Guideline Resource Unit
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Renal Cell Carcinoma

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Cancer Care Alberta

Clinical Practice Guideline GU-003 – Version 9
www.ahs.ca/guru

Background

In 2020, it is estimated that 7500 Canadians (4900 men and 2600 women) will be diagnosed with kidney and renal pelvis cancer, and that 1950 Canadians will die from kidney and renal pelvis cancer. In Alberta, 710 new kidney cancer diagnoses are anticipated in 2020.

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 contrast (or MRI)
- CBC, creatinine, urea, calcium, albumin, AST, ALT, ALP and bilirubin
- 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
  - FDG PET/CT imaging is not currently recommended or indicated as part of staging for RCC.

- Therapeutic Options
  - Active Surveillance is an appropriate option for the small renal mass (less than 4 cm) in all patients, particularly in elderly or medically compromised patients:
    - Biopsy an option initially.
    - Repeat imaging every 6 months.
    - Intervention is indicated if there is progression.
  - Surgical Intervention[1,2]
    - Partial nephrectomy should be considered in all cases where surgery is being considered especially small renal masses less than 4cm. This can be done either as an open, laparoscopic, or robotic-assisted laparoscopic procedure.
    - If partial nephrectomy is not feasible, consider minimally-invasive radical nephrectomy.
    - If a minimally-invasive surgical procedure cannot be performed due to patient or tumor characteristics, then an open nephrectomy should be done.
    - The adrenal gland should not be removed unless involved on imaging.
  - Percutaneous ablation
    - Both radiofrequency ablation (RFA) and cryoablation are possible treatments for the small renal mass[3-9]. However, this treatment decision should only be made after consultation with a urologist and discussed at multidisciplinary rounds.

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[10], and is stage dependent:

Table 1. Months Post-op & Follow-up Recommended:

	3	6	12	18	24	30	36	48	60	72
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 abdomen					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 abdomen			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 abdomen		X	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 abdomen	X	X	X	X	X	X	X	X	X	X

The necessary duration of follow-up beyond these guidelines is unclear and should be directed based on relapse risk.

Stage T4, N1, M+[11]

Indications for systemic therapy 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 favorable, intermediate, and poor-risk, respectively.[12] An online calculator is available at https://www.imdconline.com/.

Management[13]

- Staging
  - CT scan of head, chest, abdomen, pelvis with contrast (or MRI)
  - CBC, creatinine, urea, calcium, albumin, AST, ALT, ALP and bilirubin.
  - Other additional imaging modalities can be considered as clinically indicated (bone scan, MRI)
  - FDG-PET/CT is not recommended in this setting

First-line Therapies

Favorable-Risk:

Pembrolizumab/Axitinib (Pembro/Axi)[14,68]

- Indication:
  - First-line therapy for advanced 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 adjustment for pembrolizumab.
  - Axitinib should be dose adjusted to maximum treatment tolerance by titrating dose higher or lower (maximum 10 mg po twice daily and minimum 1 mg po twice daily).
  - Treatment is given until disease progression, intolerance or patient decision.
- 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. Liver tests, cortisol, and TSH amongst other bloodwork should be checked regularly. In the Phase III trial, 66.9% of the patients experienced grade 3 or higher toxicities.
  - Guidelines for managing toxicities from immunotherapy are available through ASCO (link) and ESMO (link).
- Efficacy Assessment:
  - Radiological assessment should be performed at a regular 2-3 monthly interval.
  - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.

- Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.

Sunitinib[15-25]

- Indication:
  - First-line therapy for metastatic RCC based on phase III data.
  - Can be used if intolerance (and in absence of progression) on first-line pazopanib.
- Dose and Schedule:
  - A starting dose at 50 mg/day orally for 4 weeks followed by a 2-week rest period for a 6-week treatment cycle is indicated in the product monograph. However, an individualized schedule optimizing the therapeutic ratio with anywhere from 1-4 weeks on therapy followed by a 1-week break as determined by treatment tolerance is recommended
  - Treatment is given until disease progression, intolerance or patient decision.
- Toxicity:
  - Physicians must be aware of the toxicity profile of sunitinib and follow patients accordingly with experienced nursing support. Patients should be assessed regularly for treatment tolerance.
  - Sunitinib should be dosed to maximum treatment tolerance as there is evidence that higher AUC leads to higher response rates.
  - Cardiotoxicity has become an issue and in patients with pre-existing compromised cardiac function. Monitoring of ejection fraction should be considered in high risk or symptomatic patients but routine monitoring in all patients is not indicated.
- Efficacy Assessment:
  - Radiological assessment should be performed at a regular 2-3 monthly interval.
  - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
  - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.

