Welcome to the June edition. Many of the studies and reports in this month’s review are reflecting on quality improvements in our care, addressing the questions that our patients and their cancers are asking us. For example, should I take VEGFR TKI tablets to shrink my cancer before surgery? Will immunotherapy treatment work if the cancer has spread to my brain? If immuno-therapy treatment works and my cancer is controlled, do I still have to keep taking the treatment long-term? Which patients should take adjuvant treatment after surgery? Do all older people with kidney masses need treatment? In which hospitals should kidney cancer surgery be performed? Can biopsies safely be performed to help patients understand if a kidney mass is a cancer or a benign lesion? Can radiotherapy help manage my kidney cancer, and does radiotherapy have effects beyond the radiation field? With so many new treatment ideas for people with kidney cancer these questions are increasingly important so that we can bring the best quality treatment to everyone. Thank you again for your interest.

Kind Regards,
Dr Craig Gedye
Craig.Gedye@researchreview.com.au

Evaluation of axitinib to downstage cT2a renal tumours and allow partial nephrectomy: A phase II study

Authors: Lebacle C, et al

Summary: The AXIPAN study, a prospective multicentre trial, enrolled 18 patients with clear cell renal cell carcinoma (RCC) considered not suitable for partial nephrectomy. Axitinib was administered for 2-6 months before surgery, depending on the radiological response. The authors reported after axitinib treatment, 16 tumours decreased in diameter, with a median size reduction of 17% (64.0 vs 76.5 mm; P < 0.001). In addition, 12 patients achieved the primary outcome of receiving partial nephrectomy for a tumour <7 cm in size after neoadjuvant axitinib. Sixteen patients underwent partial nephrectomy. They noted axitinib was well tolerated.

Comment: Can systemic therapy improve outcomes for people with locally advanced kidney cancers? In many other cancers, neoadjuvant therapy can downstage, even eliminate the primary tumour (pT0) improving surgical and patient outcomes. In RCC a number of studies are complete, or underway, exploring this idea using VEGFR TKI and early trials are recruiting with immune checkpoint inhibitors. This French study examines the use of axitinib to downstage large primary RCCs in an effort to allow for partial nephrectomy. Axitinib was well tolerated, treatment was feasible and a modest decrease in size of tumours was seen in some patients, but a third of patients developed metastatic disease soon after surgery and partial nephrectomy was complicated in many patients. This concept remains experimental and cannot be recommended outside clinical trials except in high-volume centres with highly selected and highly informed patients.

Reference: BJU Int 2019 May;123(5):804-810

Abstract

Stereotactic radiotherapy as a treatment option for renal tumors in the solitary kidney: A multicenter analysis from the IROCK

Authors: Corea RJM, et al

Summary: This study pooled patient data from nine International Radiosurgery Oncology Consortium for Kidney (IROCK) institutions in Germany, Australia, USA, Canada and Japan. The cohort included 81 patients with a solitary kidney who underwent stereotactic ablative radiotherapy with median follow-up of 2.6 years. Median tumour diameter was 3.7 cm and 37% of tumours were 4 cm or greater. The univariate cohort (n=138) had larger tumours and a lower baseline estimated glomerular filtration rate. The researchers reported after stereotactic ablative radiotherapy in the solitary kidney cohort the mean estimated glomerular filtration rate decrease was 5.8 ml per minute. They noted no patient with a solitary kidney required dialysis. After stereotactic ablative radiotherapy a tumour size of 4 cm or greater was associated with an estimated glomerular filtration rate decrease of 15 ml per minute or greater. At 2 years the rates of local control, progression-free, cancer specific and overall survival in the solitary cohort were 98.0%, 77.5%, 98.2% and 81.5%, respectively. The researchers also found there was no significant difference in renal function or oncologic outcomes between the cohorts.

Comment: What happens if you develop kidney cancer but you only have one kidney and your surgeon can’t operate? Focal ablative therapies such as cryoablation and radiofrequency ablation can be employed but like partial nephrectomy they risk loss of adjacent nephrons and renal function. Stereotactic radiotherapy can be employed in this setting, and this report from the IROCK registry suggests that this may be safe and effective. While only 37% of patients had tumours that absolutely mandated therapy (>4cm), local control and cancer-specific survival were excellent at 2 years, with modest loss of renal function and overall survival determined by the comorbidities that this population of people often suffer.

