Renal Cancer Research Review™

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Abbreviations used in this issue:

CSS = cancer-specific survival; **DFS** = disease-free survival; **DSS** = disease-specific survival; **eGFR** = estimated glomerular filtration rate; **IROCK** = international radiosurgery oncology consortium for kidney; **KPS** = Karnofsky Performance Scale; **LND** = lymph node dissection; **mRCC** = metastatic renal cell carcinoma; **NSS** = nephron-sparing surgery; **NLR** = neutrophil-to-lymphocyte ratio; **OS** = overall survival; **PFS** = progression-free survival; **RCT** = randomised controlled trial; **RCC** = renal cell carcinoma; **SABR** = stereotactic ablative radiotherapy; **SEER** = Surveillance, Epidemiology, and End Results.

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Welcome to the first issue of Renal Cancer Research Review.

We lead this issue with a sub-group analysis of the ASSURE trial exploring retroperitoneal lymphadenectomy for high risk, nonmetastatic renal cell carcinoma. The group conclude there was no overall survival benefit for lymphadenectomy relative to no lymphadenectomy. Another study investigated survival outcomes for patients with localised upper tract urothelial carcinoma managed with non-definitive treatment. The authors reported median overall survival was significantly shorter in the non-surgical compared to the surgical cohort (1.9 vs 7.8 years respectively). A pooled analysis of SABR found it to be well tolerated and locally effective for treating patients who have primary renal cell carcinoma. SABR also had an acceptable impact on renal function.

A number of the articles included in this issue have a focus on immunotherapy. A phase III trial compared cabozantinib to everolimus in patients with advanced renal cell carcinoma following prior VEGF targeted therapy. Cabozantinib compared to everolimus improved progression-free survival, overall survival and objective response rate. The safety profile was also acceptable. An article reports the safety and efficacy results from the phase I CheckMate 016 study of nivolumab plus ipilimumab in metastatic renal cell carcinoma. The researchers concluded the combination therapy demonstrated antitumor activity with manageable safety and durable responses. In addition, the overall survival data was promising. The concluding paper presents the pooled results from two expansion cohorts of the JAVELIN study. Avelumab showed antitumour activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma. In addition the safety profile was manageable. The authors note avelumab has received accelerated US FDA approval in this setting.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

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Retroperitoneal lymphadenectomy for high risk, nonmetastatic renal cell carcinoma: An analysis of the ASSURE (ECOG-ACRIN 2805) adjuvant trial

Authors: Ristau BT, et al

Summary: The ASSURE trial randomised patients with fully resected, high risk, nonmetastatic renal cell carcinoma (RCC) to adjuvant sorafenib, sunitinib or placebo. Lymphadenectomy was performed for cN+ disease or at surgeon discretion. Of the 1,943 patients in ASSURE 701 (36.1%) underwent lymphadenectomy. The authors note a median of 3 lymph nodes were removed and the rate of pN+ disease in the lymphadenectomy group was 23.4%. They concluded there was no overall survival (OS) benefit for lymphadenectomy relative to no lymphadenectomy (HR 1.14, 95% CI 0.93-1.39, p = 0.20) and lymphadenectomy did not confer an increased risk of surgical complications (14.2% vs 13.4%, p = 0.63).

Comment: A previous randomised controlled trial (RCT, EORTC 30881) demonstrated no survival advantage for lymph node dissection (LND) in localised node negative RCC. The current study is a sub-group analysis of the ASSURE trial, where 36% (n=701/1943), underwent lymphadenectomy for non-metastatic RCC. This included cN+ and cN0 patients. Median node yield was 3 and 18% yielded >10 nodes. Of the pre-operative cN0 patients, only 30% had LND. LND was more likely to occur in those undergoing radical nephrectomy, open surgery and concomitant adrenalectomy.

Survival analyses showed no statistical association between LND and OS, over median follow up of 68 months. LND was associated with worse disease-free survival (DFS). Furthermore, survival analyses in node positive disease, who underwent lymph node dissection, was compared against the impact of adjuvant systemic therapies, (sorafenib or sunitinib), depending on the treatment arm within ASSURE. There was no difference in five year-OS in either the sunitinib or sorafenib arm v placebo. Therefore, the oncologic benefit of LND in high risk non-metastatic renal cell cancer remains unproven and unclear.