Pazopanib[26-29,69]

- Indication:
  - First-line therapy for advanced RCC based on phase III data.
  - Can be used if intolerance (and in absence of progression) on first-line sunitinib.
- Dose and schedule
  - A starting dose 800 mg/day orally taken on a continuous basis is indicated in the product monograph. However, an individualized schedule optimizing the therapeutic ratio with anywhere from 1-4 weeks on therapy followed by a 1-week break as determined by treatment tolerance is recommended.
  - Treatment is given until disease progression, intolerance or patient decision.

- Toxicity:
  - Physicians must be aware of the toxicity profile of pazopanib and follow patients accordingly with experienced nursing support. Patients should be assessed regularly for treatment tolerance.
  - Pazopanib should be dosed to maximum treatment tolerance as there is evidence that higher AUC leads to higher response rates.
  - Liver enzymes and bilirubin should be frequently measured (at least once every two weeks initially) as they are elevated with this drug more frequently than with other VEGFR-TKIs.
  - The COMPARZ and PISCES trial reported safety and quality-of-life profiles may favor pazopanib when compared to sunitinib.
- Efficacy assessment:
  - Radiological assessment should be performed at a regular 2-3 monthly interval.
  - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
  - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.

Intermediate- and Poor-Risk:

Ipilimumab and Nivolumab (Ipi/Nivo)[30,70]

- Indication:
  - First-line therapy in mRCC patients with intermediate or poor risk disease by IMDC criteria based on phase III data. Not approved for favorable-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 3mg/kg (capped at 240mg) every 2 weeks or 6 mg/kg (capped at 480 mg) every 4 weeks. The maintenance schedule is determined at discretion of the physician and patient. Maintenance treatment can begin anywhere from 4-6 weeks after last dose of ipi/nivo assuming patient is benefiting from treatment.
  - Treatment is given until disease progression, intolerance or patient decision.
- 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. Liver enzymes, cortisol, TSH amongst other bloodwork should be checked regularly. In the Phase III trial, 28.7% of patients treated with Ipi/Nivo required high

dose corticosteroids (≥ 40 mg prednisone).
        - Guidelines for managing toxicities from immunotherapy are available through ASCO (link) and ESMO (link).
- Efficacy Assessment
    - Efficacy should be assessed after the first 4 cycles of ipi/nivo with imaging, and then every 3 months thereafter while on nivolumab.
    - Although CT scan is the most commonly used imaging modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
    - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.
    - 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.

Pembrolizumab/Axitinib[14,68]

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

Sunitinib or Pazopanib[15-29]

- Indication:
  First-line therapy for advanced RCC in intermediate/poor-risk patients who are not eligible for checkpoint inhibitor therapy (e.g. patients' comorbidities, frailty, active autoimmune disease).
    - Dose and Schedule:
      see above (same as favorable-risk)
    - Toxicity:
      see above (same as favorable-risk)
    - Efficacy Assessment:
      see above (same as favorable-risk)

Subsequent Therapies

- Nivolumab[35-38]
    - Indication:
        - Standard of care for advanced RCC treated with prior antiangiogenic therapy,

based on phase III data. Should not be given after progression on any PD1/PD-L1 checkpoint inhibitor therapy.

- Dose and Schedule:
  - 3mg/kg IV every 2 weeks (maximum dose 240mg) or 6mg/kg IV every 4 weeks (maximum dose 480mg). Treatment is given until disease progression, intolerance or patient decision.
- 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. Liver enzymes, cortisol, TSH amongst other bloodwork should be checked regularly.
  - Guidelines for managing toxicities from immunotherapy are available through ASCO (link) and ESMO (link).
- Efficacy Assessment:
  - Radiological assessment should be performed at a regular 2-3 monthly interval.
  - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
  - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.
  - 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.

- Cabozantinib[39,40]
  - Indication:
    - Treatment for advanced RCC patients having previously progressed on VEGFR-TKI as seen in phase III clinical trial.
    - Treatment for those who had prior exposure to checkpoint inhibitor based on phase 3 data and retrospective analyses (see figure 2).
  - Dose and Schedule:
    - Product monograph states starting dose at 60 mg orally once daily and dose reduce to 40 mg or 20 mg orally once daily based on tolerance. Treatment is given until disease progression, intolerance or patient

decision.
        - 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.
        - Efficacy Assessment:
            - Radiological assessment should be performed at a regular 2-3 monthly interval.
            - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
            - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.

- Axitinib[44,4571-73]
    - Indication:
        - Second-line therapy for advanced RCC as seen in the phase III AXIS clinical trial after failure of VEGFR TKI treatment, and third-line therapy based on retrospective analyses (see figure 2).
    - Dose and Schedule:
        - Starting dose at 5mg twice daily.
        - Axitinib should be dose adjusted to maximum treatment tolerance by titrating dose higher or lower (maximum 10 mg po twice daily and minimum 1 mg po twice daily).
        - Treatment is given until disease progression, intolerance or patient decision.
    - Toxicity:
        - Physicians must be aware of the toxicity profile of axitinib and follow patients accordingly with experienced nursing support. Patients should be assessed every cycle for treatment tolerance.
    - Efficacy Assessment:
        - Radiological assessment should be performed at a regular 2-3 monthly interval.
        - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
        - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.

