Review CPD

# Advances in the management of renal cell carcinoma

Luisa M. Cardenas MD, Samantha Sigurdson MD, Christopher J.D. Wallis MD PhD, Aly-Khan Lalani MD, Anand Swaminath MD

■ Cite as: *CMAJ* 2024 February 26;196:E235-40. doi: 10.1503/cmaj.230356

Renal cell carcinoma (RCC) is the 10th most common cancer in Canada, with an estimated 8100 new cases and 1950 deaths from the disease annually.[1] Renal cell carcinoma accounts for more than 90% of kidney malignancies. Its incidence increases with age, with a global median age at diagnosis of 75 years,[2] and males are twice as likely as females to be affected.[2] People of Indigenous, Asian, and African heritage have been shown to have an increased risk of RCC.[2] For localized RCC (tumour only in the kidney) cancer-specific survival is excellent at 98%, with a 5-year overall survival rate of 75%.[3] The overall survival rate for metastatic RCC is about 4 years but depends on factors such as patient age, performance status, and comorbidities.[4] The diagnosis and treatment of both localized and metastatic RCC have evolved in recent years. Use of abdominal computed tomography (CT) or magnetic resonance imaging (MRI) has contributed to an increasing incidence of asymptomatic lesions being identified. This has also led to stage migration, where patients are diagnosed earlier in the course of their disease.[2] Survival from RCC has also improved substantially with the emergence of immune checkpoint inhibitor combination therapies as a preferred first-line treatment for metastatic RCC. The evidence used in this review is described in Box 1.

## Key points

- Treatment for localized renal cell carcinoma (RCC) depends on patient factors, the size and location of the lesion, and its metastatic potential.
- Treatment options for localized RCC include surgical excision, ablation, and active surveillance.
- Immune checkpoint inhibitors have become a part of standard first-line treatments for metastatic RCC and are associated with long-term responses in some patients.
- Patients receiving immune checkpoint inhibitors should be monitored for immune-related toxicities.
- Although immune checkpoint inhibitors have improved survival among patients with metastatic RCC, most individuals eventually develop resistance to treatment.

### Box 1: Evidence used in this review

We identified articles for this review by searches of MEDLINE, the American Society of Clinical Oncology library, and references from relevant articles, with various combinations of the search terms "renal cell carcinoma," "RCC," "RCC management and treatment," "metastatic RCC," "RCC guideline," "RCC ablation," "immunotherapy," and "targeted therapy." We included articles published only in English between Jan. 1, 2000, and Dec. 1, 2022.

## Who is at risk of RCC?

Risk factors associated with development of RCC include increasing age, smoking, excess body weight, and history of hypertension.[2] Obesity is a strong risk factor for RCC. The theorized pathways linking the two are insulin resistance and abnormalities in the insulin-like growth factor 1 system, biosynthesis of sex hormones, subclinical inflammation and oxidative stress, and alterations in the gut microflora.[2]

## How is RCC diagnosed and staged?

Patients with RCC may have symptoms such as hematuria and flank pain; a flank mass may be apparent on physical examination.[2] This combination of symptoms and signs should prompt diagnostic imaging. A growing number of asymptomatic lesions are detected on incidental abdominal imaging.[5] Small renal masses are solid, enhancing lesions that measure 4 cm or smaller visualized on CT, MRI, or abdominal ultrasonography, and 10%–30% are benign.[5] Although RCC remains the leading diagnosis of small renal masses, the differential also includes acute myeloid leukemia, oncocytoma, and others. Fewer than 2% of small renal masses are metastatic at the time of diagnosis, as metastatic potential is associated with tumour size, although this risk never reaches zero.[5] When any renal mass is detected, referral should be made to a urologist. Initial investigations that should be arranged by a generalist provider are outlined in Box 2.

**Box 2: Initial investigations required when a renal mass is detected[5,6]**

**Imaging**

- Multiphase contrast-enhanced CT or gadolinium-enhanced MRI of the abdomen and pelvis
- Chest CT (preferred) or chest radiography
- If clinically indicated:
  - Bone scan for patients with bone pain or imaging findings that suggest bone metastases
  - Brain MRI for patients with neurological symptoms and signs

**Serum tests**

- CBC with differential, creatinine, electrolytes, glucose, calcium, and albumin
- If bone pain or bone metastases: alkaline phosphatase, lactate dehydrogenase
- If liver metastases: liver function tests

**Urine tests**

- Urinalysis
- If central renal mass: urine cytology

Note: CBC = complete blood count, CT = computed tomography, MRI = magnetic resonance imaging.