Reference: J Urol 2018 Jan;199(1):53-59

Abstract

Survival outcomes for patients with localised upper tract urothelial carcinoma managed with non-definitive treatment

Authors: Syed JS, et al

Summary: The population-based cohort included 8304 individuals with a localised, histologically confirmed kidney/renal pelvis and ureteric urothelial carcinoma. The researchers found individuals who did not receive surgery (n=633, 7.6%) were significantly older than surgically managed patients (median age 81 vs 71 years, P < 0.001). Median OS was significantly shorter in the non-surgical compared to the surgical cohort (1.9 vs 7.8 years, P < 0.001). They also observed 3-year disease-specific survival (DSS) for patients without surgery was significantly lower compared to those with surgery (73.7% vs 92.4%, P < 0.001). In addition, 3-year DSS for patients with high-grade tumours was worse when compared to patients with low-grade tumours (65.1% vs 82.9%, P < 0.001).

Comment: The US Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients with localised histologically confirmed kidney, renal pelvis and ureteric urothelial carcinoma. A total of 8304 were identified, of whom 633 (7.6%), did not receive definitive therapy. The remaining 7671 were within a surgical cohort who underwent radical nephroureterectomy or segmental ureterectomy. Those managed non-definitively were older (median 81 years) and had smaller tumours (median 2.4cm). The median OS in the non-definitive cohort was significantly shorter than the surgical cohort (1.9 v 7.8 years). The three-year DSS for the non-definitive cohort was 74%, significantly lower than the surgery group (92%). The median OS for the non-definitive group with high-grade disease was significantly shorter, compared to those with low-grade disease (1.5 v 3.4 years). Significant predictors of cancer specific mortality included; male sex and high tumour grade.

Ultimately, the decision to operate or not depends on age, competing co-morbidities and tumour grade versus the risk of renal failure in the event of nephroureterectomy.

Reference: BJU Int 2018 Jan;121(1):124-129
Abstract

Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the international radiosurgery oncology consortium for kidney (IROCK)

Authors: Siva S, et al

Summary: Individual patient data sets were pooled from 9 international institutions to compare safety, efficacy, and survival between single-fraction (n=118) and multifraction (n=105) stereotactic ablative radiotherapy (SABR). The investigators concluded rates of local control, cancer-specific survival (CSS), and PFS were 97.8%, 95.7%, and 77.4%, respectively, at 2 years; and they were 97.8%, 91.9%, and 65.4%, respectively, at 4 years. Tumours with a larger maximum dimension and the receipt of multifraction SABR were associated with poorer PFS and poorer CSS. SABR was well tolerated with an acceptable impact on renal function.

Comment: This multicentre study assesses SABR as an emerging technique for localised primary renal cell carcinoma. The precise delivery of radiotherapy to a renal cell carcinoma is either given in a single fraction or is multi-fractionated. A single dose is 25Gy, whereas the multi-fraction dose is 40Gy in 2 to 10 fractions. Of 223 patients, 118 were in the single-fraction arm and 105 were in the multifraction arm. The main histologic sub-type was clear cell. The mean tumour size was 43mm. The median patient age is 72 years. Local control at 2 and 4 years was 98%. CSS, OS, PFS were 96%, 82% and 77% at 2 years and 92%, 71%, 65% at 4 years. There were 3 local recurrences (1.4%) and 16 distant recurrences (7%). Grade 1-2 toxicity was 35-38% and high grade toxicity was uncommon. Preservation of renal function was good.

This initial data suggests it may be a reasonable approach in patients who would otherwise be considered for the ablative therapies, including RFA and cryotherapy.

Reference: Cancer 2018 Mar 1;124(5):934-942
Abstract

Cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor targeted therapy: Clinical trial evidence and experience

Authors: Osanto S, et al

Summary: The phase III trial compared cabozantinib (60 mg once daily) to everolimus (10 mg once daily) in 658 patients with advanced RCC of whom 71% had received one prior and 29% had received at least two prior lines of VEGR-targeted therapy. Cabozantinib compared to everolimus improved PFS (7.4 months vs 3.9 months) and OS (21.4 months vs 16.5 months, respectively). The authors also noted objective response rate was higher in cabozantinib-treated patients, 17% versus 3%. The safety profile was acceptable.

