo)

    - Indication: first-line therapy in mRCC patients with intermediate- or poor-risk disease by IMDC criteria based on phase III data showing overall survival benefit. It is not approved for favourable-risk disease.
    - Dose and schedule: nivolumab at 3 mg/kg (capped at 240 mg) and ipilimumab at 1 mg/kg every three weeks for four cycles. This is followed by nivolumab maintenance therapy at the same dose q 2 weeks. Nivolumab maintenance can be switched to q 4 weeks (6mg/kg capped at 480 mg) at physician’s discretion usually when clinical benefit established.
    - Toxicity:
      - It is extremely important to have early recognition of immune mediated
adverse events that require prompt intervention with high dose steroids. Colitis (diarrhea), pneumonitis, endocrinopathies (hypophysitis, hypothyroidism, adrenal insufficiency), hepatitis and rash are some examples. Patients should be educated about these toxicities and followed every cycle to look for these adverse events. LFTs, cortisol, TSH amongst other bloodwork should be checked regularly. In the phase III trial, 60% of patients treated with Ipi/Nivo required steroids.

- Guidelines for managing toxicities from immunotherapy are available through ASCO and ESMO.

  ▪ Efficacy assessment: efficacy should be assessed after the first 4 cycles of ipi + nivo with CT imaging, and then every 3 months thereafter while on nivolumab.

  o Pembrolizumab/Axitinib
    ▪ Pembrolizumab/Axitinib is also indicated for intermediate- and poor-risk disease. There is currently no prospective data to guide our choice in selecting Ipi/Nivo vs. Pembro/Axi.
    ▪ See above section under good risk disease for dose and schedule, toxicity and efficacy assessment.

  o Sunitinib or Pazopanib
    ▪ Indication: first-line therapy for metastatic RCC in poor-prognosis patients who are not eligible for ipilimumab/ nivolumab (e.g. patients’ comorbidities, frailty, active autoimmune disease). Sunitinib or pazopanib is indicated in patients with favourable-risk disease.
    ▪ Dose and schedule: see above (same as favourable-risk).
    ▪ Toxicity: see above (same as favourable-risk).
    ▪ Efficacy assessment: see above (same as favourable-risk).

  o Temsirolimus
    ▪ Indication:
      - The treatment options listed above are preferred over temsirolimus. However, temsirolimus can be considered in select patients with poor-prognosis metastatic RCCs.
      - 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
  o Nivolumab\textsuperscript{35-38}
    ▪ 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. Should not be given after progression on ipilimumab and nivolumab first-line.
    ▪ Dose and schedule: 3mg/kg IV q 2 weeks (maximum dose 240mg) or 6mg/kg IV q 4 weeks (maximum dose 480mg)
    ▪ Efficacy assessment: imaging every 12 weeks initially then as clinically indicated. Continue until disease progression or patient intolerance. Rarely, pseudoprogression may occur where tumours 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.
  o Cabozantinib\textsuperscript{39,40}
    ▪ Indication: 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 60 mg PO daily and dose reduce to 40 mg PO daily if not well tolerated.
    ▪ Efficacy assessment: imaging every 12 weeks initially then as clinically indicated. Continue until disease progression or patient intolerance.
    ▪ Toxicity: physicians must be aware of the toxicity profile of cabozantinib and follow patients accordingly with experienced nursing support. Patients should be assessed every cycle for treatment tolerance.
  o Everolimus\textsuperscript{41-43}
    ▪ 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**
  - **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**
  - **Indication:** the treatment options listed above are preferred over sorafenib. Sorafenib can be considered in 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\textsuperscript{12,51-53}
  o Cytoreductive nephrectomy (CN) prior to or following targeted therapy:
    ▪ Discussion at multidisciplinary tumour board is strongly advised (figure 1 provides a suggested approach).
    ▪ The phase III CARMENA\textsuperscript{53} trial randomized patients to CN with sunitinib versus sunitinib alone. It demonstrated that sunitinib alone is non-inferior to the CN arm. It should be noted that over 40\% of patients enrolled had poor-risk disease so the typical CN patient may not have been included in this trial. Thus, there remain patients that are still eligible for CN including patients with limited metastatic disease with large primary tumours and those with symptomatic primary tumours.
    ▪ Deferred CN while starting systemic therapy first could offer a litmus test for deciding whether a nephrectomy would be beneficial or not. Please see the discussion section below for more information.
    ▪ Nephrectomy has shown overall survival benefit when used in conjunction with interferon.
    ▪ Patients who appear to benefit most from nephrectomy are those with:
      1. Most of the tumour burden within the kidney (\textgreater{} 90\%)
      2. Good performance status
      3. No central nervous or liver involvement (with rare exceptions)
      4. Patients with favourable- or intermediate-risk disease for which active surveillance can be done after CN.
    ▪ Other considerations include:
      - Surgical resectability taking into consideration possible morbidity to proximal vital structures, encasement of the renal hilum, and other complicating factors\textsuperscript{54,55}
      - Laparoscopic nephrectomy is the emerging standard surgical procedure whenever technically feasible.
      - Patient selection is important and discussion at a multidisciplinary tumour 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).
  o Palliative nephrectomy: nephrectomy should be offered as a palliative procedure at any time when improvement of clinically meaningful symptoms can be achieved.
  o Renal embolization: this approach can be offered as a palliative treatment for those with local symptoms but unable to undergo a nephrectomy.
Guideline Resource Unit

