Management of advanced kidney cancer: Canadian Kidney Cancer Forum (CKCF) consensus update 2017

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Consensus report from the Kidney Cancer Research Network of Canada (KCRNC), with an update from the 8th Canadian Kidney Cancer Forum, held February 2–4, 2017 in Toronto, ON.[1-5]

Introduction

Kidney cancer, predominantly renal cell carcinoma (RCC), is the most lethal genitourinary malignancy and results in an estimated 1850 Canadian deaths per year.[6] The incidence is increasing by 2% per year, with most new cases presenting as small renal masses. For over a decade, targeted systemic therapies have been available for the management of metastatic disease and their use has continued to evolve with clinical experience. More recently, new drugs that target the immune system have been studied and will enhance the treatment landscape of RCC.

Seven previous forums were held in 2008–9, 2011, and 2013–6. As before, the 2017 meeting was by invitation and attended by survivors, caregivers, expert clinicians, and researchers in fields relevant to kidney cancer care. The attendees also included representatives of Kidney Cancer Canada, a community and advocacy group of patients and caregivers providing support and information to those affected by kidney cancer.[7]

During the 2017 conference, the advanced disease management consensus statement, published in 2015, was reviewed and updated using the same process.[5] The field of systemic therapy is evolving quickly and the recommendations made in this document reflect the available evidence at the time the consensus conference participants reached their conclusions (February 4, 2017). As new data becomes available, treatment options will invariably change. Supporting evidence detailed in the report gives priority to phase 3 data available at the time of the meeting. If no Level I evidence is available, consideration is given to the next best level of evidence.[8]

Changes

Major changes were made to sections:

- 1.2. Adjuvant therapy – new data on sunitinib
- 2.1. Clear-cell carcinoma
- 2.1.2.2. Progression after first-line targeted therapy – new data on nivolumab, axitinib, cabozantinib, and levantinib
- 2.2. Non-clear-cell RCC – new recommendation and data on first-line therapy

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- 2.4. Role of local therapy in oligometastases – new recommendation
- 2.5. Role of local therapy in oligoprogression – new section and recommendation
- 2.8. Patient and caregiver support – new section and recommendations

1. Management of locally advanced kidney cancer

1.1. Neoadjuvant therapy

- **There is no indication for neoadjuvant therapy prior to planned surgical resection outside the context of a clinical trial.**

If patients are felt to be surgically resectable at diagnosis and medically fit, then they should proceed immediately to surgery. Routine use of neoadjuvant therapies is not indicated at this time. The results of single-agent phase 2 clinical trials with neoadjuvant anti-angiogenic agents (e.g., vascular endothelial growth factor receptor tyrosine kinase inhibitors [VEGFr TKI], VEGF antibodies, mammalian target of rapamycin [mTOR] inhibitors) demonstrate feasibility but not remarkable down-staging, and results with newer agents (i.e., immuno-oncology agents) will not be available in the near future.[9-12]

Some patients deemed medically or surgically inoperable at diagnosis may have a dramatic radiological and/or clinical response to systemic therapy. A multidisciplinary team should re-evaluate them if there is any question that they may have converted to an operable state.

1.2. Adjuvant therapy

- **The use of adjuvant therapy following nephrectomy in non-metastatic RCC patients is not recommended outside the context of a clinical trial.**

Adjuvant therapy with cytokines does not improve overall survival (OS) after nephrectomy.[13] Several clinical trials with adjuvant anti-angiogenic agents (VEGFr TKI, VEGF antibodies, or mTOR inhibitors) have completed accrual with patients in followup. Two studies have published their results.

The phase 3 ASSURE three-arm, randomized, placebo-controlled trial of one year of sorafenib, sunitinib, or placebo showed no significant improvement in disease-free survival (DFS) or OS for patients treated with either of the active intervention arms or placebo.[14]

The phase 3 S-TRAC two-arm randomized, placebo-controlled trial of one year of sunitinib or placebo in patients at high risk of recurrence showed an improvement in the primary endpoint of DFS with adjuvant sunitinib comparable to the time on therapy.[15] Data for OS, a secondary endpoint, was not mature at the time of publication. Quality of life outcomes demonstrate that on most QLQ-C30 subscales, patients in the sunitinib group had lower scores than those in the placebo group.

At the time of the consensus meeting, the phase 3 study of pazopanib had finished accrual and results were yet to be reported, but a letter to investigators from the sponsor (Novartis Pharmaceuticals Corporation, January 13, 2017) had indicated the primary endpoint of improved DFS was not met and OS data is still not mature. Results were subsequently reported at the American Society of Clinical Oncology Annual Meeting in spring 2017.

Therefore, at the present time, there is no clinical trial data in support of adjuvant therapy as standard of care to improve OS in patients with RCC after curative resection of the primary tumour. Pending additional data from ongoing adjuvant trials, patients with high-risk tumours who have undergone complete resection should be encouraged to participate in clinical trials whenever possible.

2. Advanced or metastatic kidney cancer

- **Enrolling patients in clinical trials should always be considered the first option for patients with advanced or metastatic RCC.**

When prescribing systemic therapy for advanced or metastatic RCC, several key factors must be taken into account. Patients are best served if the prescribing physician is an oncology specialist knowledgeable of acute and long-term toxicities, drug interactions, and monitoring of treatment and response. Patients should be managed in a multidisciplinary environment with adequate resources, including nursing care, dietary care, and pharmacy support.

Patients must be evaluated frequently to ensure toxicities are recognized and managed appropriately. Patients and caregivers should be provided with information concerning potential side effects, as well as their prevention and management.

2.1. Clear-cell carcinoma

2.1.1. First-line therapy

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

RCC is a heterogeneous disease and there are several prognostic factors that may help clinicians risk-stratify their patients. These include clinical factors and laboratory parameters. The first of these prognostic scores was published by Motzer and colleagues and was used to define entry criteria or stratify for patient enrolment in clinical trials.[16] It is for this reason that treatment recommendations differ based on patient risk (Table

Table 1. Therapeutic options for advanced clear-cell renal cell carcinoma

Setting	Patients	Therapy (Level 1 evidence)	Other options (<Level 1 evidence)
Untreated	Good/intermediate-risk	Sunitinib Pazopanib Bevacizumab[a] + IFN	High-dose IL-2 Sorafenib Cabozantinib[a/b] Observation
	Poor-risk	Sunitinib Temsirolimus	Pazopanib
Second-line	Cytokine refractory	Sorafenib Pazopanib Axitinib	Sunitinib, Bevacizumab[a] + IFN
	Prior VEGF targeted therapy or prior mTOR	Nivolumab Axitinib Cabozantinib[a] Everolimus[c]	Targeted therapy not previously used (Lenvatinib[a] + everolimus)[b/c]
Third-line[d]	Any	Nivolumab Cabozantinib[a] Everolimus	Axitinib chemotherapy

[a]Not approved in Canada for RCC, but is approved in the U.S.; [b]phase 2 data only; [c]if prior mTOR not used in first-line; [d]no drug has Health Canada approval for third-line.
IFN: interferon; IL: interleukin; mTOR: mammalian target of rapamycin; VEGF: vascular endothelial growth factor.