Reference: J Urol 2019 Jun;201(6):1097-1104

Abstract
Selecting patients with small renal masses for active surveillance: A domain based score from a prospective cohort study

Authors: Solmehin AE, et al

Summary: The group analysed data from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry to compare active surveillance and primary intervention. Of the study cohort of 751 patients 55% elected active surveillance and 45% elected primary intervention. The authors found the domains for greatest discrimination for active surveillance were age, the Charlton comorbidity index, tumour diameter and the SF-12 Physical Component Score. These domains made up the DISSRM score and the authors demonstrated a higher DISSRM score was associated with worse overall survival.

Comment: Does everyone need an operation when they are discovered to have a small renal mass? The DISSRM Registry was established to answer this precise question, and this latest report from the registry continues to support the concept that patient characteristics can be prospectively used to advise people of their competing risks for treatment or active surveillance. The most discriminating features included the patient’s age, a validated measure of their other medical problems (the Charlton comorbidity index), the size of the kidney mass, and a brief checklist of overall health and well-being (the SF-12 Physical Component Score), suggesting which people might be offered active surveillance. The composite overall (DISSRM) score was strongly predictive of prognosis, and in real-world settings may be useful to help advise elderly people with small renal masses whether a biopsy or active surveillance would be useful.

Reference: J Urol 2019 May;201(5):886-892

Abstract

Metabolomics informs common patterns of molecular dysfunction across histologies of renal cell carcinoma

Authors: DiNatale RG, et al

Summary: This paper reviews the discoveries made in RCC with metabolomics studies. The authors focus on five concepts; metabolic phenotypes unique to certain genotypes, mitochondrial dysfunction, the oxidative stress response, epigenetics and therapy targeted to metabolism.

Comment: This review article is perhaps only for hard-core kidney cancer nerds, but nicely illustrates one of the key differences between RCC and other types of malignancies; RCCs are often found to have very few coding mutations in their DNA, and few DNA rearrangements, but more prominently have mutations in genes influencing cellular metabolism. Hence the rather extraordinary phenotypes of RCC, with clear cells full of lipids or glycogen, or mutations in proteins that are critical to the Krebs cycle (remember how you complained about having to learn that in your undergraduate degree?). These features help us understand many of the exceptionalities of RCC — active surveillance of 3cm primary masses (whereas 3mm melanoma are likely fatal), watchful waiting in metastatic disease, the protective effect of high BMI on prognosis. And more interestingly the authors propose a number of ideas that may improve kidney cancer treatment from these insights. Metabolism aficionados will enjoy.

Reference: Cancer Cytopathol 2019 May 22

Abstract

Abscopal effects in radio-immunotherapy-response analysis of metastatic cancer patients with progressive disease under anti-pd-1 immune checkpoint inhibition

Authors: Tronmer M, et al

Summary: The aim of this study was to evaluate abscopal effect (regression of non-irradiated lesions) during immune checkpoint inhibition (ICI) therapy and irradiation. The study cohort included metastatic cancer patients who started radiation therapy within 1 month after the first or last application of pembrolizumab or nivolumab and had at least one metastasis outside the irradiation field. Of the 168 patients screened 75% (126) received ICI and radiation therapy. Fifty-three percent (67/126) were treated simultaneously, and 24 of these (36%) were eligible for lesion analysis. The authors concluded abscopal effect was observed in 29% (7/24). They also highlighted strict inclusion criteria were applied to distinguish the effects of abscopal effect from the systemic effect of ICI.

Comment: Does the Loch Ness Monster exist? What’s in Area 51? Is there intelligent life in other solar systems? Does anyone understand why Australia is still in the Eurovision Song Contest? Life is full of mysteries. One of these is whether the abscopal effect is real, or just an observation bias fuelled by the hopes and dreams of overworked radiation oncologists. From Wikipedia ‘The abscopal effect is a hypothesis in the treatment of metastatic cancer whereby shrinkage of untreated tumours occurs concurrently with shrinkage of tumours within the scope of the localised treatment’. R.H. Mole proposed the term “abscopal” (“ab” - away from, ‘scopus’ - target) in 1953 to refer to effects of ionising radiation “at a distance from the irradiated volume but within the same organism.”

In the checkpoint immunotherapy era this leads to the attractive idea that we can improve outcomes by zapping a few bits of a patient suffering metastatic cancer taking an ICI. Prospective trials are underway but this retrospective case series continues to give hints that maybe there is something to this idea. In people taking ICI who then took radiation treatment at least a month after starting the ICI treatment, almost a third experienced a treatment response in metastases outside the radiation field. Whilst the background activity of ICI is around this magnitude, the radiation being needed after systemic treatment was started implies that patients had progressive disease at the time of radiation. We await the results of prospective trials and the SETI program with great interest.