Figure 1. Proposed Approach to Integrating Surgery and Systemic Therapy for Newly Diagnosed mRCC (Adapted from Bhindi et al. 2018⁵⁶)

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center, LOE = level of evidence

* IMDC/MSKCC risk group is determined at the time of receipt of systemic therapy. The risk grouping can therefore only be approximated at the time of diagnosis prior to the receipt of systemic therapy. Favourable-risk assumes that patients will be able to go one year prior to initiating systemic therapy. If a patient receives systemic therapy upfront, they are by definition at least intermediate-risk. Of note, the MSKCC risk classification was used in both CARMENA and SURTIME trials, while the IMDC risk classification has only been used in observational analyses relevant to this topic.

** Limited metastatic burden is defined based on the extent of disease being amenable to complete metastasectomy or surveillance (i.e., deferred systemic therapy) after CN.

- Treatment to Metastatic Sites
  - Oligometastatic disease:
    - In patients with limited (e.g. solitary) and resectable metastatic disease, surgical intervention (metastasectomy) 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 tumour 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 compromised. 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 an 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%.\(^3\)\(^-\)\(^8\) 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).\(^9\)

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.\(^1\) 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.\(^2\)
**Advanced Stage Disease**

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

**First-line Therapy:**
The combination of ipilimumab and nivolumab (ipi/nivo) compared to sunitinib alone was studied in the CHECKMATE 214 study.\(^{29}\) In the extended follow up (32 months) analyses,\(^{68}\) for ipi/nivo versus sunitinib in the IMDC intermediate- and poor-risk categories, OS was not reached vs 26.6 months (HR 0.66 [95% CI 0.54-0.80]; P < 0.0001) and response rate was 42% vs 29% p<0.0001 with 11% vs 1% complete responses both in favor of ipi/nivo. The PFS was 8.2 months [95% CI 6.9-10.0] vs 8.3 months [7.0-8.8]; HR 0.77 [95% CI 0.65-0.90],p=0.0014) in favor of ipi/nivo. However, in the exploratory analyses of favourable-risk patients, sunitinib showed a higher objective response rate compared to ipi/nivo (52% [95%CI 9.7 to 20.3] vs 29% [95% CI 21-38]; p<0.001) and there was no statistically significant difference in OS and PFS. Thus, we do not recommend ipi/nivo for favourable-risk patients. Ipi/nivo was approved by Health Canada and is currently one of the preferred first-line option for patients with intermediate- or poor-risk disease.