- Everolimus[41-43]
    - Indication:
        - Subsequent therapy for advanced RCC after progression on 1st line VEGFR-TKI based on phase III data.

        - Subsequent therapy for advanced RCC after progression on pazopanib based on non-inferiority results of COMPARZ study.
    - Dose and Schedule:
        - Starting dose at 10 mg/day orally. Continue treatment until disease progression or patient intolerance.
    - Toxicity:
        - Physicians must be aware of the toxicity profile of everolimus and follow patients accordingly with experienced nursing support. Patients should be assessed every cycle for treatment tolerance.
        - 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 in around 20% of patients and should be monitored
    - Efficacy Assessment:
        - Radiological assessment should be performed at a regular 2-3 monthly interval.
        - Although CT scan is the most commonly used modality, MRI and bone scan can be used as adjunct based on tumour location and distribution.
        - Interval between scans can be increased if patients have achieved a good durable response to therapy in order to minimize radiation exposure.
- Sunitinib or Pazopanib
    - Indication:

      Second-line therapy for metastatic RCC who progress on first-line ipilimumab/ nivolumab or any first-line checkpoint inhibitor and VEGFR TKI combination regimens as based on real-world and retrospective studies (see figure 2).
    - Dose and Schedule:

      see above
    - Toxicity:

      see above
    - Efficacy Assessment:

      see above

Local Therapy[12,51-53]

Cytoreductive nephrectomy (CN) prior to or following targeted therapy

- Discussion at multidisciplinary tumor board is strongly advised (figure 1 provides a suggested approach). The phase III CARMENA[53] trial randomized patients to cytoreductive nephrectomy with sunitinib versus sunitinib alone. It demonstrated that sunitinib alone is non-inferior to the cytoreductive nephrectomy arm. It should

be noted that over 40% of patients enrolled had poor-risk disease and this may not be representative of patients typically undergoing cytoreductive surgery. Patients eligible for cytoreductive nephrectomy including those with adequate performance status, limited metastatic disease with large primary tumors and those with symptomatic primary tumors and intractable hematuria. Deferred cytoreductive nephrectomy after starting systemic therapy could offer a litmus test for deciding whether a nephrectomy would be beneficial or not. Please see the discussion section below for more information.

- Cytoreductive nephrectomy has historically shown a modest OS benefit when used in conjunction with interferon.[74]
- Patients who appear to benefit most from nephrectomy are those with:
    1. Most of the tumor burden within the kidney ($\underline{\geq}$ 90%)
    2. Good performance status
    3. No central nervous system or liver involvement (with rare exceptions)
    4. Patients with favorable- or intermediate-risk disease for which active surveillance can be done after cytoreductive nephrectomy.
- Other considerations include:
    1. Surgical resectability: need for adjacent organ resection, encasement of the renal hilum, and other complicating factors[54,55]
    2. Minimally-invasive cytoreductive nephrectomy may be considered when technically feasible.
    3. Patient selection is important and discussion at a multidisciplinary tumor board is recommended.
    4. 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).