For patients with renal masses on imaging suspicious for RCC, urologists typically offer a percutaneous biopsy to confirm the histologic diagnosis, which is recommended for renal masses of any size.[5,6] However, a biopsy is not suitable for all patients; for example, if a patient is not fit for invasive treatment, a biopsy may not be warranted when the results will not change management.[5]

Renal cell carcinoma is staged with the standard tumour, node, metastasis (TNM) nomenclature (Table 1).[7] Metastatic RCC is further divided into 3 prognostic groups based on presence of 6 risk factors described in Table 2 as per the International Metastatic RCC Database Consortium (IMDC).[8]

## What are the treatment options for patients with localized RCC?

Patients with small renal masses (≤ 4 cm, clinical stage T1a disease) can be considered for surgical management (partial or radical nephrectomy), ablative approaches, active surveillance, or observation. High-quality evidence comparing surgery, ablative approaches, and active surveillance is lacking. Treatment decisions are individualized and should consider patient factors and tumour characteristics, in addition to patients' values and preferences.[5] For stages I to III RCC, partial or radical nephrectomy is the preferred treatment for patients who are surgical candidates.[6]

### Surgical management

Treatment options include either radical nephrectomy (removal of the kidney with the Gerota fascia) or partial nephrectomy (removal of the tumour with a margin of benign tissue).[9] A surgical approach is guided by the feasibility of partial nephrectomy, as tumour size and location may make this option impossible. When feasible, partial nephrectomy is preferred because of the decreased risk of long-term renal dysfunction associated with this nephron-sparing approach. Nephron sparing is particularly important for patients with renal-threatening conditions such as diabetes. Whereas partial nephrectomy preserves renal function, there are increased risks of complications, including bleeding, with severe hemorrhage occurring in approximately 3% of patients, as well as urinary fistulae.[10,11] These procedures may be achieved via open, laparoscopic, or robotic approaches.[12] The decision will depend on patient and tumour factors as well as the expertise of the urologist.

Clinical and pathologic features (Table 1) determine recurrence risk and the surveillance strategy. After surgical resection, RCC can recur in 20%–40% of patients, with the highest risk in the first 5 years after nephrectomy.[13] Renal cell carcinoma can metastasize to almost any soft tissue in the body, but most commonly to the lung, followed by bone, liver, brain, and local recurrence around the surgical bed.[13]

### Nonsurgical management

For patients with localized RCC, several nonoperative approaches, with varying degrees of invasiveness and oncologic efficacy, may be used. For example, for some patients with tumours measuring less than 2 cm or with substantial frailty, the risk of disease progression may be outweighed by the risks of treatment, and active surveillance may be the most reasonable option.[14] Longitudinal follow-up is performed with the goal of intervening with curative intent if oncologic risk increases and treatment is required.[5,14] Intervention is often recommended if the overall growth rate is greater than 0.5 cm per year or when tumour size is greater than 4 cm,[14] as the risk of metastatic potential increases. As per Canadian Urological Association guidelines, patients on active surveillance require abdominal imaging every 3–6 months during the first year, and every 6–12 months thereafter with either multiphase contrast-enhanced CT or ultrasonography, which can be alternated to reduce radiation exposure.[5] Chest imaging should be done up to once a year to assess for pulmonary metastases.[5]

Ablative approaches for renal tumours include radiofrequency ablation, cryoablation, and stereotactic body radiotherapy (SBRT). These offer several advantages for frail patients or patients who decline surgery for other reasons. Ablation techniques reduce perioperative morbidity, avoid admission, and involve faster recovery time. Local control is excellent and can be greater than 90% for tumours measuring 4 cm or less.[15] To date, no randomized studies have investigated ablative approaches compared with surgical techniques.[15]

Thermal ablation is the most common type of ablation available in Canada and includes radiofrequency ablation and cryoablation. Both are performed either percutaneously or through a minor open procedure using local anesthesia. Thermal ablation is an outpatient procedure and is generally well tolerated. Local control is more than 90%, with the potential to repeat the procedure if failure occurs.[3] Local control for thermal ablation is commonly defined as absence of contrast enhancement within the tumour on