1); however, the Motzer prognostication system was developed in the cytokine era. In the targeted therapy era, Heng and colleagues have published a similar, but not identical, risk-stratification score based on information obtained from the International Metastatic Renal Cell Database Consortium (IMDC), which is applicable to patients receiving targeted therapy.[17] Four of the five adverse prognostic factors according to the Motzer criteria were still independent predictors of short survival: hemoglobin less than the lower limit of normal, corrected calcium greater than the upper limit of normal (ULN), Karnofsky performance status less than 80%, and time from diagnosis to treatment of less than one year. In addition, neutrophils greater than the ULN ($p<0.0001$) and platelets greater than the ULN were independent adverse prognostic factors. Patients were segregated into three risk categories: the favourable-risk group (no prognostic factors), intermediate-risk group (one or two prognostic factors), and the poor-risk group (three to six prognostic factors). The IMDC criteria should now be used as the standard prognostication criteria for patient counselling, treatment selection (e.g., intial observation, systemic therapy, cytoreductive nephrectomy), and future research studies.

Initial observation

In the opinion of attendees, an initial period of observation is a reasonable option in select patients given that no systemic therapies are currently considered curative, that all available treatments can be associated with side effects, and that some patients may experience an indolent clinical course with stable or slow-growing, low-volume, and/or asymptomatic metastases. This is supported by prospective observational data presented by Rini and colleagues.[18]

Sunitinib

In a pivotal phase 3 trial, oral sunitinib (VEGFr TKI) produced higher response rates, improved quality of life, and resulted in longer progression-free survival (PFS) than interferon-alfa in patients with metastatic clear cell RCC.[19] Subsequent survival analysis showed that patients treated with sunitinib had a longer OS than patients treated with interferon.[20] In addition, population-based studies from British Columbia and Alberta have shown an almost doubling of OS of metastatic RCC since the introduction of sunitinib and sorafenib.[21,22]

The dose and schedule of sunitinib should be optimized for each patient in order to derive the most benefit.[23] It is still recommended to start with the monograph standard of four-week-on/two-week-off dosing schedule. After evaluation of type and timing of toxicities, patients may require adjustments to the schedule and/or dose. Bjarnason and colleagues have published a single-institution, retrospective review of patients treated with alternate dose and schedule of sunitinib compared to product monograph-recommended dosing; they found improved PFS and OS compared to the standard dosing group.[24] A prospective clinical trial conducted across Canada examining this individualized dose titration scheme has completed enrolment and results are pending (NCT01499121).

Pazopanib

Based on phase 3 trial data, oral pazopanib (VEGFr TKI) produces an improvement in PFS compared to placebo in both cytokine-naive and refractory patients.[25] As first-line therapy, pazopanib has also been shown to be non-inferior to sunitinib with respect to PFS in the phase 3 COMPARZ clinical trial.[26] Toxicity profiles were different, with sunitinib-treated patients experiencing more fatigue, hand-foot syndrome,

and thrombocytopenia, whereas pazopanib-treated patients experienced more elevations in hepatic transaminases.

Data from Canadian Kidney Cancer Information System (CKCis) database shows that patients treated with sunitinib have a greater OS than pazopanib.[27] Plausible explanations for this include small sample size and potential bias secondary to patient selection; however, another explanation for this difference may be the practice of individualized dose and schedule changes that Canadian medical oncologists employ with sunitinib, in accordance with data from Bjarnason.[24,28] Publications from other retrospective patient cohorts show similar outcomes with either sunitinib or pazopanib in concordance with COMPARZ data.[29]

Bevacizumab and interferon

Based on phase 3 AVOREN and CALGB 90206 trial data, the combination of intravenous bevacizumab (monoclonal antibody targeting VEGF) plus subcutaneous interferon improves PFS over interferon alone.[30,31] At this time, there has been no application submitted regarding bevacizumab for kidney cancer in Canada, and so it is not an option for Canadian patients.

Cabozantinib

The randomized, phase 2 CABOSUN trial compared oral cabozantinib (a dual VEGFr/MET and AXL inhibitor) to oral sunitinib.[32] This small-sized, investigator-initiated trial (n=157) had 81% intermediate- and 19% poor-risk patients and demonstrated a significant improvement in PFS for the combination. In unplanned analyses, it showed particularly promising activity in patients with bone metastases, although this was a very small subset of patients. It should be noted that the control arm median PFS was significantly shorter than expected, but may reflect the population studied.

In addition to not fulfilling Level 1 evidence criteria, cabozantinib is not yet approved for patients with metastatic RCC or any other tumour site in Canada, and so it is not considered an option for Canadian patients.

Temsirolimus

The phase 3 ARCC trial data showed that, in poorer-risk patients, intravenous temsirolimus (mTOR inhibitor) produces an improvement in PFS and OS compared to interferon alone, and that the combination of temsirolimus and interferon did not improve OS over interferon alone.[33] Poorer risk was defined by patients having at least three out of the following six criteria: Karnofsky Performance Scale (KPS) 60–70, increased calcium, decreased hemoglobin, increased lactate dehydrogenase, <1 year from nephrectomy to treatment, or multiple metastatic sites.

First-line mTOR inhibition

The phase 2 RECORD-3 trial was a non-inferiority trial that examined oral sunitinib followed by oral everolimus (mTOR inhibitor) at progression or the alternate order of drug administration in all risk groups of patients with metastatic RCC.[34] Non-inferiority of first-line everolimus was rejected. Thus, data for first-line mTOR inhibitors only supports the use of temsirolimus, and only in poorer-risk patients, as defined in the ARCC trial.

VEGFr TKI and poor-risk patients

It should be noted that poorer-risk patients were treated with VEGFr TKI therapy in pivotal trials as well. The consensus was that these agents would still be preferentially used in patients whose poor clinical condition was due to extensive RCC and in those who needed a more rapid response to therapy. It should also be noted that in sunitinib-intolerant, poor-risk patients, pazopanib or sorafenib[35] remain options for treatment.