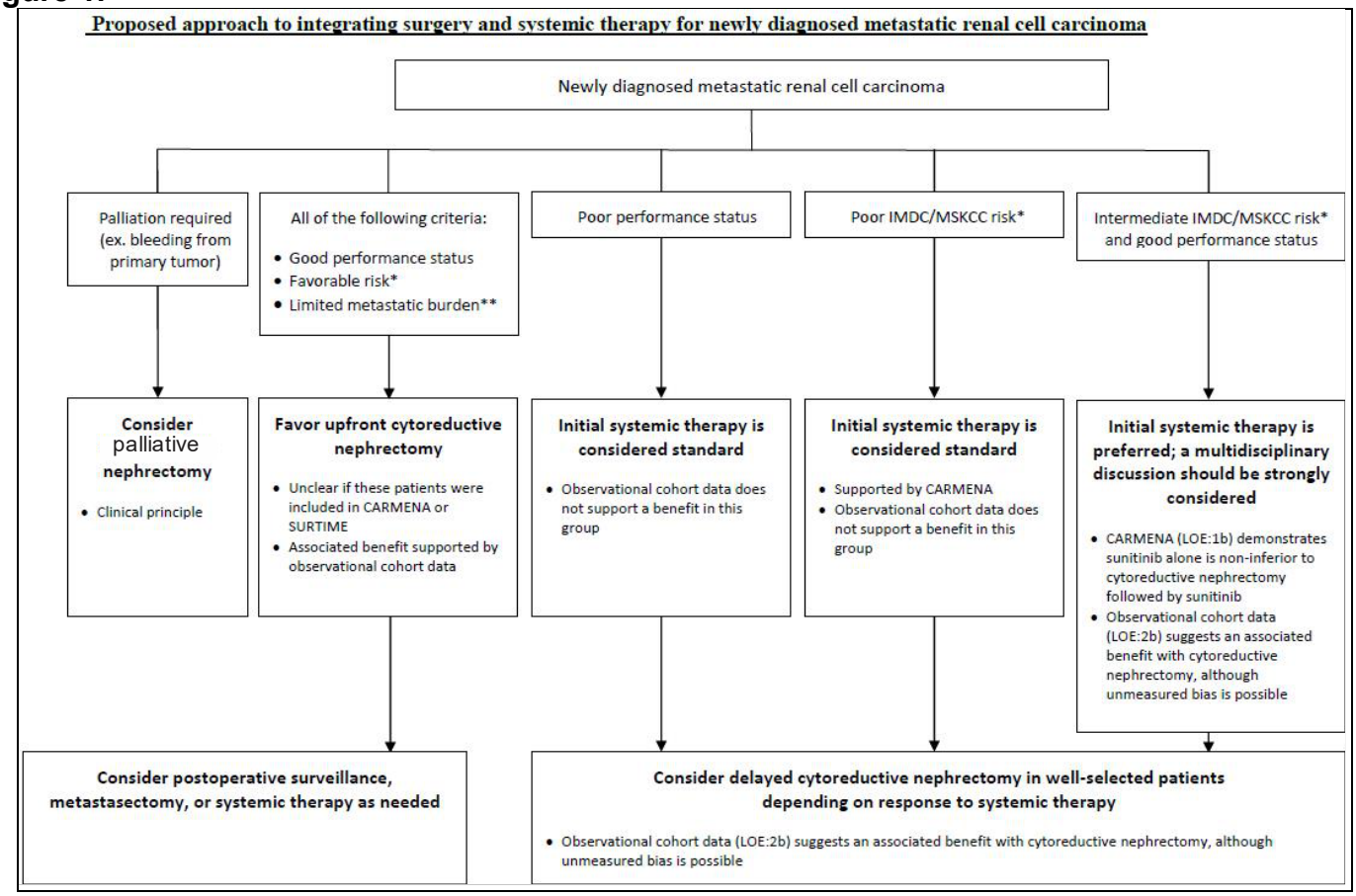
Palliative Nephrectomy

- Nephrectomy can 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 (commonly intractable hematuria) but unable to undergo a nephrectomy.

Figure 1.



Adapted from Bhindi et al. 2018[56]

* 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. Favorable-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 cytoreductive nephrectomy.

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

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 of metastasis, 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 radiation therapy (SBRT), radiofrequency ablation, and cryotherapy. These cases should be discussed in a multidisciplinary tumor board.

- Palliative Radiation
  - Bone metastases
    - For symptomatic lesions, radiation therapy should be considered.
    - Bisphosphonates or other inhibitors of bone resorption may be considered as an adjunctive therapy.
  - Brain metastases
    - Recent data have suggested utility of stereotactic radiosurgery (SRS) particularly to RCC brain metastases given its radio-resistance to standard dosing of radiation.
    - The optimal treatment modality such as SRS, surgery or whole brain radiotherapy (WBRT) should be reviewed by Radiation Oncology and Neurosurgery.
- Follow-up for patients who had treatment of oligometastses and have N.E.D (no evidence of disease)
    - For those not on active treatments, follow-up as clinically indicated and routine imaging.
    - 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 small renal masses, 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

Systemic Therapy:

For patients with advanced 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 (minimum 4 years) analyses[70], for ipi/nivo versus sunitinib in the IMDC intermediate and poor risk categories (primary efficacy population), OS was 48.1 vs 26.6 months (HR 0.65 [95% CI 0.54-0.78]) and objective response rate (ORR) was 42% vs 27% with 10% vs 1% complete responses (CR) both in favor of ipi/nivo. The PFS was 11.2 months vs. 8.3 months [HR 0.74 [95% CI 0.62 – 0.88]) in favor of ipi/nivo. PFS curves plateaued after 30 months at ~35% with ipi/nivo in both the ITT and the intermediate-and poor-risk patients. The plateau

effect suggests that one third of patients have achieved a durable and long-term response to treatment. In the exploratory analyses of favorable-risk patients, sunitinib showed a higher ORR compared to ipi/nivo (52% vs 30%) and there was no statistically significant difference in OS and PFS. Grade 3 - 4 adverse events (AEs) occurred in 47.9% of the patients in the ipi/nivo group and in 64.1% of the patients in the sunitinib group. Currently, Ipi/nivo is approved by Health Canada and is funded as first-line option for patients with intermediate/poor risk disease only.