Comment: Metastatic RCC is insensitive to chemotherapy and IL-2 was associated with poor response and toxicity. Alterations in the VHL tumour suppressor gene leads to increased levels of angiogenic factors, including VEGF. First line treatments include drugs that target receptors of VEGF. Such first line drugs include sunitinib, pazopanib, bevacizumab and temsirolimus. Once resistance to these first line agents developed, second line treatments included everolimus.

The METEOR trial is an RCT comparing the novel multi-TKI inhibitor cabozantinib versus everolimus. The patient cohort includes metastatic advanced RCC with or without bone metastases in whom first line targeted therapies had failed or their disease had progressed. Cabozantinib has better median-PFS over everolimus, (7.4 v. 3.9 months). OS is also improved. Adverse events occurred in 30% of either treatment arm.

Reference: Therapeutic Advances in Urology, Vol 10, Issue 3, pp. 109 – 123. First Published January 9, 2018
Abstract

Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: Subgroup analyses and updated overall survival results

Authors: Motzer RJ, et al

Summary: This sub-group analysis of the S-TRAC trial assessed DFS by baseline risk factors including staging, age, gender, ECOG, weight, neutrophil-to-lymphocyte ratio (NLR) and Fuhrman grade. The researchers reported of 615 patients, 97 and 122 in the sunitinib and placebo arms developed metastatic disease. The most common sites of distant recurrence were lung (40 and 49), lymph node (21 and 26), and liver (11 and 14), respectively. A benefit of adjuvant sunitinib over placebo was observed across subgroups, including: higher risk (T3, no or undetermined nodal involvement, Fuhrman grade ≥2, ECOG PS ≥1, T4 and/or nodal involvement), NLR ≤3, and Fuhrman grade 3/4. Median OS was not reached in either arm; 67 and 74 patients died in the sunitinib and placebo arms, respectively.

Comment: A DFS benefit with adjuvant sunitinib, over placebo, in locoregional RCC at high risk of recurrence, has been already demonstrated in the S-TRAC trial (n=615, randomised to sunitinib n=309 v. placebo n=306). Adjuvant sunitinib improved DFS over placebo; 6.8 v. 5.6 yr. At 5 years, the DFS gain was 8% in favour of sunitinib. 71% tolerated sunitinib for 8 months (50mg/day; 4 weeks on/2 weeks off) and 56% completed the full year of treatment. Within the sunitinib arm 28% discontinued due to adverse events such as hand-foot syndrome, neutropenia, hypertension, thrombocytopenia.

Distant recurrence developed in 31% within the sunitinib and 40% within the placebo arms. Almost all subgroups, including those with higher recurrence risk (T3, no or undetermined nodal involvement, Fuhrman 2,3,4, ECOG PS >0, T4 and/or nodal involvement), experienced improved DFS with adjuvant sunitinib. OS data was not mature.

Reference: Eur Urol 2018 Jan;73(1):62-68
Abstract

References: 1. OPDIVO® (nivolumab) Product Information (http://www.medicines.org.au/files/bqpopdiv.pdf). **2.** Motzer *et al. N Engl J Med* 2015; 373:1803–13. **3.** Sharma P *et al.* Three-year efficacy and safety update from the phase III CheckMate 025 study of nivolumab versus everolimus in patients with advanced renal cell carcinoma. Poster presentation at the International Kidney Cancer Symposium; November 3–4, 2017; Miami, FL, USA.

Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The checkmate 016 study

Authors: Hammers HJ, et al

Summary: This article presents the safety and efficacy results from the phase I CheckMate 016 study of nivolumab plus ipilimumab in metastatic renal cell carcinoma (mRCC). The researchers concluded the combination therapy demonstrated antitumor activity with manageable safety and durable responses. In addition, the OS data was promising.