In 2019, the KEYNOTE-426 study examined the combination of pembrolizumab and axitinib (pembrolizumab/axitinib) compared to sunitinib alone.\(^{66}\) After a median follow up of 12.8 months, patients receiving the combination treatment had improved overall survival (HR 0.53 [95% CI 0.38-0.74]; p< 0.0001), progression-free survival (HR 0.69 [95% CI 0.57-0.84]; p=0.0001), and objective response rates (59.3% vs 35.7%; p<0.0001). The median progression-free survival was 15.1 months in the combination arm and 11.1 months in the sunitinib arm (HR 0.69 [95% CI 0.57-0.84]; p<0.001). The benefit of pembrolizumab/axitinib over sunitinib was observed in all IMDC risk groups and PD-L1 expression subgroups. Grade 3 or higher adverse events of any cause occurred in 75.8% of patients in the pembrolizumab/axitinib group and in 70.6% in the sunitinib group. This combination was approved by Health Canada and can be used in patients with favourable-, intermediate- or poor-risk disease. At the time of writing, this combination is not yet reimbursed but is available by an access program.

The JAVELIN Renal 101 trial compared the combination of avelumab + axitinib (avelumab/axitinib) to sunitinib alone.\(^{67}\) Avelumab/axitinib significantly improved median progression-free survival compared with sunitinib alone 13.8 months vs 8.4 months (HR 0.69 [95% CI 0.56-0.84] p=0.0002). The overall survival data was immature. This combination is not yet Health Canada approved (Feb 2020).

Sunitinib and pazopanib may be treatment options first line, but the options mentioned above have demonstrated their superiority to sunitinib. Historically, Temsirolimus is another option for first-line therapy, especially in poor-risk patients.\(^{30,45}\) However, this combination is rarely used now because of the availability of other more efficacious treatment options detailed above.
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.\textsuperscript{36,38} Median OS was 25.0 months in the nivolumab arm vs. 19.6 months in the everolimus arm (N=821). Median PFS 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.\textsuperscript{38}

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-alfa, temsirolimus, or cytokines. Median PFS was 6.7 months for axitinib versus 4.7 months in patients receiving sorafenib, with non-significant differences regarding toxicity.\textsuperscript{42}

Cabozantinib (VEGF/Met inhibitor): The METEOR trial has reported PFS benefit and an OS benefit for cabozantinib when compared to everolimus in patients that progressed after VEGFR-targeted therapy.\textsuperscript{39} Median PFS 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). OS was longer with cabozantinib when compared to everolimus HR 0.66 (95%CI: 0.53-0.83).\textsuperscript{40} 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).

Historically, everolimus and sorafenib were considered as treatment options but these are now superseded by the options discussed above. Although everolimus and sorafenib are funded treatment options, their use is uncommon because the above agents have demonstrated superiority to everolimus.

The appropriate sequencing of these agents after first-line therapy is unknown. The current recommended treatment options in Alberta are shown in figure 2. Third- and fourth-line regimens would use drugs not previously used in the patient.
Local Therapy:
Prior to 2018, there is little data to guide clinical practice in relation to cytoreductive nephrectomy (CN) 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.\textsuperscript{16,50,57} Nephrectomy has proven overall survival benefit when used in conjunction with interferon.\textsuperscript{58,59} 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.\textsuperscript{59} 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; \(p=.05\)).\textsuperscript{58,59} Patients who appear to benefit most from nephrectomy are those with most of the tumour burden within the kidney, good performance status, and no central nervous or liver involvement (with rare exceptions).\textsuperscript{58,59} Other considerations include surgical resectability, including possible morbidity to proximal vital structures, encasement of the renal hilum and other complicating factors.\textsuperscript{54,55} Laparoscopic nephrectomy is the emerging standard surgical procedure and should be considered whenever technically feasible.\textsuperscript{60,61}

The phase III CARMENA trial was published in 2018 and it randomized patients to CN with sunitinib versus sunitinib alone.\textsuperscript{53} It demonstrated that sunitinib alone was non-inferior to the CN arm. It should be noted that over 40% of patients enrolled had poor-risk disease so the typical CN patient may not have been included in this trial. Thus, there remain patients that are still eligible for CN including patients with limited metastatic disease with large primary tumours and those with symptomatic primary tumours. A retrospective series of 198 patients presented at GU ASCO 2020 showed that CN
was associated with improved survival for patients with metastatic renal cell carcinoma treated with immunotherapy. However, there is no prospective data on CN with first line checkpoint inhibitor combinations. Currently, upfront CN should be considered in the following clinical scenarios:

1. patients with favourable-/intermediate-risk disease who are candidates for active surveillance
2. patients who are candidates for oligo-metastasectomy
3. patients who have symptomatic kidney masses

Deferred CN should be considered in patients with strong responses to systemic therapy. CN should rarely be performed in patients with poor-risk disease or patients with rapidly progressive disease or high disease burden who need systemic therapy.