In 2019, the KEYNOTE-426 study examined the combination of pembrolizumab and axitinib (pembro/axi) compared to sunitinib alone[66]. After a minimum follow-up of 23 months,[68] patients receiving the combination treatment had improved OS (HR 0.68 [95% CI 0.55-0.85]; p< 0.001), PFS (HR 0.71 [95% CI 0.60-0.84]; p=0.0001), and ORR (60.2% vs 39.9%; p<0.0001), with 9% achieving CR in combination treatment group vs. 3% in sunitinib group. The median PFS was 15.4 months in the combination arm and 11.1 months in the sunitinib arm (HR 0.71 [95% CI 0.60-0.84]; p<0.0001). The magnitude of OS benefit appeared to be more robust in patients with intermediate/poor risk disease, with OS in favorable risk patient being immature with no difference between the two arms currently. However, there was PFS and ORR benefit in favorable risk patients with combination therapy vs. sunitinib. Grade 3 or higher AEs of any cause occurred in 66.9% of patients in the pembro/axi group and in 62.4% in the sunitinib group. However, grade 3-4 AEs of interests (adrenal insufficiency, colitis, hepatitis, hypo/hyperthyroidism, hypophysitis, myasthenic syndrome, myocarditis, myositis, nephritis, pancreatitis, pneumonitis, severe skin reactions, thyroiditis, diabetes mellitus type 1, and uveitis) occurred only in 12% of patients in the pembro/axi group, and 2% of patients in the sunitinib group. This combination was approved by Health Canada and can be used in patients with favorable-, intermediate- or poor-risk disease. At the time of writing, this combination is not yet reimbursed but is available via an access program.

The JAVELIN Renal 101 trial compared the combination of avelumab + axitinib (ave/axi) to sunitinib alone[67]. As per the updated efficacy results based on minimum follow-up period of 13 months,[75] ave/axi significantly improved median PFS compared with sunitinib alone at 13.3 months vs 8.0 months (HR 0.69 [95% CI 0.574-0.825] p < 0.0001). The overall survival data showed no difference between the two arms however this data is immature. This combination is not Health Canada approved at the time of writing.

The CheckMate 9ER trial compared the combination of nivolumab + cabozantinib (nivo/cabo)[76] to sunitinib alone. At a median follow-up of 18.1 months, nivo/cabo was superior to sunitinib in terms of PFS (16.6 months vs. 8.3 months, HR 0.51 [95% CI 0.41-0.64] p < 0.001). The secondary endpoint of OS was not reached in either arm (NR vs. NR, HR 0.60 [98.89% CI 0.40 – 0.89] p = 0.0010) but statistically significant favoring the nivo/cabo arm. The combination was superior to sunitinib in terms of ORR of 55.7% vs. 27.1%. CR rate was nearly doubled with 8% vs. 4.6%. Grade 3 or higher AEs occurred in 75% of patients in nivo/cabo arm and in 71% of patients in sunitinib arm. Overall, 19% of patients treated with nivo/cabo received corticosteroids (≥ 40 mg of prednisone daily or equivalent).

Health-related quality of life was superior in combination arm compared to sunitinib. At the time of this update, this combination is not yet Health Canada approved.

Sunitinib and pazopanib may be treatment options first line, but the above mentioned options have demonstrated superiority to sunitinib. Only in patients in whom checkpoint inhibitors are contraindicated or in patients who refuse checkpoint inhibitor therapy should sunitinb or pazopanib be considered in the first line setting.

After First-line Therapy:

The CheckMate 025 trial demonstrated an overall survival benefit of nivolumab compared to everolimus with fewer grade 3 or 4 adverse events in patients previously treated either 1 or 2 VEGFR-TKIs[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[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 RCC 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[42]. Axitinib demonstrated activity in patients previously treated with checkpoint inhibitor in a non-randomized phase 2 trial (n = 40), with a median PFS of 8.8 months.[77] Retrospective analyses have also shown benefits of axitinib in the second and third-line setting, including those who have had previous exposure to checkpoint inhibitor. As of the time of writing this document, axitinib is funded as a treatment after 1 prior VEGFR-TKI but it is not funded as the next immediate option for patients who progressed on first-line checkpoint inhibitor-based regimens.[71,72]

Cabozantinib is multi-targeted TKI that uniquely not only target VEGFR but also MET and AXL. Resistance to PD-1/PD-L1 inhibition has been associated with increased expression of VEGFR, MET and AXL.[78] 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[39]. Median PFS was 7.4 months with cabozantinib and 3.8 months with everolimus ($p<0.001$) and the ORR 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][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.

In the METEOR trial, a minority of patients had also received immunotherapy in addition to one or two lines of TKI prior to start of cabozantinib. Furthermore, retrospective series from real-world setting have demonstrated the effectiveness of cabozantinib after failure of first-line immunotherapy, as well as those who have been heavily-pretreated,[79,80] with median time-to-treatment failure (TTF) of 8.0 months. In the absence of prospective data, cabozantinib should be a valid treatment option for those who progress on first-line immunotherapy regimen. Currently, it can be accessed through Director's Privilege as a second-line option for patients who progress on first-line pembro/axi. However, it is not funded as a second-line option for those who progress on first-line ipi/nivo.

