Practice-changing publications: Kidney cancer

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Introduction

The management of patients with kidney cancers has evolved tremendously in recent years. This includes improved counselling and diagnostic techniques for patients with small renal masses (SRMs), improvements in surgical technique for patients with localized disease, and dramatic changes to the approach and therapies used in patients with metastatic disease. This article reviews several recent, noteworthy publications relevant for physicians caring for patients with kidney cancer.

Counselling patients with SRMs

Paper: Shared decision-making for the management of small renal masses — development and acceptability testing of a novel patient decision aid

This Canadian group of investigators created a decision aid for patients with a SRM.[1] They followed international standards for creating the tool and tested it with patients and urologists, with almost all respondents reporting the aid facilitated management decisions. The aid reviews treatment choices, including surveillance, surgery, and ablation. It summarizes each treatment's respective benefits and risks using simple language and figures to illustrate differences. The purpose of a decision aid is to improve patient understanding of their diagnosis, ensure all patients are exposed to all treatment options, and most importantly, improve satisfaction with care. This tool was endorsed by Kidney Cancer Canada and is freely available in English and French on the KCC website (*https://www.kidneycancercanada.ca/*).

Renal hypothermia during partial nephrectomy

Paper: Hypothermia during partial nephrectomy for patients with renal tumors: A randomized controlled trial

This Canadian Institutes of Health Research-funded Canadian, multicenter, randomized controlled trial, led by Drs. Rodney Breau and Ilias Cagiannos, enrolled over 180 patients and evaluated if renal hypothermia improved renal function after open partial nephrectomy compared to warm ischemia.[2] For decades, surgeons have routinely applied ice slush around the kidney during open partial nephrectomy to reduce ischemic damage. Evidence supporting routine use of ice slush was predominantly from animal models or indirect from the transplant literature. This trial challenged existing dogma and rigorously evaluated renal function before and after surgery using nuclear medicine renal scans. One year after surgery, authors found no difference in renal function for patients receiving renal hypothermia compared to those receiving no hypothermia. As a result of this trial, the standard of care has changed, and surgeons can confidently exclude the application of ice slush around the kidney during vascular clamping in open partial nephrectomy.

Adjuvant therapy for RCC

Paper: Adjuvant pembrolizumab after nephrectomy in renal cell carcinoma

The Keynote-564 study evaluated if adjuvant pembrolizumab improved outcomes after surgery for patients with clear-cell renal cell carcinoma (RCC) at high-risk of recurrence. The trial randomized 994 patients with high-risk features after surgery to receive adjuvant pembrolizumab or placebo every three weeks for one year.[3] High-risk features included any of stage T2 grade 4 or sarcomatoid differentiation, ≥T3, N1, or M1 with no evidence of remaining disease after surgery. At

two years median followup, the trial reported an improvement in disease-free survival (assessed by investigators) in the pembrolizumab group compared to placebo (77% vs. 68%). Adjuvant pembrolizumab was generally well-tolerated, however, more patients experienced grade 3 or higher adverse events in the pembrolizumab group (32% vs. 18%). At the time of publication, no significant differences were seen in overall survival (OS). This is not surprising, as the followup time remains relatively short, with the median OS not met in either group.

Overall, this landmark trial provides hope for improved outcomes in high-risk patients. However, until OS outcomes are reported, the question of whether adjuvant therapy is superior to salvage therapy for high-risk patients remains.[4] It is possible similar long-term outcomes could be achieved with salvage therapy provided to patients with a recurrence, sparing some patients who are cured with surgery one year of unnecessary therapy. Appropriate patient selection for adjuvant therapy will be paramount.

Cytoreductive nephrectomy

Paper: Sunitinib alone or after nephrectomy for patients with metastatic renal cell carcinoma: Is there still a role for cytoreductive nephrectomy?

An update of the CARMENA trial was published examining if cytoreductive nephrectomy was beneficial in any patient subgroups.[5] CARMENA was a randomized trial that enrolled 450 patients between 2009 and 2017. It previously reported no benefit of cytoreductive nephrectomy in addition to sunitinib compared to sunitinib alone in patients with metastatic RCC. In this updated analysis, the impact of cytoreductive nephrectomy on OS was reported for patient groups stratified by the International Metastatic RCC Database Consortium (IMDC) criteria (favorable, intermediate, poor).[6] The authors found that most patients do not benefit from cytoreductive nephrectomy. Patients with IMDC intermediate-risk (score 1) had a non-statistically significant benefit in OS (31 vs. 25 months at data cut) from the addition of cytoreductive nephrectomy to sunitinib. This study confirms that upfront systemic therapy is the standard of care for metastatic RCC.