Lastly, 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 randomized patients between sunitinib, sorafenib and placebo and did not demonstrate any benefit. The S-TRAC trial 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. Additionally, the PROTECT clinical trial of adjuvant pazopanib vs placebo was negative for the primary endpoint. Also the phase III ATLAS trial evaluating axitinib as adjuvant therapy for patients at high risk of recurrent RCC after nephrectomy was halted after interim analysis due to futility. We are awaiting the results of other adjuvant clinical trials before we can recommend adjuvant therapy routinely in this setting. Enrollment of these patients into a clinical trial is encouraged.
References


## Table 1. Summary of the Systemic Therapy Trials for the Treatment of Advanced/Metastatic Renal Cell Carcinoma Patients Recommended in the First-line.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>Indication</th>
<th>Arms of Study</th>
<th>PFS</th>
<th>p-value</th>
<th>Median OS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab and Axitinib</td>
<td>Keynote-426 (NCT02853331)</td>
<td>Previously untreated clear-cell advanced RCC (All risk groups)</td>
<td>Pembrolizumab (200mg) IV every 3 weeks + Axitinib (5mg) orally twice daily Vs. Sunitinib 50mg orally once daily for 4 weeks (6-week cycle)</td>
<td>Pembro/Axi: 15.1m vs. Sunitinib: 11.1m</td>
<td>HR 0.69; 95% CI: 0.57-0.84; p&lt;0.001</td>
<td>12 months OS: Pembro/Axi: 89.9% vs. Sunitinib: 78.3%</td>
<td>HR 0.53; 95% CI: 0.38-0.74; p&lt;0.0001</td>
</tr>
<tr>
<td>Ipilimumab and Nivolumab</td>
<td>CheckMate 214 (NCT02231749)</td>
<td>Previously untreated clear-cell advanced RCC (int-/poor-risk)</td>
<td>Nivolumab (3mg/kg) + ipilimumab (1mg/kg) x4 followed by: Nivolumab (3mg/kg) every 2 weeks Vs. Sunitinib (50mg) orally once daily for 4 weeks (6-week cycle)</td>
<td>Ipi/Nivo: 11.6m vs. Sunitinib: 8.4m</td>
<td>HR: 0.82; p=0.03 (not sign. by the prespecified 0.009 threshold)</td>
<td>18m-OS: Ipi/Nivo: 75% (95%CI: 70-78%) vs. Sunitinib: 60% (95%CI: 55-65%)</td>
<td>HR 0.63; p&lt;0.001</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>N/A (NCT00077974)</td>
<td>Cytokine-refractory metastatic RCC (2nd-line)</td>
<td>Single-arm (N=106) -6 week cycles sunitinib 50mg/day (4wk on 2wk off)</td>
<td>8.3 months (95%CI: 7.8-14.5m)</td>
<td>N/A</td>
<td>Not reached. 6-month survival 79% (95%CI: 70-86%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>N/A (NCT00083889)</td>
<td>Previously untreated, metastatic RCC</td>
<td>(N=750) Interferon-alfa Vs. Sunitinib 50mg/day (4wk on 2wk off)</td>
<td>Interferon: 5m vs. Sunitinib: 11m</td>
<td>HR: 0.42, 95%CI: 0.32-0.54, p&lt;0.001</td>
<td>Interferon: 21.8m vs. Sunitinib: 26.4m</td>
<td>HR 0.82; 95% CI: 0.67 to 1.01; P=0.051</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEG105192 (NCT00334282)</td>
<td>Measurable, locally advanced, and/or metastatic RCC (54% treatment naive, 46% received cytokines) (2nd-line)</td>
<td>Placebo Vs. Pazopanib (800mg daily)</td>
<td>Placebo: 4.2m vs. Pazopanib: 9.2m</td>
<td>HR: 0.46, 95%CI: 0.34-0.62, p&lt;0.001</td>
<td>Placebo: 20.5m vs. Pazopanib: 22.9m</td>
<td>HR: 0.91; 95%CI 0.71-1.16; P=0.224</td>
</tr>
<tr>
<td>Pazopanib vs. Sunitinib</td>
<td>COMPARZ (NCT00720941)</td>
<td>Clear-cell mRCC</td>
<td>(N=1110) Pazopanib (800mg/ daily) Vs. Sunitinib 50mg/daily (4wk on 2wk off)</td>
<td>Pazopanib: 8.4m (95%CI: 8.3-10.9) vs. Sunitinib: 9.5 (95%CI: 8.3-11.1)</td>
<td>HR1.05, 95%CI: 0.9-1.22</td>
<td>Pazopanib: 28.4m vs. Sunitinib: 29.3m</td>
<td>HR: 0.91, 95%CI: 0.76-1.08</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Global ARCC (NCT00065468)</td>
<td>Untreated, poor-risk mRCC</td>