Targeted therapy and brain metastases

Most targeted therapy studies excluded patients with brain metastases. A review of the IMDC database revealed central nervous system (CNS) responses to targeted therapy.[36] A single-centre, retrospective cohort review demonstrated improved survival for patients with brain metastases treated with targeted therapy;[37] however, the mainstay of brain metastases management remains local therapies, such as neurosurgery and radiotherapy, as discussed later in this document.

Cytokines

No phase 3 studies on the use of intravenous interleukin-2 (IL-2) have shown an improvement in survival, and thus it is not considered a standard of care; however, based on phase 2 data, a very select group of patients may be considered for high-dose IL-2, including those with clear-cell histology, previous nephrectomy, and low UCLA SANI score (regional lymph node status, constitutional symptoms, location of metastases, sarcomatoid histology, and thyroid-stimulating hormone [TSH] levels).[38,39] Durable remissions can occur in a small minority of patients. High-dose IL-2 must be delivered in specialized and experienced centres and ideally in the context of a clinical trial or investigational setting. Low-dose IL-2 should not be given.[40]

Subcutaneous interferon has low response rate, significant toxicity, and a modest survival benefit relative to newer agents.[41]As mentioned above, interferon was found to be inferior to sunitinib in the first-line setting.[19] The role for using interferon beyond the first-line is unclear, but likely quite minimal.

Chemotherapy

Historical data shows very low response rates of RCC to older chemotherapy;[42] however, combination chemotherapy with newer agents has shown modest increase in activity (e.g., gemcitabine and 5-fluorouracil).[43] Given the activity of the other agents listed above, chemotherapy would not be considered standard first-line therapy in 2017.

Immune checkpoint inhibitors

There is currently much research underway with new agents that modulate the immune system alone or in combination with targeted therapy. Specifically, checkpoint inhibition (CI) targeting the programmed cell death-1 (PD-1) receptor and its ligand (PD-L1), as well as the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) pathway, is being examined. Initial results in the second-line and beyond second-line setting are discussed in section 2.1.2.2. Ongoing trials are testing these agents either alone or in combination with each other or other standard therapies in the first-line setting. Results from these trials are pending and, at this point in time, they are not recommended in the first-line setting outside of a clinical trial.

2.1.2. Second-line and later therapy options

2.1.2.1. Progression on or intolerance to first-line cytokine therapy

- **Targeted therapy is the mainstay for treatment post-cytokine therapy in the first-line setting.**

Sorafenib

Phase 3 trial data demonstrated oral sorafenib (VEGFr TKI) improved PFS compared to best supportive care alone in previously treated patients who had received interleukin-2 or interferon.[44] OS data was confounded by crossover, but reached significance when censored at crossover.

Pazopanib

Oral pazopanib improved PFS compared to placebo in a phase 3 trial.[25]

Axitinib

Oral axitinib (VEGFr TKI) and sorafenib were compared head to head in the AXIS phase 3 trial, with one-third of patients receiving cytokine therapy prior.[45] In this study, axitinib demonstrated a better PFS compared to sorafenib.

Sunitinib

Oral sunitinib is another option for therapy in this setting. Two phase 2 trials using sunitinib in this setting demonstrated significant response rates and increased PFS compared to historical controls.[46]

2.1.2.2. Progression on first-line targeted therapy

- **Clinical trials in this population should be supported, as the optimal sequence of therapies is unknown.**
- **Outside the context of a clinical trial, treatment options include checkpoint inhibition with nivolumab or switch to another targeted agent (Table 1).**

Intolerance to first-line VEGF-targeted therapy

If patients stop first-line therapy due to toxicity and not progression, another first-line therapy is very reasonable to try. Data from the IMDC shows the outcomes when therapies are switched due to toxicity, and not progression, are better than would be seen as second-line therapy after progression.[47]

Nivolumab

In the phase 3 CHECKMATE 025 trial, intravenous nivolumab (monoclonal antibody targeting the PD-1 receptor) produced better response rates and a significantly longer OS compared to oral everolimus in patients who had failed one or two previous lines of systemic therapy regardless of the MSKCC prognostic score or number of previous antiangiogenic therapies.[48] Benefit was also observed with nivolumab irrespective of PD-L1 expression. In addition, Grade 3 or 4 treatment-related adverse events and treatment-related adverse events leading to discontinuation were less frequent with nivolumab than with everolimus. Quality of life outcomes increased over time in the nivolumab group and were significantly better than the everolimus group at each assessment point.

There is also data to support the use of nivolumab in the third-line setting. In the CHECKMATE 025 trial, 28% of randomized subjects had received two prior VEGFr TKI therapies. OS results suggest a benefit of nivolumab over everolimus in this setting.

The phenomena of pseudoprogression and delayed responses on immuno-oncology agents may make monitoring of efficacy difficult, but it should be noted this occurs in a small minority of patients.[49,50] Thus, treatment beyond progression should be restricted to patients showing clinical benefit or stability.

Monitoring for both acute and chronic immune-mediated toxicities is essential and should not be forgotten beyond treatment discontinuation. Consultation with experts in immuno-oncology and other subspecialties for management of severe and unusual immune toxicities is strongly encouraged. It should be noted, patients with active immune related comorbid diseases might not be eligible, as they were often excluded from immunotherapy clinical trials; however, data is emerging on safe use in patients with chronic stable immune-related diseases.[51-54]

Targeted therapy

Should nivolumab not be an option, there is currently no good data to indicate which second-line targeted therapy is superior after first-line VEGFr TKI (Table 1). Therefore, treatment choices should be made with consideration to drug toxicity profiles, comorbidities, and patient preference.

For patients whose first-line therapy was an mTOR inhibitor, there is no Level I evidence to guide treatment decisions in the second-line setting. The use of a VEGFr TKI in this setting is a very reasonable option.[55]

Axitinib

In the phase 3 AXIS trial, oral axitinib (VEGFr TKI) has shown improved PFS compared to oral sorafenib as second-line therapy in patients progressing after first-line therapy with sunitinib.[45]

Data on axitinib in the third-line setting are more limited; however, there are patients who went on to receive axitinib post-nivolumab or cabozantinib in CHECKMATE 025 and METEOR studies, respectively. Retrospective analyses suggest patients demonstrate benefit to VEGFr TKIs in the third-line setting, with axitinib falling in that category.[56,57]

Cabozantinib

The randomized, phase 3 METEOR trial compared oral cabozantinib (a dual VEGFr/MET and AXL inhibitor) to everolimus and demonstrated a significant improvement in ORR, PFS (primary endpoint), and OS in patients who had received a prior VEGFr TKI.[58]

In the METEOR trial, around 30% of patients had received at least two prior VEGFr TKI therapies with notable benefit in PFS and OS in patients receiving cabozantinib over everolimus.