**Table 1: Staging for renal cell carcinoma[7]**

| Category | | Description | | |
|---|---|---|---|---|
| **T — Primary tumour** | | | | |
| T1 | Tumour ≤ 7 cm in greatest dimension, limited to the kidney | | | |
| | T1a | Tumour ≤ 4 cm | | |
| | T1b | Tumour > 4 cm but ≤ 7 cm | | |
| T2 | Tumour > 7 cm in greatest dimension, limited to the kidney | | | |
| | T2a | Tumour > 7 cm but ≤ 10 cm | | |
| | T2b | Tumour > 10 cm but limited to the kidney | | |
| T3 | Tumour extends into major veins or perinephric tissues but not into ipsilateral adrenal gland and not beyond the Gerota fascia | | | |
| | T3a | Tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or perirenal or renal sinus fat | | |
| | T3b | Tumour grossly extends into the vena cava below the diaphragm | | |
| | T3c | Tumour grossly extends into the vena cave above the diaphragm or the wall of the vena cava | | |
| T4 | Tumour invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland) | | | |
| **N — Regional lymph nodes** | | | | |
| N0 | No regional lymph node metastasis | | | |
| N1 | Metastasis in regional lymph node(s) | | | |
| **M — Distant metastasis** | | | | |
| M0 | No distant metastasis | | | |
| M1 | Distant metastasis | | | |
| **TNM stage grouping** | | | | |
| Stage I | | T1 | N0 | M0 |
| Stage II | | T2 | N0 | M0 |
| Stage III | | T3 | N0 | M0 |
| | | T1, T2, or T3 | N1 | M0 |
| Stage IV | | T4 | Any N | M0 |
| | | Any T | Any N | M1 |

Note: TNM = tumour, node, metastasis.

**Table 2: International Metastatic RCC Database Consortium risk stratification criteria for metastatic disease[8]**

| IMDC criteria | |
|---|---|
| • Hemoglobin < LLN | |
| • Platelets > ULN | |
| • Neutrophil count > ULN | |
| • Corrected calcium > ULN | |
| • Karnofsky Performance Scale score < 80% | |
| • Time from diagnosis to systemic treatment < 1 year | |
| **IMDC risk group** | **Score** |
| Favourable risk | 0 |
| Intermediate risk | 1–2 |
| Poor risk | 3–6 |

Note: IMDC = International Metastatic RCC Database Consortium, LLN = lower limit of normal, RCC = renal cell carcinoma, ULN = upper limit of normal.

contrast-enhanced CT or MRI.[3] Common adverse effects of thermal ablation include pain at the incision site, fever, nausea, and small reduction in the estimated glomerular filtration rate; less common risks are bleeding and infection. Small tumours measuring less than 3 cm that are exophytic (tumour protrudes from the kidney's surface) are ideal for thermal ablation, whereas larger or more central tumours have inferior control rates.[3] Thermal ablation is generally recommended for stage T1a RCC.[6]

Stereotactic body radiotherapy is a form of external beam radiotherapy that delivers targeted radiation to the tumour over 1–5 outpatient sessions, which combines to an ablative dose to the tumour. Common adverse effects are fatigue, nausea, and a small reduction in estimated glomerular filtration rate;[16] uncommon risks are damage to nearby bowel and rib fracture. Data that directly compare SBRT with other local treatments are lacking. A recent meta-analysis involving 190 patients treated with SBRT found that 94.5% achieved local control at 5 years for tumours measuring up to 7 cm.[17] In comparison to thermal ablation, SBRT

is less invasive and less limited by tumour size and location. It can be considered for patients who are not candidates for surgical resection, with stage I RCC and possibly stages II to III localized RCC, although experts disagree.[6] Long-term data are still needed for SBRT as initial reports have indicated viable tumour cells present on posttreatment biopsy.[18] However, objective responses may occur months or years following treatment, due to delayed senescence of tumour cells.[19]

### Role of postoperative systemic therapy

Pembrolizumab, an anti–programmed death-1 (anti-PD-1) antibody, is approved by Health Canada in the adjuvant setting for patients at higher risk of disease recurrence after nephrectomy based on pathological findings, including pT4 tumour, lymph node involvement, high grade, and presence of sarcomatoid features. Pembrolizumab showed a disease-free survival advantage compared with placebo,[20] and a recent updated analysis confirmed an overall survival advantage (overall survival medians not reached; hazard ratio 0.62, 95% confidence interval 0.44–0.87; $p = 0.0024$) after a median follow-up of 57 months.[21] Other trials of adjuvant immune checkpoint inhibitor have not replicated the benefit seen with pembrolizumab. This may be due to important differences in patient population, and type and duration of therapy.[22–25]