<td>(N=626) Interferon alfa (Ia) Vs. Temsirolimus (Tem) 25mg weekly Vs. Tem (15mg weekly) + Ia (6 million U 3 times weekly)</td>
<td>Ia: 3.1m Vs. Tem: 5.5m Vs. Ia + Tem: 4.7m</td>
<td>Not reported</td>
<td>Ia: 7.3m Tem: 10.9m Tem + Ia: 8.4m</td>
<td>(tem alone vs. Ia) HR: 0.73, 95%CI: 0.58-0.92, p=0.008 (tem + Ia vs. Ia) HR: 0.96, p=0.70</td>
</tr>
</tbody>
</table>
Table 2. Summary of the Systemic Therapy Trials for the Treatment of Advanced/Metastatic Renal Cell Carcinoma Patients Recommended in the SECOND-line and BEYOND.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>Indication</th>
<th>Arms of Study</th>
<th>PFS</th>
<th>p-value</th>
<th>Median OS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib vs. Everolimus or Combined&lt;sup&gt;57&lt;/sup&gt;</td>
<td>(NCT01136733)</td>
<td>Advanced/metastatic clear-cell RCC with prior VEGF-targeted therapy and progressed on or within 9 months</td>
<td>(N=153) (L) Lenvatinib (24 mg/d) Vs. (E) Everolimus (10 mg/d) Vs. (L+E) Lenvatinib (18 mg/d) + Everolimus (5 mg/d)</td>
<td>L: 7.4m (95%CI: 5.6-10.2m) E: 5.5m (95%CI: 3.5-7.1) L+E: 14.6m (95%CI: 5.9-20.1)</td>
<td>L+E vs. E P&lt;0.001 L+E vs. L P=0.12 L vs E P=0.048</td>
<td>L: 18.4m (95%CI: 13.3-19.5) E: 17.4m (95%CI: 11.8-22.6) L+E: 25.5m (95%CI: 20.8-25.5)</td>
<td>All p&gt;0.05</td>
</tr>
<tr>
<td>Nivolumab vs. everolimus&lt;sup&gt;36,38&lt;/sup&gt;</td>
<td>CheckMate 025 (NCT01668784)</td>
<td>Advanced clear cell RCC, with one or two prior regimens of antiangiogenic therapy</td>
<td>(N=821) Nivolumab (Nivo) (3mg/kg IV every 2 weeks) Vs. Everolimus (Evero) (10mg /day)</td>
<td>Nivo: 4.6m Evero: 4.4m HR: 0.88, p=0.11</td>
<td>Nivo: 25.0m Evero: 19.6m And Nivo: 23.6m Evero: 19.8m in those with prior sunitinib, and Nivo: not estimable vs. Evero: 17.6m in those with prior pazopanib (Favor Nivo) HR: 0.73, 95%CI: 0.57-0.93, p=0.002</td>
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<tr>
<td>Cabozantinib vs. Everolimus&lt;sup&gt;39,40&lt;/sup&gt;</td>
<td>METEOR (NCT01865747)</td>
<td>Advanced/metastatic RCC with previous treatment with VEGFR TKI</td>
<td>(N=658) Carbozantinib (Carbo) 60mg/daily Vs. Everolimus (Evero) 10mg/daily</td>
<td>Carbo: 7.4m Evero: 3.8m HR: 0.58, 95%CI: 0.45-0.75, p=0.001</td>
<td>Carbo: 21.4m Evero: 16.5m HR: 0.66, 95%CI: 0.53-0.83, p&lt;0.001</td>
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<tr>
<td>Everolimus&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>RECORD-1 (NCT00410124)</td>
<td>mRCC with progression on sunitinib, sorafenib or both</td>
<td>(n=272) Everolimus (Evero) (10mg/d) Vs. placebo (n=138) Placebo</td>
<td>E: 4.9m Placebo: 1.9m HR: 0.30, 95%CI: 0.22-0.40, p&lt;0.001</td>
<td>E: 14.8 Placebo: 14.4m HR: 0.87, p=0.162 (80% cross over)</td>
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</tr>
<tr>
<td>Axitinib vs. sorafenib&lt;sup&gt;43,44&lt;/sup&gt;</td>
<td>AXIS (NCT00678392)</td>
<td>Clear-cell RCC with progression on sunitinib bevacizumab plus interferon, temsirolimus, or cytokines</td>
<td>(N=723) Axitinib (Axi) 5mg twice daily (up to 10mg in select pts) Vs. Sorafenib (Sora) 400mg twice daily</td>
<td>Axi: 6.7m Sora: 4.7m HR: 0.67, 95%CI: 0.54-0.81, p=0.001</td>
<td>Axi: 20.1m Sora: 19.2m HR: 0.97, p=0.374</td>
<td></td>
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<tr>
<td>Sorafenib&lt;sup&gt;45,50&lt;/sup&gt;</td>
<td>TARGET (NCT00073307)</td>
<td>RCC that was resistant to standard therapy</td>
<td>(N=903) Sorafenib (Sora) 400mg twice daily Vs. placebo</td>
<td>Sora: 5.5m Placebo: 2.8m HR: 0.44, 95%CI: 0.35-0.55, p&lt;0.01</td>
<td>Sora: 17.8m Placebo: 14.3m HR: 0.78 P=0.029 (16m post-crossover)</td>
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</tr>
</tbody>
</table>
Cancer Staging Manual (American Joint Committee on Cancer, 8th edition 2017)