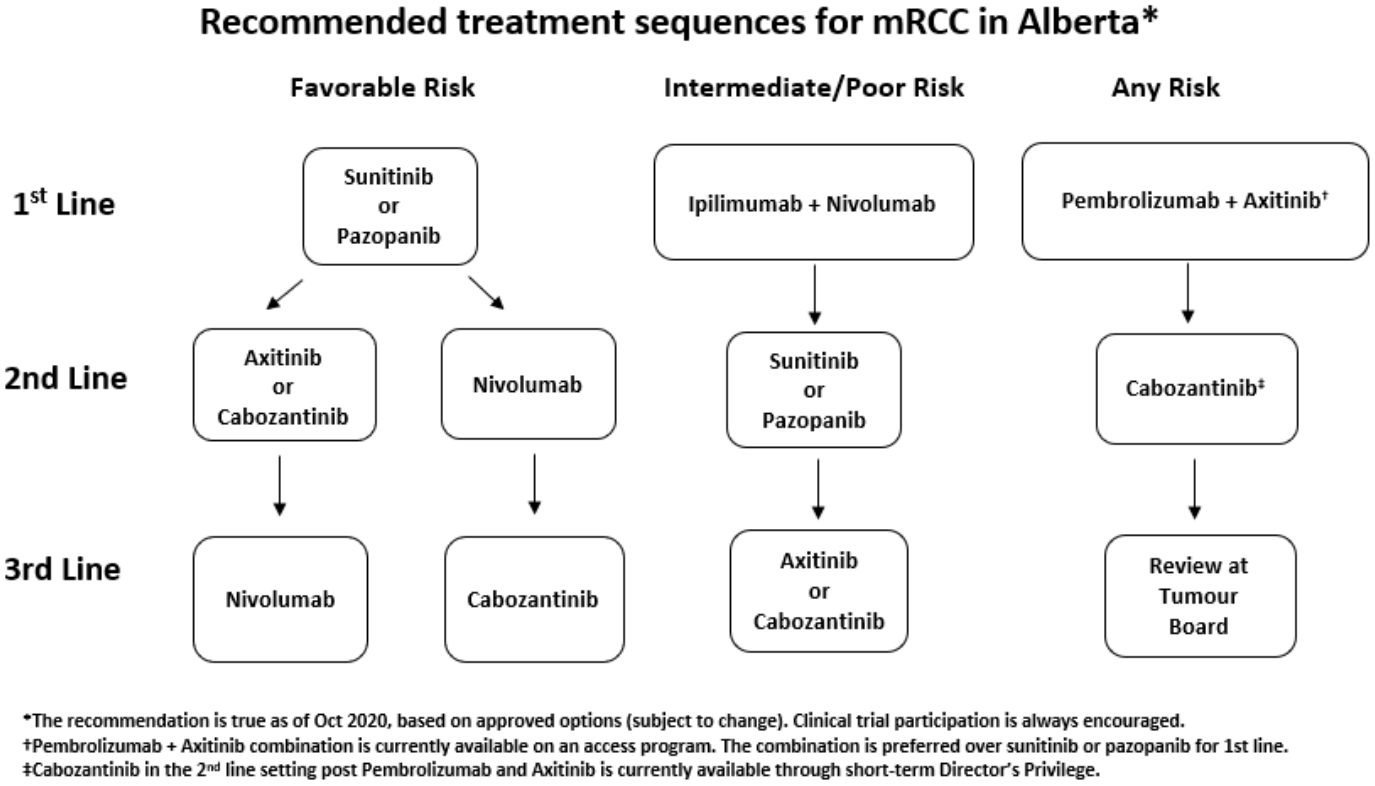
There is also evidence from retrospective analyses supporting the use of sunitinib or pazopanib post-progression on first-line checkpoint inhibitor, with median PFS reported in the range of 6 to 13 months.[73,81,82] Both treatments are currently funded as a second-line option following ipi/nivo in intermediate or poor risk patients. However, they are not funded as a second-line option following pembro/axi.

A small, randomized, three-arm, phase 2 trial of oral multi-targeted TKI lenvatinib, everolimus, and the combination of both was conducted in patients who progressed after one previous VEGFR TKI. This study demonstrated improved PFS for the combination arm over everolimus alone (median 14.6 months vs. 5.5 months; HR 0.40 [95% CI 0.24 – 0.68; p = 0.0005).[83] The combination numerically prolonged PFS compared with lenvatinib alone although this was not statistically significant (median 14.6 months vs. 7.4 months; HR 0.66 [95% CI 0.3 – 1.10]; p = 0.12). Single agent lenvatinib significantly prolonged PFS compared with everolimus alone (median 7.4 months vs. 5.5 months; HR 0.61 [95% CI 0.38 – 0.98]; p = 0.048). Currently, combination lenvatinib and everolimus are Health Canada approved but not funded.