A recent consensus statement from the Canadian Kidney Cancer forum suggests that patients at increased risk of disease recurrence should be informed of the role of adjuvant therapy, the uncertainties regarding a survival benefit, and the risk of immune-related toxicities which, in rare cases, can cause lifelong morbidity.[26]

## How should patients with metastatic disease be managed?

A review found that 20%–40% of patients present with metastatic disease at the time of initial diagnosis.[27,28] Treatment of metastatic disease is mostly palliative in nature, aimed at improving symptoms and quality of life, and increasing lifespan. Patients with metastatic disease are first stratified into favourable-, intermediate-, and poor-risk groups per the IMDC score based on clinical and laboratory criteria, informing prognosis and guiding treatment approaches[8] (Table 2).

### Systemic therapy

The treatment landscape of metastatic clear cell RCC has greatly expanded over the last 20 years, moving away from first-generation immunotherapies, such as interferon and interleukin-2, to systemic therapies targeting the vascular endothelial growth factor (VEGF) receptor, to immune checkpoint inhibitors for most patients with metastatic RCC. In the immune system, checkpoints regulate the amplitude and quality of immune responses and prevent autoimmunity.[29] Cancer cells should, under regular circumstances, be recognized by the immune system as "foreign" but can find ways to evade immune responses. The cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and PD-1 are immune checkpoint pathways that can be inhibited with immune checkpoint inhibitors, subsequently activating the immune system against cancer cells.[30]

Several immune checkpoint inhibitor–based regimens have shown improved outcomes for patients with metastatic RCC compared with the previous standard sunitinib, a tyrosine kinase inhibitor (TKI), and are now approved for first-line treatment (Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230356/tab-related-content). The chance of complete response with sunitinib was in the order of 1%; however, combination immune checkpoint inhibitor therapy offers a 10% or greater chance for complete response (Appendix 1). Approved regimens include doublet immune checkpoint inhibitor therapies such as ipilimumab (anti-CTLA-4 antibody) plus nivolumab (anti-PD-1 antibody), or immune checkpoint inhibitor plus VEGF-TKI combinations, such as pembrolizumab plus axitinib, pembrolizumab plus lenvatinib, and nivolumab plus cabozantinib. With nearly 8 years of follow-up from pivotal clinical trials, median survival for metastatic RCC can now approach 47–55 months.[4,31–34] In patients with IMDC intermediate- and poor-risk disease, survival has improved to 47 months compared with 27 months with sunitinib.[4]

Patients who receive immune checkpoint inhibitor–based therapies are at high risk of immune-related adverse events, which can affect any organ system but most commonly include skin rashes, pruritus, diarrhea, and hypothyroidism.[35] Onset can occur more than 1 year after treatment completion.[36] Among patients treated with ipilimumab plus nivolumab, as many as 35% require high-dose corticosteroids to manage toxicity.[35] Most patients with immune-related adverse events will require systemic corticosteroids, such as prednisone 0.5–1 mg/kg taken orally, which should be managed in consultation with their oncologist. For patients refractory to steroids, consultation with other specialists and initiation of alternative immunosuppressive agents is often required.[36]

The choice of initial systemic therapy is based on several factors, including IMDC risk group, patient comorbidities, and patient preference. Clinical trial participation is strongly encouraged in any treatment setting, as it may be a way for patients to access promising therapies that remain under investigation. Ipilimumab plus nivolumab is approved by Health Canada only in patients with intermediate- or poor-risk disease, whereas the immune checkpoint inhibitor plus VEGF-TKI combinations are approved regardless of IMDC risk group. In patients with bulky metastatic disease causing discomfort, immune checkpoint inhibitor–VEGF-TKI combination may be preferred owing to higher objective response rates.[37] For patients with multiple comorbidities, and particularly with contraindications to immunotherapy, first-line single-agent VEGF-TKI (sunitinib or pazopanib) can be considered.[38] Active surveillance is an option for some patients with a low burden of metastatic disease who are asymptomatic.[38] After progression on or intolerance to first-line immune checkpoint inhibitor–based regimens, guidance from randomized trials for subsequent therapy is lacking, and the choice is made based on patient comorbidities, previous systemic therapy, and drug access through provincial funding or patient support programs.[39]

Despite the important advances in the treatment of metastatic RCC, most patients will develop resistance to treatment, leading to cancer-related morbidity and mortality. Use of predictive biomarkers to optimize treatment selection for individual patients is an area of ongoing investigation.