Primary Tumour (T)
TX: Primary tumor not evaluated.

T1: The tumor is found only in the kidney and is 7 centimeters (cm) or smaller at its largest area.
   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. However, it has not grown into the adrenal gland on the same side of the body as the tumor.
   T3a: The tumor extends into renal vein or segmental branches.
   T3b: The tumour extends into the vena cava below the diaphragm.
   T3c: The tumour extends into the vena cava above the diaphragm.

T4: Direct invasion into the adrenal gland.

Regional Lymph Nodes (N)
NX: Regional lymph nodes not evaluated.
N0: The cancer has not spread to the regional lymph nodes.
N1: The cancer has spread to regional lymph nodes

Distant Metastasis (M)
M0: The disease has not metastasized.
M1: The cancer has spread to other parts of the body beyond the kidney area.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>NX, N0, or N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Development and Revision History
This guideline was reviewed and endorsed by the Alberta GU Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2005.

Levels of Evidence

<table>
<thead>
<tr>
<th>I</th>
<th>Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinion</td>
</tr>
</tbody>
</table>

Strength of Recommendations

<table>
<thead>
<tr>
<th>A</th>
<th>Strong evidence for efficacy with a substantial clinical benefit; strongly recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.): optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome; generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome; never recommended</td>
</tr>
</tbody>
</table>

Maintenance
A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations
AHS, Alberta Health Services; CCA, CancerControl Alberta

Disclaimer
The recommendations contained in this guideline are a consensus of the Alberta Provincial GU 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.