Cabozantinib is not yet approved for patients with metastatic RCC or any other tumour site in Canada, and so it is not considered an option for Canadian patients.

Everolimus

In the phase 3 RECORD-1 trial, oral everolimus (mTOR inhibitor) produced a significantly longer PFS than placebo, with an acceptable toxicity profile in patients who had failed sunitinib or sorafenib or both.[59] Should everolimus not be available, intravenous temsirolimus should not be substituted, given its inferior outcomes when compared to sorafenib in patients who progressed on first-line sunitinib, as demonstrated in the INTORSECT study.[60]

Furthermore, everolimus was found to be inferior to the experimental arm in two large, randomized, phase 3 clinical trials, CHECKMATE 025 and METEOR, where the majority of patients were studied in the second-line setting.[48,58] Given these results, everolimus is likely not the optimal agent of choice for most patients post-initial VEGFr TKI.

In the RECORD-1 trial, 25% of subjects randomized had received two prior VEGFr TKI therapies and a significant improvement in PFS was seen in the everolimus arm vs. the placebo arm.

Lenvatinib

A three-arm randomized phase 2 trial of oral lenvatinib, oral everolimus, and the combination demonstrated improved PFS for the combination arm and lenvatinib alone arms over everolimus alone.[61] Currently, lenvatinib is approved in Canada for iodine-refractory thyroid cancer, but not RCC, and so it is not considered a standard option for Canadian RCC patients.[62] Further phase 3 studies with this drug in combination are ongoing.

2.2. Non-clear-cell histology

- **There is no standard therapy for non-clear-cell RCC and enrollment in clinical trial is the preferred option.**

In patients with metastatic or advanced RCC with non-clear cell histologies, enrolment in clinical trials should be encouraged. Other options include sunitinib, sorafenib, temsirolimus, and pazopanib (Table 2).[63-67]

Two phase 2 trials randomized patients to everolimus vs. sunitinib as first-line therapy for non-clear-cell pathologies with crossover allowed at progression. The ESPN trial futility analysis resulted in early termination of the trial due to inferior PFS and OS for everolimus.[68] The ASPEN trial demonstrated sunitinib was superior to everolimus for PFS.[69] Thus, sunitinib is the preferred first-line treatment for non-clear-cell RCC.

In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options show modest responses and include sunitinib, sorafenib, temsirolimus, and chemotherapy (Table 3).[63-65,70] In a phase 2 study, the combination of sunitinib and gemcitabine has been shown to be tolerable and the combination may be more efficacious than either therapy alone.[71]

2.3. Role of cytoreductive nephrectomy

- **Cytoreductive nephrectomy should be considered in appropriately selected patients presenting with de novo metastatic RCC, ideally after a multidisciplinary discussion.**

Recommendation for this section is based on Level I evidence from two studies in RCC patients treated with interferon who underwent cytoreductive nephrectomy (CN) showing an improvement in OS.[72] Data from IMDC found that patients undergoing CN in the targeted therapy era had improved survival compared to those who did not after controlling for IMDC risk factors (KPS <80%, diagnosis to treatment interval <1 year, hypercalcemia, neutrophilia, anemia, and throm-

Table 2. Options for patients with metastatic or advanced non-clear-cell renal cell carcinoma in the absence of clinical trials

Therapy	Rationale
Sunitinib	Based on randomized, phase 2 data and subgroup analyses from the Expanded Access trial showing safety and activity
Sorafenib	Based on subgroup analyses from the ARCCS Expanded Access trial showing safety and activity
Temsirolimus	Based on subgroup analysis of phase 3 data

ARCCS: Advanced Renal Cell Carcinoma Sorafenib.

Table 3. Options for patients with advanced metastatic sarcomatoid or poorly differentiated renal cell carcinoma in the absence of clinical trials

Therapy	Rationale
Sunitinib	Based on prospective, non-randomized data from the Expanded Access Program
Sorafenib	Based on prospective, non-randomized data from the ARCCS Expanded Access trial
Temsirolimus	Based on subgroup analysis from the pivotal phase 3 trial in which these patients were eligible
Chemotherapy	Based on phase 2 data using agents such as 5-fluorouracil, gemcitabine, doxorubicin, and combinations of these showing activity
Sunitnib + gemcitabine	Single-arm, phase 2 trial

ARCCS: Advanced Renal Cell Carcinoma Sorafenib.

bocytosis).[73] Analyses of the Surveillance Epidemiology and End Results (SEER) database has found that CN in the targeted therapy era is associated with improved patient outcomes.[74,75]

Therefore, at this point, there is no prospective, randomized data on the use of CN in the era of targeted therapy. Decisions are based on extrapolation from the interferon data, retrospective North American data showing improved outcomes in patients with CN prior to targeted therapy, the fact that most patients (>90%) enrolled in the VEGFr TKI phase 3 clinical trials had a prior nephrectomy, and clinical judgement.[16,33,70,72,76,77] Prospective studies on the benefit of CN are required and trials are currently underway (CARMENA: NCT0093033 and SURTIME: NCT01099423).

Consensus participants felt that, until proven otherwise, CN should be considered the standard of care for eligible patients if the majority of the tumour burden is within the kidney.[78,79] Patients being considered for CN should be reviewed by multidisciplinary tumour teams/boards to appropriately identify best candidates for surgery.

It is important to ensure that patients undergoing CN are properly selected to maximize its benefit. Appropriately selected patients for CN include: patients with a primary tumour amenable to surgical extirpation, a low risk of perioperative morbidity, good performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1), no evidence of active brain metastases, and a low number of MD Anderson risk factors (elevated lactate dehydrogenase [LDH], low albumin, symptomatic metastases, sites of disease, and clinical ≥T3 primary tumour), and less than four IMDC adverse risk features.[73,80] Moreover, there should be a low risk of rapid disease progression that would not be compatible with the delay of systemic therapy required for recovery from surgery (e.g., no high-grade or sarcomatoid features).[81]

In patients who do not undergo upfront CN, but have a good response to VEGFr TKI or targeted therapy, limited metastatic disease, and good performance status, it is reasonable that CN be considered during the course of their treatment.