Reference: Front Pharmacol 2019 May 14;10:511

Abstract

Needle track seeding in renal mass biopsies

Authors: Renshaw AA, et al

Summary: This literature review and analysis found needle track seeding in renal mass biopsy has been reported 16 times. The authors note it occurs almost exclusively among patients with papillary renal cell carcinoma and the incidence is associated with multiple punctures of the mass, the use of large core biopsy needles of ≥20 gauge and lack of a coaxial sheath. A renal mass biopsy would therefore seem a reasonable choice in people with renal masses without an immediate indication for nephrectomy (i.e. >4 cm large masses, family history, metastatic disease, the protective effect of high BMI on prognosis. And more interestingly the authors propose a number of ideas that may improve kidney cancer treatment from these insights. Metabolism aficionados will enjoy.


Abstract

Independent commentary by Dr Craig Gedyne BSc(Hons) MBCHB FRACP PhD

Dr Gedyne is a physician/scientist, dual trained as a medical oncologist, clinical trialist and basic science researcher. He works for patients with melanoma, brain, kidney, prostate, testis, and bladder cancer at the Calvary Mater Newcastle, and is the Clinical Research Director at the NSW Statewide Biobank. He chairs the Renal Cancer Subcommittee for ANZUP Cancer Trials Group, and is the coordinating principal investigator for the KeyPAD and UNISON trials. He undertakes translational and basic cancer research at the Hunter Medical Research Institute, University of Newcastle. Dr Gedyne’s research focus is on cancer heterogeneity; why treatments work for some patients but not others. This challenging research spans the translational spectrum from patient experience to basic science.
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30-month follow-up: mOS not reached vs 26.6 months with sunitinib (HR 0.66; p<0.0001); investigator-assessed CR 11% vs 1% with sunitinib (p-value not reported) in intermediate/poor-risk, treatment-naive advanced RCC

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PBS INFORMATION: OPDIVO monotherapy – Authority required (STREAMLINED) for the treatment of patients with advanced (Stage IV) clear cell variant renal cell carcinoma. OPDIVO in combination with YERVOY – Authority required (STREAMLINED) for the treatment of patients with intermediate/poor-risk, previously untreated advanced clear cell variant renal cell carcinoma. Refer to PBS Schedule for full authority information.

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OS = overall survival; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma.

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A phase II trial of intermittent nivolumab in patients with metastatic renal cell carcinoma (mRCC) who have received prior anti-angiogenic therapy

Authors: Ornstein MC, et al

Summary: The study cohort included mRCC patients who were previously treated with at least one antiangiogenic therapy. Patients were treated with nivolumab for twelve weeks. Patients with progressive disease by RECIST assessment were removed from the trial. Patients who did not initially achieve ≥10% reduction in tumour burden continued nivolumab, while patients with <10% tumour burden reduction entered a treatment-free observation phase with re-imaging every 12 weeks. Nivolumab was re-started in patients with ≥10% tumour burden increase and again held with tumour burden reduction <10%. The investigators continued intermittent dosing until progressive disease by RECIST assessment while on nivolumab. The 14 patients enrolled had a prior nephrectomy and 12 were intermediate-risk by IMDC criteria. Five patients (36%) met the criteria for the intermittent phase of the trial (median tumour burden decrease 46%) and only one patient restarted therapy (median follow-up of 48 weeks). The four remaining patients had a sustained response for a median of 34 weeks off therapy. No patients developed progressive disease by RECIST while off therapy.

Comment: Checkpoint immunotherapy fails many people with different cancers, but when it does work it can be dramatic, durable and tolerable. One of the many unanswered questions in treating people with immunotherapy is how long to treat if you are winning? Should you treat for a fixed period of time that was defined arbitrarily in clinical trials? Or should one take a more patient-centred approach? Given that many people who must stop taking checkpoint immunotherapy for toxicity continue to experience benefit from the treatment, it is a reasonable hypothesis that in patients experiencing a substantial benefit from treatment that one could pause infusions and retreat if needed. The CCTG trial STOPGAP is asking this question prospectively in a randomised phase III study in melanoma; this report from the Cleveland Clinic hints that this may be feasible in renal cell carcinoma too. In fact, Ornstein, Rini and colleagues stopped therapy in people experiencing minor responses from therapy (10%+) rather than the conventional trigger point of maximal tumour response being used in STOPGAP. In a very small number of patients 80% of people who stopped treatment remained well without needing further therapy. Prospective randomised studies are needed.