Systemic therapy for renal masses with von Hippel-Lindau mutation

Paper: Belzutifan for renal cell carcinoma in von Hippel-Lindau disease

Patients with von Hippel- Lindau (VHL) mutation may develop multiple renal tumors over their lifetime. VHL inactivation results in accumulation of HIF-2alpha, which in turn drives tumor growth. Patients may develop clear-cell RCCs, pancreatic neuroendocrine tumors, and central nervous system and retinal hemangioblastomas. Belzutifan is a selective HIF-2alpha inhibitor with anti-tumor activity.[7] This prospective, phase 2 study gave 61 VHL patients belzutifan 120 mg with a primary endpoint of objective response rate (ORR). The ORR was 49.2%, with 91.8% of patients (56/61) having a decrease in the size of their VHL-related tumors. Median time to response was 8.2 months. Progression-free survival (PFS) was 96.5% at 24 months. Grade 3 adverse events occurred in 32.8% (20/61) of patients, including anemia, fatigue, dyspnea, myalgia, and hypertension, and there were no grade 4–5 toxicities. After belzutifan initiation, only 3/61 patients required an anti-tumor procedure for a VHL-related neoplasm. Overall, belzutifan demonstrated durable efficacy in VHL-related RCC with a favorable safety profile.

Selection of first-line therapy for metastatic RCC

Papers: (1) Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma; (2) Pembrolizumab plus axitinib vs. sunitinib for advanced renal cell carcinoma; (3) Nivolumab plus cabozantinib vs. sunitinib for advanced renal cell carcinoma; (4) Nivolumab plus ipilimumab vs. sunitinib for first-line treatment of advanced renal cell carcinoma: Extended 4-year followup of the phase 3 CheckMate 214 trial

These four landmark papers form the new foundation for the first-line treatment of metastatic kidney cancer.[8-11] For IMDC favorable-risk disease, current standards are immunotherapy + tyrosine kinase inhibitor (IO-TKI) with pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib, or nivolumab plus cabozantinib. For IMDC intermediate-risk or poor-risk disease, options are the same, with a fourth option of IO-IO with nivolumab plus ipilimumab.

How to choose first-line therapy from these four new standard options continues to challenge clinicians. The choice is an individualized decision for clinicians and patients. IO-TKI are indicated for all IMDC risk groups, whereas IO-IO are indicated for intermediate/poor IMDC risk groups. Those patients who are symptomatic or have significant tumor burden may benefit more from the initiation of IO-TKI because TKIs may reduce tumor burden more rapidly, reflected in the high ORR and long PFS. For durable, long-term OS advantages, IO-IO has demonstrated more than four-year followup durable responses, including complete response (CR) in over 10%. Of note, at shorter followup compared to IO-IO, the IO-TKI have CRs of 8% for cabo-nivo, 9% for axi-pembro, and 16 % for len-pembro.

Future directions include biomarker research to personalize the optimal patient treatment. A summary of these landmark studies can be found in the KCRNC consensus of the management of advanced kidney cancer.[12] *(Editor's Note: Click here to view the consensus statement)*.

Competing interests: Dr. Lavallée has been an advisory board member for Astellas, Bayer, Ferring, Janssen, Knight, and Sanofi. Dr. Kapoor has been an advisory board member for Abbvie, Astellas, AstraZeneca, BMS, Eisai, Ipsen, Janssen, and Merck; a speakers' bureau member for Eisai, Ipsen, and Merck; holds investments in Point Biopharma and Verity Pharmaceuticals; and has participated in clinical trials supported by Eisai, Janssen, and Merck.

References

1. McAlpine K, Breau RH, Stacey D, et al. Shared decision-making for the management of small renal masses – development and acceptability testing of a novel patient decision aid. *Can Urol Assoc J* 2020;14:385-91. https://doi.org/10.5489/cuaj.6575
2. Breau RH, Fergusson DA, Knoll G, et al. Hypothermia during partial nephrectomy for patients with renal tumors: A randomized controlled trial. *J Urol* 2021;205:1303-9. https://doi.org/10.1097/JU.0000000000001517
3. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal cell carcinoma. *N Engl J Med* 2021;385:683-94. https://doi.org/10.1056/NEJMoa2106391
4. McAlpine K, Lavallée LT, Breau RH. Evidence-based urology: Surrogate endpoints – *Con. Eur Urol Focus* 2021;7:1219-21. https://doi.org/10.1016/j.euf.2021.10.008
5. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy for patients with metastatic renal cell carcinoma: Is there still a role for cytoreductive nephrectomy? [Formula presented]. *Eur Urol* 2021;80:417-24. https://doi.org/10.1016/j.eururo.2021.06.009
6. 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. https://doi.org/10.1200/JCO.2008.21.4809
7. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Engl J Med* 2021;385:2036-46. https://doi.org/10.1056/NEJMoa2103425
8. Motzer R, Alekseev B, Rha S-Y, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021;384:1289-1300. https://doi.org/10.1056/NEJMoa2035716
9. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib vs. sunitinib for advanced renal cell carcinoma. *N Engl J Med* 2019;380:1116-27. https://doi.org/10.1056/NEJMoa1816714
10. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib vs. sunitinib for advanced renal cell carcinoma. *N Engl J Med* 2021;384:829-41. https://doi.org/10.1056/NEJMoa2026982
11. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: Extended 4-year followup of the phase 3 CheckMate 214 trial. *ESMO Open* 2020;5:e00107. https://doi.org/10.1136/esmoopen-2020-001079
12. 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. https://doi.org/10.5489/cuaj.7245

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