2.4. Role of local therapy in oligometastases

- **In select patients with limited number of sites of metastatic disease and stable clinical condition, local therapy, such as resection and/or stereotactic body radiotherapy to treat of all sites of metastatic disease may be a reasonable option.**

There are no randomized trials showing the benefit of metastasectomy in RCC with oligometastatic disease; however, among patients with metachronous metastases after nephrectomy, about one-third are eligible for metastasectomy and several large cohorts report 50% five-year survival following complete resection of metastases.[82-84] Based on available observational data, patients most likely to benefit from metastasectomy are those diagnosed with metastases after at least a two-year disease-free interval, those with isolated metastases, and those with surgically favourable metastatic locations (e.g., lung, thyroid, and adrenal).[85] A period of observation is reasonable to confirm that the metastatic disease is not rapidly progressing. In addition, patients on systemic therapy should be re-evaluated during their course of disease for the option of metastasectomy to render no evidence of disease (NED) either due to favourable response or oligoprogression (see section 2.5). There is no defined role for adjuvant systemic therapy after metastasectomy if patient rendered NED.

Stereotactic body radiotherapy (SBRT) is another option for oligometastases. Unlike conventional radiotherapy, SBRT involves delivery of very conformal, ultra-hypofractionated radiation over 1–5 fractions where the goal is to eradicate or provide long-term local control of the treated tumour(s). In patients with medically inoperable, early-stage RCC, SBRT to the primary tumour results in very high local control rates.[86,87] Similar high local control rates of ~ 90% are observed when using SBRT to treat RCC metastases in various body sites (thoracic, abdominal, soft tissue, bone, brain).[88,89] Such data refutes the previously held notion that RCC is radio-resistant.

Thus SBRT can be an alternative to metastasectomy in patients who are inoperable or whose tumour(s) are not easily resectable without morbidity. It can also be complimentary to surgical resection when there are multiple metastases where a combined approach can be considered to spare patients multiple surgical procedures.

2.5. Role of local therapy in oligoprogression

- **Local therapy may be considered in the setting of oligoprogression, preferably in the context of a clinical trial.**

There are no randomized trials for the management of metastatic RCC patients with sites of oligoprogression. Treatment with local therapy (surgery, SBRT, cryotherapy, and/or radiofrequency ablation [RFA]) may be considered, with the goal

of delaying the need to start or change systemic therapy. Such an approach has been studied primarily in metastatic non-small-cell lung cancer patients who developed oligoprogression while on tyrosine kinase inhibitors.[90] A Canadian phase 2 trial using SBRT in metastatic RCC patients with oligoprogression while on sunitinib is currently accruing (NCT02019576).

2.6. Role of radiation therapy in symptom control

- **Radiation therapy may be considered to palliate symptoms from the primary tumour and metastases.**

RCC is not a radio-resistant tumour and many patients can achieve palliation of symptoms related to their cancer through radiation therapy (RT). New radiation techniques, such as stereotactic RT, may improve outcomes compared to traditional external beam RT; several ongoing trials are in progress.[91] Clinical trials involving RT should be supported.

2.7. Role of bone-modifying agents for patients with skeletal metastases

- **Bone modifying agents can be considered for patients with bone metastases to decrease skeletal related events.**

About one-third of patients with metastatic RCC will develop bone metastases, which can lead to skeletal-related events (SRE) as part of their disease.[91] Currently available bone-modifying agents have been shown to reduce SREs in this population.

In a phase 3 trial of zoledronic acid (ZA) vs. placebo, a subset analysis of 74 RCC patients showed that administration of ZA compared to placebo resulted in a significant decrease in SREs in the ZA group.[92,93] Thus, monthly administration of ZA is a reasonable option. Careful monitoring of renal function is required.

Denosumab is an inhibitor of the receptor activator of nuclear factor kappa-B (RANK) ligand. In a phase 3 trial of denosumab vs. ZA for treatment of malignancy with bone metastases (excluding breast or prostate cancer patients), a subset of patients enrolled on this trial had metastatic RCC.[94] This trial demonstrated non-inferiority for denosumab compared to ZA in terms of SRE reduction for the group overall, although no subgroup analysis for RCC patients was done. Thus, denosumab could also be considered a reasonable option for this population of patients.

Patients receiving bone-modifying agents are at risk of hypocalcemia, therefore calcium and vitamin D supplements are recommended; however, paraneoplastic hypercalcemia can also occur in RCC, so monitoring of serum calcium levels is important regardless. Patients starting on any bone-targeted therapy should ensure they have had a thorough dental history and recent dental examination prior to starting therapy, given the risk for osteonecrosis of the jaw developing. Patients should also be monitored for this throughout the course of their therapy.

2.8. Patient and caregiver issues

- **Patients should be provided access to multidisciplinary care, including kidney cancer specialists and health professionals with expertise in supportive care.**
- **Information should be provided to patients and caregivers on community resources.**
- **Screening of patients for hereditary kidney cancer risk should be the standard of care.**
- **Patient enrolment in the CKCis database is strongly encouraged.**

Patient care should involve a multidisciplinary team with expertise in the management of RCC, which may involve communication with and/or referral to another centre.

All patients and caregivers should be referred to a reputable patient group, such as Kidney Cancer Canada[7] and Canadian Cancer Society,[95] for information and support. These groups provide accurate information that has been expertly reviewed and presented in a format that is easy for patients to understand. They also provide support to help patients and caregivers cope with a cancer diagnosis. Patients and caregivers should be asked at visits if they are connected to a patient group and have the information and support they need.

While a minority of patients has hereditary RCC, every patient should be screened for hereditary RCC risk using the Canadian consensus guidelines that include risk factors, such as first- or second-degree relative with renal tumour, young age (<45 year old), bilateral disease, uncommon histology, and associated hereditary conditions.[96]

In order to improve the ability of Canadian researchers to study kidney cancer, the CKCis was developed to facilitate population-based research. Voluntary patient enrolment is strongly encouraged.

Summary

Advanced RCC has seen many treatment advances in the last several years, with the introduction of many novel therapies. Therapy should be individualized based on patient profiles and disease characteristics, and each agent chosen should be optimized to obtain best results, with multidisciplinary care being paramount in achieving maximal benefit for patients. The optimal sequence of agents in second-line and beyond is unclear and it is hopeful that ongoing clinical trials will provide some clarity. Despite recent advances, many patients still succumb to this disease and ongoing participation in research and clinical trials to further our knowledge in this field is essential.