## Focal therapies for patients with metastatic disease

Cytoreductive nephrectomy refers to the surgical removal of the kidney and primary tumour even though the patient has known metastatic disease. Historically, cytoreductive nephrectomy was a standard of care based on evidence from randomized trials that the procedure improved survival in patients treated with interferon.[40] This practice continued after tyrosine kinase inhibitors became standard systemic therapy based on several large retrospective and population-based database studies showing improved survival.[41,42] However, in 2018, the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial showed noninferiority of sunitinib alone compared with cytoreductive nephrectomy and sunitinib for patients with intermediate or poor IMDC risk disease.[43] Cytoreductive nephrectomy has not been compared with the current standard of care, immunotherapy, and therefore is currently a controversial treatment option; however, cytoreductive nephrectomy is still discussed for some patients with metastatic disease. Further, the CARMENA study showed that about 1 in 5 patients who do not receive cytoreductive nephrectomy will require palliative nephrectomy owing to pain or bleeding. Better defining the role of cytoreductive nephrectomy in metastatic RCC is the subject of ongoing clinical trials as some subgroups of patients will benefit from this surgery, for example, those who are otherwise fit with oligometastatic disease (e.g., ≤ 5 metastases). Currently the American Society of Clinical Oncology recommends that only select patients with 0–1 IMDC risk factors who can have a majority of their tumour burden removed at the time of surgery should be offered cytoreductive nephrectomy.[44]

Definitive metastasis-directed therapies, which include surgical resection or SBRT to all sites of disease, are recommended for patients with oligometastatic disease.[5,44] Metastasis-directed therapies are associated with low toxicity rates and excellent local control (> 90%), which extend patients' time on their current systemic treatment by approximately 9 months, and lead to improved progression-free survival ranging from 8 to 15 months.[45] A single-arm feasibility trial found that patients with low-volume disease (≤ 5 metastatic lesions) treated with SBRT to all metastatic sites had a progression-free survival of 22.7 months,[46] and 82% of patients were alive and not on systemic therapy at 1 year. Clinical trials are ongoing to determine whether there is an overall survival benefit.[47]

## Novel therapies for metastatic disease

Although some patients benefit from durable responses to immune checkpoint inhibitor–based treatments, most eventually develop disease progression. Different combination strategies involving immune checkpoint inhibitors and several novel therapies that overcome acquired resistance and modulate immune responses are being actively studied.[48] Potentially promising therapeutic targets that remain under investigation include hypoxia-inducible factor 2 α inhibitor combinations, metabolomics, chimeric antigen receptor–T cell therapy, and modulation of the gut microbiome.[48]

## Conclusion

The treatment of RCC has greatly expanded in the last 2 decades, ranging from minimally invasive surgical and ablative options, and active surveillance for selected patients with localized disease, to immune checkpoint inhibitor–based treatments becoming standard for patients with metastatic disease. Systemic therapy is now being used in earlier disease stages, and ongoing efforts are needed to better risk-stratify patients who would benefit from adjuvant therapy. Immune checkpoint inhibitor–based therapies have changed the treatment of metastatic disease, with a subset of patients benefiting from long-term responses. As novel therapies emerge, the identification of biomarkers to guide treatment selection will become crucial. Questions for future research are listed in Box 3.

### Box 3: Questions for future research

- Does the addition of metastasis-directed therapy (surgery or ablative radiotherapy) for patients with oligometastatic disease (5 sites of distant disease) improve survival compared with systemic therapy alone?
- Can biomarkers predict response to therapy and assist with better selection of first-line therapies as well as guide subsequent treatment after failure of immune checkpoint inhibitors?