Comment: Nivolumab is an Ig G4 PD-1 inhibitor antibody. Its superiority over everolimus has been demonstrated in mRCC. Ipilimumab is a CTLA-4 inhibitor antibody. Combination checkpoint inhibitors have shown benefit over monotherapy in other tumours. Dosing combinations were; N3 I1 (n=47); nivolumab 3mg/kg + ipilimumab 1mg/kg, or N1 I3 (n=47); nivolumab 1mg/kg + ipilimumab 3mg/kg, or N3 I3 (n=6); nivolumab 3mg/kg + ipilimumab 3mg/kg. Patients were advanced RCC or mRCC, clear cell, KPS (KPS) >80%, treatment naive or had received prior systemic therapy. Median follow up was 22.3 months. Grade 3 or 4 adverse events were 38%, and 61%, and discontinuation was 10.6%, and 27.7%, in N3 I1, and N1 I3 respectively. N3 I1 arm had fewer adverse events, and less discontinuation rates. Objective response rate was 40.4%. Responses were rapid and sustained. 50% experienced a reduction in tumour burden of 30%. The PFS was 55% at 6 months to 40%, 29%, 19% at 12, 18, 24 months. Combination therapy is beneficial and safe over monotherapy in mRCC, where prior systemic therapy had failed.

Reference: J Clin Oncol 2017 Dec 1;35(34):3851-3858
Abstract

Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: A double-blind, clinically-integrated, randomized trial

Authors: Spaliviero M, et al

Summary: This group assessed the effect on renal function outcomes in 199 patients undergoing nephron-sparing surgery (NSS) randomised to receive mannitol (12.5g) or placebo intravenously within 30min prior to renal vascular clamping. They found there was no significant difference in estimated glomerular filtration rate (eGFR) between the two groups at 6 months following surgery. The group noted study limitations included evaluation of a single mannitol dose and patients all had excellent preoperative renal function.

Comment: In this RCT patients were randomly allocated to mannitol (n=101) or normal saline hydration/placebo (n=98). Mannitol 12.5mg versus IV fluid were given within 30 minutes of arterial clamping, with the renal vein un-clamped in both arms. The study outcome was eGFR at 6 months post surgery. Both groups had similar baseline characteristics. There was no difference in eGFR at 6 months post-operative between the groups. There was no difference whether it was open versus minimally invasive surgery, and there was no interaction between mannitol and clamp time.

Despite theoretical potential advantages of mannitol reducing ischaemic injury, there was no statistically significant difference in eGFR at 6 months after NSS. The routine use of mannitol in NSS is not supported by this RCT data.

Reference: Eur Urol 2018 Jan;73(1):53-59
Abstract

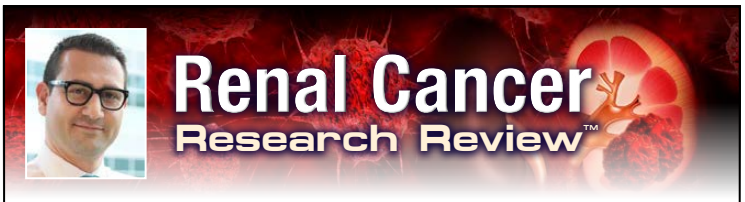
Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial

Authors: Patel MR, et al

Summary: The objective of this study was to assess the safety profile in patients (both post-platinum therapy and cisplatin-naive) treated with avelumab and to assess antitumour activity. Patients (n=249) with histologically or cytologically confirmed locally advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy were enrolled from 80 centres. Patients received avelumab treatment for a median of 12 weeks with median follow up of 9·9 months. The team concluded avelumab showed antitumour activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma with a manageable safety profile.

Comment: Avelumab is a monoclonal anti-PD-L1 antibody. Cisplatin-based regimens provide a median OS of 15 months in metastatic urothelial carcinoma. Eligible patients had locally advanced metastatic urothelial carcinoma and had progressed on or were ineligible for platinum-based chemotherapy. Tumour burden was assessed by CT and/or MRI. 249 patients were eligible. Median age was 68, most having visceral non-nodal disease. Median treatment was 12 weeks, and median follow-up was 10 months. 76% discontinued due to progression of disease. In 161 with at least 6 months of avelumab treatment, the "best" objective response rate was 17%. The disease control rate was 40%. 22% had a tumour burden reduction of 30%. Median time to response was 11 weeks. 23% were progression-free at 24 weeks. Treatment toxicity was safe and manageable. These results led to accelerated US FDA approval.

Reference: Lancet Oncol 2018 Jan;19(1):51-64
Abstract



Independent commentary by Richard Laurence Haddad
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