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References

1. Canadian Kidney Cancer Forum. Management of kidney cancer: Canadian Kidney Cancer Forum consensus statement. *Can Urol Assoc J* 2008;2:175-82.
2. Canadian Kidney Cancer Forum. Management of kidney cancer: Canadian Kidney Cancer Forum consensus update. *Can Urol Assoc J* 2009;3:200-4. https://doi.org/10.5489/cuaj.1069
3. Jewett M, Finelli A, Kollmannsberger C, et al. Management of kidney cancer: Canadian Kidney Cancer Forum consensus update 2011. *Can Urol Assoc J* 2012;6:16-22. https://doi.org/10.5489/cuaj.11273
4. North S, Basappa N, Bjarnason G, et al. Management of advanced kidney cancer: Canadian Kidney Cancer Forum 2013 consensus update. *Canadian Urol Assoc J* 2013;7:238-43. https://doi.org/10.5489/cuaj.536
5. North SA, Basappa N, Basiuk J, et al. Management of advanced kidney cancer: Canadian Kidney Cancer Forum consensus update. *Can Urol Assoc J* 2015;9:164-70. https://doi.org/10.5489/cuaj.2894
6. Canadian Cancer Society's Advisory Committee on Cancer Statistics 2016. Canadian Cancer Society 2016; Toronto, ON.
7. Kidney Cancer Canada. Available at http://www.kidneycancercanada.ca/. Accessed Feb 19, 2017.
8. Centre for Evidence Based Medicine. Available at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed March 10, 2017.
9. Posadas EM, Figlin RA. Kidney cancer: Progress and controversies in neoadjuvant therapy. *Nat Rev Urol* 2014;11:254-5. https://doi.org/10.1038/nrurol.2014.89
10. Rini BI, Plimack ER, Takagi T, et al. A phase 2 study of pazopanib in patients with localized renal cell carcinoma to optimize preservation of renal parenchyma. *J Urol* 2015;194(2):297-303. https://doi.org/10.1016/j.juro.2015.03.096
11. Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear-cell renal cancer. *JAMA Oncol* 2016;2:1303-9. https://doi.org/10.1001/jamaoncol.2016.1197
12. Kawakami F, Rao P, Tamboli P. Study of the kidney tumour-parenchymal interface after neoadjuvant treatment with axitinib for locally advanced clear-cell renal cell carcinoma: Matched analysis from a phase 2 trial. *J Urol* 2017;197:559-65. https://doi.org/10.1016/j.juro.2016.09.081
13. Messing EM, Manola J, Wilding G, et al. Phase 3 study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: An Eastern Cooperative Oncology Group/Intergroup trial. *J Clin Oncol* 2003;21:1214-22. https://doi.org/10.1200/JCO.2003.02.005
14. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomized, phase 3 trial. *Lancet* 2016;387:2008-16. https://doi.org/10.1016/S0140-6736(16)00559-6
15. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal cell carcinoma after nephrectomy. *N Engl J Med* 2016;375:2246-54. https://doi.org/10.1056/NEJMoa1611406
16. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;22:454-63. https://doi.org/10.1200/JCO.2004.06.132
17. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicentre study. *J Clin Oncol* 2009;27:5794-9. https://doi.org/10.1200/JCO.2008.21.4809
18. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal cell carcinoma: A prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-24. https://doi.org/10.1016/S1470-2045(16)30196-6
19. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib vs. interferon alfa in metastatic renal-cell carcinoma. *N Engl J of Med* 2007;356:115-24. https://doi.org/10.1056/NEJMoa065044
20. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-90. https://doi.org/10.1200/JCO.2008.20.1293
21. Heng DY, Chi KN, Murray N, et al. A population-based study evaluating the impact of sunitinib on overall survival in the treatment of patients with metastatic renal cell cancer. *Cancer* 2009;115:776-83. https://doi.org/10.1002/cncr.24051
22. Warren M, Venner PM, North S, et al. A population-based study examining the effect of tyrosine kinase inhibitors on survival in metastatic renal cell carcinoma in Alberta and the role of nephrectomy prior to treatment. *Can Urol Assoc J* 2009;3:281-9. https://doi.org/10.5489/cuaj.1121
23. Bjarnason GA. Can individualized sunitinib dose and schedule changes optimize outcomes for kidney cancer patients? *Can Urol Assoc J* 2016;10:S252-5. https://doi.org/10.5489/cuaj.4293
24. Bjarnason GA, Khalil B, Hudson JM, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: Correlation with dynamic microbubble ultrasound data and review of the literature. *Urol Oncol* 2014;32:480-7. https://doi.org/10.1016/j.urolonc.2013.10.004
25. Sternberg CN. Pazopanib in renal cell carcinoma. *Clin Adv Hematol Oncol* 2010;8:232-3.
26. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib vs. sunitinib in metastatic renal cell carcinoma. *N Engl J Med* 2013;369:722-31. https://doi.org/10.1056/NEJMoa1303989
27. Lalani AA, Li H, Heng DYC, et al. Real-world outcomes of patients with metastatic renal cell carcinoma using first-line sunitinib or pazopanib: The Canadian experience. *Can Urol Assoc J* 2017;11:112-7. http://dx.doi.org/10.5489/cuaj.4398
28. Basappa N, Lalani AA, Kalirai A, et al. Individualized treatment with sunitinib vs. standard dosing with sunitinib or pazopanib in patients with metastatic renal cell carcinoma (mRCC): Results from the Canadian Kidney Cancer information system (CKCis). *J Clin Oncol* 2017 [Epub ahead of print].
29. Ruiz-Morales JM, Swierkowski M, Wells JC, et al. First-line sunitinib vs. pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur J Cancer* 2016;65:102-8. https://doi.org/10.1016/j.ejca.2016.06.016
30. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomized, double-blind, phase 3 trial. *Lancet* 2007;370:2103-11. https://doi.org/10.1016/S0140-6736(07)61904-7
31. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 2008;26:5422-8. https://doi.org/10.1200/JCO.2008.16.9847
32. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib vs. sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor- or intermediate-risk: The Alliance A031203 CABOSUN trial. *J Clin Oncol* 2017;35:591-7. https://doi.org/10.1200/JCO.2016.70.7398
33. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. *N Engl J Med* 2007;356:2271-81. https://doi.org/10.1056/NEJMoa066838
34. Motzer RJ, Barrios CH, Kim TM, et al. Phase 2 randomized trial comparing sequential first-line everolimus and second-line sunitinib vs. first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2014;32:2765-72. https://doi.org/10.1200/JCO.2013.54.6911
35. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal cell carcinoma. *New Engl J Med* 2007;356:125-34. https://doi.org/10.1056/NEJMoa060655
36. Vickers MM, Al-Harbi H, Choueiri TK, et al. Prognostic factors of survival for patients with metastatic renal cell carcinoma with brain metastases treated with targeted therapy: Results from the international metastatic renal cell carcinoma database consortium. *Clin Genitourin Cancer* 2013;11:311-5. https://doi.org/10.1016/j.clgc.2013.04.012