## References


1. Brenner DR, Poirier A, Woods RR, et al. Projected estimates of cancer in Canada in 2022. *CMAJ* 2022;194:E601-7.
2. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell carcinoma: 2022 update. *Eur Urol* 2022;82:529-42.
3. Wah TM, Irving HC, Gregory W, et al. Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. *BJU Int* 2014;113:416-28.
4. Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 2022;128:2085-97.
5. Richard PO, Violette PD, Bhindi B, et al. Canadian Urological Association guideline: Management of small renal masses: full text. *Can Urol Assoc J* 2022;16:E61-75.
6. Kidney cancer v1.2024. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2024. Available: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (accessed 2023 Oct. 2). Login required to access content.
7. Amin MB, Edge SB, Greene FL. *AJCC cancer staging manual. 8th edition.* Springer; 2017.
8. Heng DYC, 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, multicenter study. *J Clin Oncol* 2009;27:5794-9.
9. Kalapara AA, Frydenberg M. The role of open radical nephrectomy in contemporary management of renal cell carcinoma. *Transl Androl Urol* 2020;9:3123-39.
10. Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2007;51:1606-15.
11. Lesage K, Joniau S, Fransis K, et al. Comparison between open partial and radical nephrectomy for renal tumours: perioperative outcome and health-related quality of life. *Eur Urol* 2007;51:614-20.
12. Rendon RA, Kapoor A, Breau R, et al. Surgical management of renal cell carcinoma: Canadian Kidney Cancer Forum Consensus. *Can Urol Assoc J* 2014;8:E398-412.
13. Chin AI, Lam JS, Figlin RA, et al. Surveillance strategies for renal cell carcinoma patients following nephrectomy. *Rev Urol* 2006;8:1-7.
14. Gordetsky J, Eich ML, Garapati M, et al. Active surveillance of small renal masses. *Urology* 2019;123:157-66.

15. Prins FM, Kerkmeijer LGW, Pronk AA, et al. Renal cell carcinoma: alternative nephron-sparing treatment options for small renal masses, a systematic review. *J Endourol* 2017;31:963-75.
16. Siva S, Jackson P, Kron T, et al. Impact of stereotactic radiotherapy on kidney function in primary renal cell carcinoma: establishing a dose-response relationship. *Radiother Oncol* 2016;118:540-6.
17. Siva S, Ali M, Correa RJM, et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). *Lancet Oncol* 2022;23:1508-16.
18. Hoogenes J, Swaminath A, Mironov O, et al. A prospective randomized parallel-controlled pilot trial of stereotactic body radiation therapy versus radiofrequency ablation for the management of small renal masses. *J Clin Oncol* 2022;40(Suppl 6):363.
19. Hannan R, McLaughlin MF, Pop LM, et al. Phase 2 trial of stereotactic ablative radiotherapy for patients with primary renal cancer. *Eur Urol* 2023;84:275-86.
20. Choueiri TK, Tomczak P, Park SH, et al. Pembrolizumab as post nephrectomy adjuvant therapy for patients with renal cell carcinoma: results from 30-month follow-up of KEYNOTE-564. *J Clin Oncol* 2022;40(Suppl 6):290.
21. Choueiri TK, Tomczak P, Park SH, et al. Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC). *J Clin Oncol* 2024;42(4_suppl):LBA359-LBA.
22. Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2022;400:1103-16.
23. Motzer RJ, Russo P, Gruenwald V, et al. Adjuvant nivolumab plus ipilimumab (NIVO+IPI) vs placebo (PBO) for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy: results from the randomized, phase III CheckMate 914 trial. *Ann Oncol* 2022;(Suppl 7):1430.
24. Allaf M, Kim SE, Harshman LC, et al. Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol* 2022;(Suppl 7):S1432-S1433.
25. Dibajnia P, Cardenas LM, Lalani AA. The emerging landscape of neo/adjuvant immunotherapy in renal cell carcinoma. *Hum Vaccin Immunother* 2023;19:2178217. doi: 10.1080/21645515.2023.2178217.
26. Lalani AA, Kapoor A, Basappa NS, et al. Adjuvant therapy for renal cell carcinoma: 2023 Canadian Kidney Cancer Forum consensus statement. *Can Urol Assoc J* 2023;17:E154-63.
27. Tran J, Ornstein MC. Clinical review on the management of metastatic renal cell carcinoma. *JCO Oncol Pract* 2022;18:187-96.
28. Takahiro Osawa, Ario Takeuchi, Takahiro Kojima, et al. Overview of current and future systemic therapy for metastatic renal cell carcinoma. *Jpn J Clin Oncol* 2019;49:395–403.
29. Mondlane ER, Abreu-Mendes P, Martins D, et al. The role of immunotherapy in advanced renal cell carcinoma [review]. *Int Braz J Urol* 2021;47:1228-42.
30. Deleuze A, Saout J, Dugay F, et al. Immunotherapy in renal cell carcinoma: the future is now. *Int J Mol Sci* 2020;21:25-32.
31. Motzer RJ, Porta C, Eto M, et al. Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). *J Clin Oncol* 2023;41(Suppl 16):4502.
32. Plimack ER, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. *J Clin Oncol* 2023;41(Suppl 17):LBA4501.
33. Burotto M, Powles T, Escudier B, et al. Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate 9ER trial. *J Clin Oncol* 2023;41(Suppl 6):603.
34. Tannir NM, Escudier B, McDermott DF, et al. Nivolumab plus ipilimumab (NIVO+IPI) vs sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC): long-term follow-up data from the phase 3 CheckMate 214 trial. *J Clin Oncol* 2024;42(4_suppl):363.
35. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277-90.
36. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers* 2020;6:38.
37. Porta CG, Eto M, Motzer RJ, et al. 1449MO updated efficacy of lenvatinib (LEN) + pembrolizumab (PEMBRO) vs sunitinib (SUN) in patients (pts) with advanced renal cell carcinoma (aRCC) in the CLEAR study. *Ann Oncol* 2022;33:S1205-6.
38. Canil C, Kapoor A, Basappa NS, et al. Management of advanced kidney cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2021. *Can Urol Assoc J* 2021;15:84-97.
39. Provisional Funding Algorithm. Indication: renal cell carcinoma. Ottawa: The Canadian Agency for Drugs and Technologies in Health; 2023 Available: https://www.cadth.ca/sites/default/files/pdf/PH0019-Adjuvant%20RCC-CAPCA%20Endorsement.pdf (accessed 2023 July 30).
40. 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.
41. 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.
42. Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a national cancer data base study. *J Clin Oncol* 2016;34:3267-75.
43. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med* 2018;379:417-27.
44. Rathmell WK, Rumble RB, Van Veldhuizen PJ, et al. Management of metastatic clear cell renal cell carcinoma: ASCO guideline. *J Clin Oncol* 2022;40:2957-95.
45. Le Guevelou J, Sargos P, Siva S, et al. The emerging role of extracranial stereotactic ablative radiotherapy for metastatic renal cell carcinoma: a systematic review. *Eur Urol Focus* 2023;9:114-24.
46. Tang C, Msaouel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial. *Lancet Oncol* 2021;22:1732-9.
47. Hsieh PY, Hung SC, Li JR, et al. The effect of metastasectomy on overall survival in metastatic renal cell carcinoma: a systematic review and meta-analysis. *Urol Oncol* 2021;39:422-30.
48. Cardenas LM, Deluce JE, Khan S, et al. Next wave of targets in the treatment of advanced renal cell carcinoma. *Curr Oncol* 2022;29:5426-41.