Historically, everolimus monotherapy was considered a reasonable treatment option post progression on a VEGFR-TKI but this is now superseded by the above. There may be rare instances where a VEGFR-TKI is not recommended or tolerated such that everolimus can be considered.

The appropriate sequencing of these agents after first-line therapy is unknown. The current recommended treatment options in Alberta are shown in figure 2.

Figure 2.



*The recommendation is true as of Oct 2020, based on approved options (subject to change). Clinical trial participation is always encouraged.
†Pembrolizumab + Axitinib combination is currently available on an access program. The combination is preferred over sunitinib or pazopanib for 1st line.
‡Cabozantinib in the 2nd line setting post Pembrolizumab and Axitinib is currently available through short-term Director's Privilege.

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[16,50,57]. Nephrectomy has proven overall survival benefit when used in conjunction with interferon[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[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)[58,59]. 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 system or liver involvement (with rare exceptions)[58,59]. Other considerations include surgical resectability, including possible morbidity to proximal vital structures, encasement of the renal hilum and other complicating factors[54,55]. Laparoscopic nephrectomy is the emerging standard surgical procedure and should be considered whenever technically feasible[60,61].

The phase III CARMENA[53] trial was published in 2018 and it randomized patients to cytoreductive nephrectomy with sunitinib versus sunitinib alone. It demonstrated that sunitinib alone is non-inferior

to the cytoreductive nephrectomy 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 should still be considered for CN including patients with limited metastatic disease with large primary tumors and those with symptomatic primary tumors. A retrospective series of 198 patients presented at GU ASCO 2020[62] showed that cytoreductive nephrectomy 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 scenario[63]:

1. patients with favorable-/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 cytoreductive nephrectomy 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[64] randomized patients between sunitinib, sorafenib and placebo and did not demonstrate any benefit. The S-TRAC trial[65] 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. The phase III ATLAS trial evaluating axitinib (Inlyta) as adjuvant therapy for patients at high risk of recurrent RCC after nephrectomy was halted after interim analysis due to futility[66]. 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.

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Appendix

Table 1. Summary of the Systemic Therapy Trials for the Treatment of Advanced/Metastatic Renal Cell Carcinoma Patients Recommended in the First-line (not all studies discussed above are listed here).

Drug	Trial Name	Indication	Arms of Study	Median PFS	p-value	Median OS	p-value
Pembrolizumab and Axitinib[14]	Keynote-426 (NCT02853331)	Previously untreated clear-cell advanced RCC (all risk groups)	Pembrolizumab (200mg) IV every 3 weeks + Axitinib (5mg) orally twice daily Vs. Sunitinib 50mg orally once daily for 4 weeks (6-week cycle)	Pembro/Axi: 15.4m Sunitinib: 11.1m	HR 0.71; 95% CI, 0.60-0.84; p<0.0001	Pembro/Axi: NR Sunitinib: 35.7m	HR 0.68; 95% CI, 0.55-0.85; p<0.001
Ipilimumab and Nivolumab[30]	CheckMate 214 (NCT02231749)	Previously untreated clear-cell advanced RCC (int-/poor-risk)	Nivolumab (3mg/kg) IV + ipilimumab (1mg/kg) IV x4 followed by: Nivolumab (3mg/kg) IV every 2 weeks Vs. Sunitinib (50mg) orally once daily for 4 weeks (6-week cycle)	Ipi/Nivo: 11.2m Sunitinib: 8.3m	HR: 0.74; 95% CI, 0.62 – 0.88; P<0.01	Ipi/Nivo: 47.0m(95%CI: 35.6-NE) Sunitinib: 26.6m (95%CI: 22.1-33.5	HR 0.66;95% CI, 0.55 – 0.80; p<0.0001
Avelumab and Axitinib	JAVELIN Renal 101 (NCT02684006)	Previously untreated clear-cell advanced RCC (All risk groups)	Avelumab (10mg/kg) IV every 2 weeks + Axitinib (5mg) orally twice daily vs. Sunitinib (50mg) orally once daily for 4 weeks (6-week cycle)	Ave/Axi: 13.3 m Sunitinib: 8.0m	HR 0.69; 95% CI, 0.574-0.825; PC<0.0001	Immature	Immature
Cabozantinib and Nivolumab	CheckMate 9ER (NCT03141177)	Previously untreated clear-cell advanced RCC (All risk groups)	Nivolumab (240mg) IV every 2 weeks + cabozantinib (40mg) orally daily vs. Sunitinib (50mg) orally once daily for 4 weeks (6-week cycle)	Nivo/Cabo: 16.6 m Sunitinib: 8.3m	HR 0.51; 95% CI, 0.41-0.64; P < 0.0001	NR vs. NR	HR 0.60; 98.89% CI, 0.40 – 0.89; p = 0.0010.
Sunitinib [15]	N/A (NCT00077974)	Cytokine-refractory metastatic RCC (**2nd-line**)	Single-arm (N=106) -6 week cycles sunitinib 50mg/day (4wk on 2wk off)	8.3 months (95%CI: 7.8-14.5m)	N/A	Not reached. 6-month survival 79% (95%CI: 70-86%)	N/A
Sunitinib [16,21]	N/A (NCT00083889)	Previously untreated, metastatic RCC	(N=750) Interferon-alfa Vs. Sunitinib 50mg/day (4wk on 2wk off)	Interferon: 5m Sunitinib: 11m	HR: 0.42, 95%CI: 0.32-0.54, p<0.001	Interferon: 21.8m Sunitinib: 26.4m	HR 0.82; 95% CI, 0.67 to 1.01; P=0.051
Pazopanib [27,29]	VEG105192 (NCT00334282)	Measurable, locally advanced, and/or metastatic RCC (54% treatment naïve, 46% received cytokines) (**2nd-line)**	Placebo Vs. Pazopanib (800mg daily)	Placebo: 4.2m Pazopanib: 9.2m	HR: 0.46, 95%CI: 0.34-0.62, p<0.001	Placebo: 20.5m Pazopanib: 22.9m	HR: 0.91; 95%CI 0.71-1.16; P=0.224
Pazopanib vs. Sunitinib [26]	COMPARZ (NCT00720941)	Clear-cell mRCC	(N=1110) Pazopanib (800mg/ daily) Vs. Sunitinib 50mg/daily (4wk on 2wk off)	Pazopanib: 8.4m (95%CI: 8.3-10.9) Sunitinib: 9.5 (95%CI: 8.3-11.1)	HR1.05, 95%CI 0.9-1.22)	Pazopanib: 28.4m Sunitinib: 29.3m	HR: 0.91, 95%CI: 0.76-1.08