37. Vanhuyse M, Penel N, Caty A, et al. Brain metastasis in metastatic renal cell carcinoma: Predictive factors of occurrence and survival with or without antiangiogenic therapy. *J Clin Oncol* 2011;29:394. https://doi.org/10.1200/jco.2011.29.7_suppl.394
38. McDermott DF, Cheng SC, Signoretti S, et al. The high-dose aldesleukin "select" trial: A trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2015;21:561-8. https://doi.org/10.1158/1078-0432.CCR-14-1520
39. Leibovich BC, Han KR, Bui MH, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: A stratification tool for prospective clinical trials. *Cancer* 2003;98:2566-75. https://doi.org/10.1002/cncr.11851
40. Negrier S, Perol D, Ravaud A, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: Results of a randomized, controlled trial. *Cancer* 2007;110:2468-77. https://doi.org/10.1002/cncr.23056
41. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: Early results of a randomized, controlled trial. *Lancet* 1999;353:14-7. https://doi.org/10.1016/S0140-6736(98)03544-2
42. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol* 2000;163:408-17. https://doi.org/10.1016/S0022-5347(05)67889-5
43. Rini BI, Vogelzang NJ, Dumas MC, et al. Phase 2 trial of weekly intravenous gemcitabine with continuous infusion fluorouracil in patients with metastatic renal cell cancer. *J Clin Oncol* 2000;18:2419-26. https://doi.org/10.1200/JCO.2000.18.12.2419
44. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase 3 treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009;27:3312-8. https://doi.org/10.1200/JCO.2008.19.5511
45. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib vs. sorafenib in advanced renal cell carcinoma (AXIS): A randomized, phase 3 trial. *Lancet* 2011;378:1931-9. https://doi.org/10.1016/S0140-6736(11)61613-9
46. Motzer RJ, Basch E. Targeted drugs for metastatic renal cell carcinoma. *Lancet* 2007;370:2071-3. https://doi.org/10.1016/S0140-6736(07)61874-1
47. De Velasco G, Xie W, Donskov F, et al. Discontinuing VEGF-targeted therapy for progression vs. toxicity affects outcomes of second-line therapies in metastatic renal cell carcinoma. *Clin Genitouriin Cancer* 2017;15:403-10. https://doi.org/10.1016/j.clgc.2017.01.005
48. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab vs. everolimus in advanced renal cell carcinoma. *N Engl J Med* 2015;373:1803-13. https://doi.org/10.1056/NEJMoa1510665
49. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumours. *J Clin Oncol* 2015;33:3541-3. https://doi.org/10.1200/JCO.2015.61.6870
50. Weinstock C. FDA analysis of treatment beyond progressive disease (PD) in patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab vs. everolimus. *J Clin Oncol* 2016;34:Abstr 4508.
51. Pedersen M, Andersen R, Norgaard P, et al. Successful treatment with ipilimumab and interleukin-2 in two patients with metastatic melanoma and systemic autoimmune disease. *Cancer Immunol Immunother* 2014;63:1341-6. https://doi.org/10.1007/s00262-014-1607-y
52. Kyi C, Carvajal RD, Wolchok JD, et al. Ipilimumab in patients with melanoma and autoimmune disease. *J Immunother Cancer* 2014;2:35. https://doi.org/10.1186/s40425-014-0035-z
53. Lee B, Wong A, Kee D, et al. The use of ipilimumab in patients with rheumatoid arthritis and metastatic melanoma. *Ann Oncol* 2016;27:1174-7. https://doi.org/10.1093/annonc/mdw056
54. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2017;28:368-76.
55. Grunwald V, Weikert S, Seidel C, et al. Efficacy of sunitinib re-exposure after failure of an mTOR inhibitor in patients with metastatic RCC. *Onkologie* 2011;34:310-4. https://doi.org/10.1159/000328575
56. Wells JC, Stukalin I, Norton C, et al. Third-line targeted therapy in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2017;71:204-9. https://doi.org/10.1016/j.eururo.2016.05.049
57. Albiges L, Fay AP, Xie W, et al. Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma. *Eur J Cancer* 2015;51:2580-6. https://doi.org/10.1016/j.ejca.2015.08.017
58. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib vs. everolimus in advanced renal cell carcinoma (METEOR): Final results from a randomized, open-label, phase 3 trial. *Lancet Oncol* 2016;17:917-27. https://doi.org/10.1016/S1470-2045(16)30107-3
59. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomzed, placebo-controlled, phase 3 trial. *Lancet* 2008;372:449-56. https://doi.org/10.1016/S0140-6736(08)61039-9
60. Hutson TE, Escudier B, Esteban E, et al. Randomized phase 3 trial of temsirolimus vs. sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2014;32:760-7. https://doi.org/10.1200/JCO.2013.50.3961
61. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomized, phase 2, open-label, multicentre trial. *Lancet Oncol* 2015;16:1473-82. https://doi.org/10.1016/S1470-2045(15)00290-9
62. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib vs. placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:621-30. https://doi.org/10.1056/NEJMoa1406470
63. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: An expanded-access trial. *Lancet Oncol* 2009;10:757-63. https://doi.org/10.1016/S1470-2045(09)70162-7
64. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 2010;116:1272-80. https://doi.org/10.1002/cncr.24864
65. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus vs. interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumour histologies. *Med Oncol* 2009;26:202-9. https://doi.org/10.1007/s12032-009-9177-0
66. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 2008;26:127-31. https://doi.org/10.1200/JCO.2007.13.3223
67. Buti S, Bersanelli M, Maines F, et al. First-line pazopanib in non-clear-cell renal carcinoma: The Italian retrospective multicentre PANORAMA Study. *Clin Genitourin Cancer* 2017;15:e609-14. https://doi.org/10.1016/j.clgc.2016.12.024
68. Tannir NM, Jonasch E, Albiges L, et al. Everolimus vs. sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): A randomized, multicentre, phase 2 trial. *Eur Urol* 2016;69:866-74. https://doi.org/10.1016/j.eururo.2015.10.049
69. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus vs. sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomized, phase 2 trial. *Lancet Oncol* 2016;17:378-88. https://doi.org/10.1016/S1470-2045(15)00515-X
70. Nanus DM, Garino A, Milowsky MI, et al. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. *Cancer* 2004;101:1545-51. https://doi.org/10.1002/cncr.20541
71. Michaelson MD, McKay RR, Werner L, et al. Phase 2 trial of sunitinib and gemcitabine in patients with sarcomatoid and/or poor-risk metastatic renal cell carcinoma. *Cancer* 2015;121:3435-43. https://doi.org/10.1002/cncr.29503
72. Flanigan RC, Mickisch G, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: A combined analysis. *J Urol* 2004;171:1071-6. https://doi.org/10.1097/01.ju.0000110610.61545.ae
73. Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2014;66:704-10. https://doi.org/10.1016/j.eururo.2014.05.034
74. Abern MR, Scosyrev E, Tsivian M, et al. Survival of patients undergoing cytoreductive surgery for metastatic renal cell carcinoma in the targeted-therapy era. *Anticancer Res* 2014;34:2405-11.
75. Culp SH, Karam JA, Wood CG. Population-based analysis of factors associated with survival in patients undergoing cytoreductive nephrectomy in the targeted therapy era. *Urol Oncol* 2014;32:561-8. https://doi.org/10.1016/j.urolonc.2013.12.003
76. Mickisch GH. Urological approaches to metastatic renal cell carcinoma. *Onkologie* 2001;24:122-6. https://doi.org/10.1159/000050298
77. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol* 2011;185:60-6. https://doi.org/10.1016/j.juro.2010.09.012
78. Pierorazio PM, McKiernan JM, McCann TR, et al. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. *BJU Int* 2007;100:755-9. https://doi.org/10.1111/j.1464-410X.2007.07108.x
79. Barbastefano J, Garcia JA, Elson P, et al. Association of percentage of tumour burden removed with debulking nephrectomy and progression-free survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *BJU Int* 2010;106:1266-9. https://doi.org/10.1111/j.1464-410X.2010.09323.x
80. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 2010;116:3378-88. https://doi.org/10.1002/cncr.25046
81. Kutikov A, Uzzo RG, Caraway A, et al. Use of systemic therapy and factors affecting survival for patients undergoing cytoreductive nephrectomy. *BJU Int* 2010;106:218-23. https://doi.org/10.1111/j.1464-410X.2009.09079.x
82. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib vs. sunitinib-sorafenib in the treatment of metastatic renal cell cancer. *Eur Urol* 2015;68:837-47. https://doi.org/10.1016/j.eururo.2015.04.017