Impact of hospital nephrectomy volume on intermediate to long-term survival in renal cell carcinoma

Authors: Hsu RCJ, et al

Summary: RCC patients (n=12,912) treated with nephrectomy between 2000 and 2010 were identified from an English national data repository. Patients with nodal or metastatic disease were excluded. Hospitals were categorised based on annual cases 2010 were identified from an English national data repository. Patients with nodal or metastatic disease were excluded. Hospitals were categorised based on annual cases. The authors showed most models only marginally outperformed standard staging. Furthermore, all models demonstrated statistically significant variability in their predictive ability over time and were most useful within the first 2 years after diagnosis.

Comment: This study on the relationship between hospital volume and patient outcome comes from the NHS in this report. Almost 13,000 patients were identified from an English national data repository. Patients with nodal or metastatic disease were excluded. Hospitals were categorised based on annual cases. The authors showed most models only marginally outperformed standard staging. Furthermore, all models demonstrated statistically significant variability in their predictive ability over time and were most useful within the first 2 years after diagnosis.

Reference: BJU Int 2019 Jun 17

Safety and efficacy of nivolumab in brain metastases from renal cell carcinoma: Results of the GETUG-AFU 26 NIVOREN multicenter phase II study

Authors: Flippot R, et al

Summary: The study assessed nivolumab in patients with metastatic clear cell RCC who failed VEGFR-directed therapies. The cohort comprised of 39 patients with previously untreated brain metastases, and 34 patients whose brain metastases underwent prior therapy. Intracranial response rate was 12% in the untreated brain metastases cohort; no objective response was reported in patients with brain lesions that were multiple or larger than 1 cm. Median intracranial progression-free survival was 2.7 months in the untreated brain metastases cohort and 4.8 months in the pre-treated cohort, with adjusted hazard ratio of 2.0. Overall survival rate at 12 months was 67% in the untreated brain metastases cohort and 59% in the pre-treated cohort. Most patients in the untreated brain metastases cohort (72%) needed subsequent focal brain therapy.

Comment: Checkpoint immunotherapy fails many people with different cancers, but when it does work it can be dramatic, durable and tolerable. One of the many unanswered questions in treating people with immunotherapy is how long to treat if you are winning? Should you treat for a fixed period of time that was defined arbitrarily in clinical trials? Or should one take a more patient-centred approach? Given that many people who must stop taking checkpoint immunotherapy for toxicity continue to experience benefit from the treatment, it is a reasonable hypothesis that in patients experiencing a substantial benefit from treatment that one could pause infusions and retreat if needed. The CCTG trial STOPGAP is asking this question prospectively in a randomised phase III study in melanoma; this report from the Cleveland Clinic hints that this may be feasible in renal cell carcinoma too. In fact, Ornstein, Rini and colleagues stopped therapy in people experiencing minor responses from therapy (10%+) rather than the conventional trigger point of maximal tumour response being used in STOPGAP. In a very small number of patients 80% of people who stopped treatment remained well without needing further therapy. Prospective randomised studies are needed.

Reference: J Clin Oncol 2019 Jun 13;JCO1802218

Predicting renal cancer recurrence: Defining limitations of existing prognostic models with prospective trial-based validation

Authors: Correa AF, et al

Summary: The authors used prospective data from the ASSURE trial to validate eight currently used recurrence prediction models for RCC along with the TNM staging system. The ASSURE cohort includes 47 patients with the cancers were high-grade or locally advanced. The authors showed most models only marginally outperformed standard staging. Furthermore, all models demonstrated statistically significant variability in their predictive ability over time and were most useful within the first 2 years after diagnosis.

Comment: The study cohort included mRCC patients who were previously treated with at least one antiangiogenic therapy. Patients were treated with nivolumab for twelve weeks. Patients with progressive disease by RECIST assessment were removed from the trial. Patients who did not initially achieve ≥10% reduction in tumour burden continued nivolumab, while patients with <10% tumour burden reduction entered a treatment-free observation phase with re-imaging every 12 weeks. Nivolumab was re-started in patients with ≥10% tumour burden increase and again held with tumour burden reduction <10%. The investigators continued intermittent dosing until progressive disease by RECIST assessment while on nivolumab. The 14 patients enrolled had a prior nephrectomy and 12 were intermediate-risk by IMDC criteria. Five patients (36%) met the criteria for the intermittent phase of the trial (median tumour burden decrease 46%) and only one patient restarted therapy (median follow-up of 48 weeks). The four remaining patients had a sustained response for a median of 34 weeks off therapy. No patients developed progressive disease by RECIST while off therapy.

Reference: J Clin Oncol 2019 Jun 19;JCO1900107

Abstract

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