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.

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Lenvatinib vs. Everolimus or Combined[67]	(NCT01136733)	Advanced/ metastatic clear-cell RCC with prior VEGF-targeted therapy and progressed on or within 9 months	(N=153) (L) Lenvatinib (24 mg/d) Vs. (E) Everolimus (10 mg/d) Vs. (L+E) Lenvatinib (18 mg/d) + Everolimus (5 mg/d)	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)	L+E vs. E P<0.001 L+E vs. L P=0.12 L vs E P=0.048	L: 18.4m (95%CI: 13.3-NR) E: 17.4m (95%CI: 11.8-NR) L+E: 25.5m (95%CI: 20.8-25.5)	All p>0.05
Nivolumab vs. everolimus[36,38]	CheckMate 025 (NCT01668784)	Advanced clear cell RCC, with one or two prior regimens of antiangiogenic therapy	(N=821) Nivolumab (Nivo) (3mg/kg IV every 2 weeks) Vs. Everolimus (Evero) (10mg /day)	Nivo: 4.6m Evero: 4.4m	HR: 0.88, p=0.11	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
Cabozantinib vs. Everolimus[39,40]	METEOR (NCT01865747)	Advanced/ metastatic RCC with previous treatment with VEGFR TKI	(N=658) Carbozantinib (Carbo) 60mg/daily Vs. Everolimus (Evero) 10mg/daily	Carbo:7.4m Evero:3.8m	HR: 0.58, 95%CI: 0.45-0.75, p<0.001	Carbo:21.4m Evero:16.5m	HR: 0.66, 95%CI: 0.53-0.83, p<0.001
Everolimus [41,42]	RECORD-1 (NCT00410124)	mRCC with progression on sunitinib, sorafenib or both	(n=272) Everolimus (Evero) (10mg/day) Vs. (n=138) Placebo	Evero: 4.9m Placebo: 1.9m	HR: 0.30, 95%CI: 0.22-0.40, p<0.001	Evero: 14.8 Placebo: 14.4m	HR: 0.87, p=0.162 (80% cross over)
Axitinib vs. sorafenib[44,45]	AXIS (NCT00678392	Clear-cell RCC with progression on sunitinib, bevacizumab plus interferon, temsirolimus, or cytokines	(N=723) Axitinib (Axi) 5mg twice daily (up to 10mg in select pts) Vs. Sorafenib (Sora) 400mg twice daily	Axi: 6.7m Sora: 4.7m	HR: 0.67, 95%CI: 0.54-0.81, p<0.001	Axi: 20.1m Sora: 19.2m	HR: 0.97, p=0.374
Axitinib	(NCT02579811)	Advanced/metastatic clear cell RCC progression on checkpoint inhibitor therapy	(N = 40) Axitinib (Axi) 5mg twice daily (up to 10mg in select pts)	Axi: 8.8 m	NA	NA	NA

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.

Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
III	T1-2	N1	M0
	T3	NX, N0, or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

Development and Revision History

This guideline was reviewed and endorsed by the Alberta GU Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, urologist, 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.

Maintenance

A formal review of the guideline will be conducted in 2022. 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, Cancer Care 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.

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Conflict of Interest Statements

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