83. Eggener SE, Yossepowitch O, Pettus JA, et al. Renal cell carcinoma recurrence after nephrectomy for localized disease: Predicting survival from time of recurrence. *J Clin Oncol* 2006;24:3101-6. https://doi.org/10.1200/JCO.2005.04.8280
84. Breau RH, Blute ML. Surgery for renal cell carcinoma metastases. *Curr Opin Urol* 2010;20:375-81. https://doi.org/10.1097/MOU.0b013e32833c7ada
85. Kim DY, Karam JA, Wood CG. Role of metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. *World J Urol* 2014;32:631-42. https://doi.org/10.1007/s00345-014-1293-6
86. Siva S, Pham D, Gill S, et al. A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. *BJU Int* 2012;110:E737-43. https://doi.org/10.1111/j.1464-410X.2012.11550.x
87. Siva S, Pham D, Kron T, et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: A prospective clinical trial. *BJU Int* 2017 [Epub ahead of print]. https://doi.org/10.1111/bju.13811
88. Cheung P, Thibault I, Bjarnason GA. The emerging roles of stereotactic ablative radiotherapy for metastatic renal cell carcinoma. *Current Opin Support Palliat Care* 2014;8:258-64. https://doi.org/10.1097/SPC.0000000000000074
89. Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: A systematic review. *Acta Oncol* 2015;54:148-57. https://doi.org/10.3109/0284186X.2014.939298
90. Cheung P. Stereotactic body radiotherapy for oligoprogressive cancer. *B J Radiol* 2016;89:20160251. https://doi.org/10.1259/bjr.20160251
91. Sahi C, Knox JJ, Clemons M, et al. Renal cell carcinoma bone metastases: Clinical advances. *Ther Adv Med Oncol* 2010;2:75-83. https://doi.org/10.1177/1758834009358417
92. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid vs. placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumours: A phase 3, double-blind, randomized trial — the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150-7. https://doi.org/10.1200/JCO.2003.04.105
93. Lipton A, Colombo-Berra A, Bukowski RM, et al. Skeletal complications in patients with bone metastases from renal cell carcinoma and therapeutic benefits of zoledronic acid. *Clin Cancer Res* 2004;10:S6397-403. https://doi.org/10.1158/1078-0432.CCR-040030
94. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab vs. zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125-32. https://doi.org/10.1200/JCO.2010.31.3304
95. Canadian Cancer Society. Available at http://www.cancer.ca. Accessed Feb 19, 2017.
96. Reaume MN, Graham GE, Tomiak E, et al. Canadian guideline on genetic screening for hereditary renal cell cancers. *Can Urol Assoc J* 2013;7:319-23. https://doi.org/10.5489/cuaj.1496

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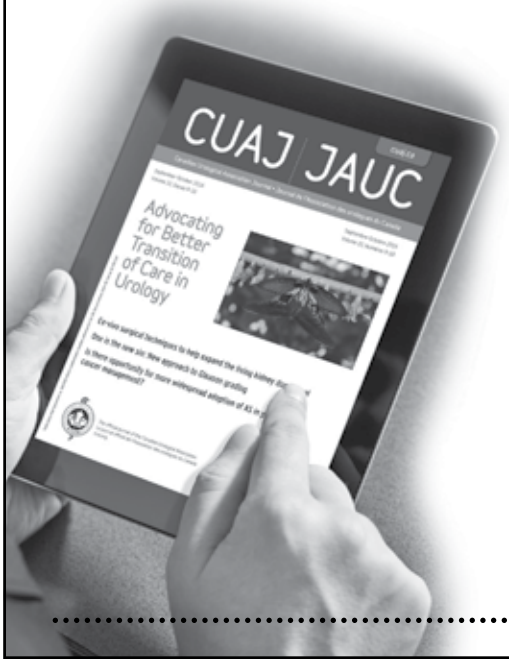

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