**Competing interests:** Christopher Wallis has received consulting fees from Janssen Oncology, Nanostics, Inc., Precision Point Specialty LLC, Sesen Bio; honoraria or travel fees from AbbVie, Astellas, AstraZeneca, Bayer, EMD Serono, Haymarket Media, Healing and Cancer Foundation, Janssen, Knight Therapeutics, Merck, Science & Medicine Canada, TerSera Canada, and Tolmar Pharmaceuticals Canada; research funding from Knight Therapeutics, Tolmar Pharmaceuticals and Bayer. Aly-Khan Lalani has received honoraria and/or consultancy fees from AbbVie, Astellas Pharma, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche/Genentech and TerSera, and research funding from Bristol Myers Squibb, BioCanRx, EMD Serono, Ipsen, Novartis and Roche. Anand Swaminath has received honoraria from Bristol Myers Squibb, Eisai, and AstraZeneca, and holds a voluntary position on the medical advisory board for Kidney Cancer Canada.

This article has been peer reviewed.

**Affiliations:** Department of Oncology (Cardenas, Sigurdson, Lalani, Swaminath), Juravinski Cancer Centre, McMaster University, Hamilton, Ont.; Division of Urology, Department of Surgery (Wallis), University of Toronto; Division of Urology, Department of Surgery (Wallis), Mount Sinai Hospital; Department of Surgical Oncology (Wallis), University Health Network, Toronto, Ont.

**Contributors:** All authors substantially contributed to the conception and design of the work. All authors drafted and reviewed the manuscript, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Aly-Khan Lalani and Anand Swaminath share equal senior author contribution.



**Correspondence to:** Anand Swaminath, swaminath@HHSC.CA; and Aly-Khan Lalani, lalania@hhsc.ca