Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

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The blood metabolome of incident kidney cancer: A case-control study nested within the MetKid consortium. Guida F et al. PLoS Med. 2021 Sep 20;18(9):e1003786.

Methods and findings: We assessed the association between circulating levels of 1,416 metabolites and incident kidney cancer using pre-diagnostic blood samples from up to 1,305 kidney cancer case-control pairs from 5 prospective cohort studies. Cases were diagnosed on average 8 years after blood collection. We found 25 metabolites robustly associated with kidney cancer risk. In particular, 14 glycerophospholipids (GPLs) were inversely associated with risk, including 8 phosphatidylcholines (PCs) and 2 plasmalogens. The PC with the strongest association was PC ae C34:3 with an odds ratio (OR) for 1 standard deviation (SD) increment of 0.75 (95% confidence interval [CI]: 0.68 to 0.83, p = 2.6 × 10-8). In contrast, 4 amino acids, including glutamate (OR for 1 SD = 1.39, 95% CI: 1.20 to 1.60, p = 1.6 × 10-5), were positively associated with risk. Adjusting for BMI partly attenuated the risk association for some-but not all-metabolites, whereas other known risk factors of kidney cancer, such as smoking and alcohol consumption, had minimal impact on the observed associations. A mendelian randomisation (MR) analysis of the influence of BMI on the blood metabolome highlighted that some metabolites associated with kidney cancer risk are influenced by BMI. Specifically, elevated BMI appeared to decrease levels of several GPLs that were also found inversely associated with kidney cancer risk (e.g., -0.17 SD change [ßBMI] in 1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2) levels per SD change in BMI, p = 3.4 × 10-5). BMI was also associated with increased levels of glutamate (ßBMI: 0.12, p = 1.5 × 10-3). While our results were robust across the participating studies, they were limited to study participants of European descent, and it will, therefore, be important to evaluate if our findings can be generalised to populations with different genetic backgrounds.

Conclusions: This study suggests a potentially important role of the blood metabolome in kidney cancer aetiology by highlighting a wide range of metabolites associated with the risk of developing kidney cancer and the extent to which changes in levels of these metabolites are driven by BMI-the principal modifiable risk factor of kidney cancer.

Kidney cancer mortality disparities among Hispanics in the US Paulo S Pinheiro 1, Heidy N Medina et al. Cancer Epidemiol. 2021 Jun;72:101938. PMID: 33862414

Methods: Introduction: Kidney cancer incidence is increasing among Hispanics but rate differences by distinct group, such as Cuban, Puerto Rican, and Mexican have not been studied. To fill this knowledge gap, we use mortality data, reflecting fatal kidney cancers, to examine patterns by race-ethnicity, including detailed Hispanic groups, and correlate the mortality rates with each group's prevalence of known kidney cancer risk factors: smoking, obesity, hypertension, diabetes, and chronic kidney disease.

Methods: We used individual-level death data for California, Florida, and New York (2008-2018), and population prevalence data from the National Health Interview Surveys (2008-2018). Age-adjusted mortality rates (AAMRs) and regression-derived mortality rate ratios (MRRs) were computed. Pearson correlation analyses assessed the extent to which group-specific risk factor prevalence explained variability in observed AAMRs.

Results: US-born Mexican Americans and American Indians had the highest rates and MRRs compared to Whites: 1.44 (95 %CI: 1.35-1.53) and 1.51 (1.38-1.64) for Mexican American men and women, respectively, and 1.54 (95 %CI: 1.25-1.89) and 1.53 (95 %CI: 1.15-2.04) for American Indians. In contrast, non-Mexican Hispanics had lower rates than Whites. Among males, positive correlations between AAMRs and smoking, obesity, and chronic kidney disease prevalence by race-ethnicity were found.

Conclusion: Mexican Americans and American Indians are high-risk for fatal kidney cancer. Disparities are only partially attributable to higher smoking and obesity prevalence, and more so among men than women. A shared risk factor profile, as well as possible genetic similarities, may explain their disproportionately higher kidney cancer mortality, but further research is warranted.

Occupational exposure to asbestos and risk of kidney cancer: an updated meta-analysis. Eur J Epidemiol 2021 Sep;36(9):927-936.

Abstract: Limited information is available on carcinogenicity of asbestos on non-respiratory organs. We aimed at conducted an updated systematic review and meta-analysis of cohort studies on occupational exposure to asbestos and risk of kidney cancer. We searched through three databases, PubMed, Embase and Scopus for article published after 2000, and after eliminating duplicates and non-relevant studies, we identified 13 studies. We combined their results with those of 31 non-overlapping studies included in a previous review up to 2000. We conducted a meta-analysis based on random-effects models. The pooled relative risk of kidney cancer for asbestos exposure was 0.94 (95% confidence interval, 0.84-1.04), with no differences according to type of asbestos fiber, geographic region, period of exposure, or estimated quality of the study. Our results showed a lack of association between occupational asbestos exposure and risk of kidney cancer.

Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. Jonasch E et al. 2021 Nov 25;385(22):2036-2046.

Abstract: Background: Patients with von Hippel-Lindau (VHL) disease have a high incidence of renal cell carcinoma owing to VHL gene inactivation and constitutive activation of the transcription factor hypoxia-inducible factor 2a (HIF-2a).

Methods: In this phase 2, open-label, single-group trial, we investigated the efficacy and safety of the HIF-2a inhibitor belzutifan (MK-6482, previously called PT2977), administered orally at a dose of 120 mg daily, in patients with renal cell carcinoma associated with VHL disease. The primary end point was objective response (complete or partial response) as measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent central radiology review committee. We also assessed responses to belzutifan in patients with non-renal cell carcinoma neoplasms and the safety of belzutifan.

Results: After a median follow-up of 21.8 months (range, 20.2 to 30.1), the percentage of patients with renal cell carcinoma who had an objective response was 49% (95% confidence interval, 36 to 62). Responses were also observed in patients with pancreatic lesions (47 of 61 patients [77%]) and central nervous

system hemangioblastomas (15 of 50 patients [30%]). Among the 16 eyes that could be evaluated in 12 patients with retinal hemangioblastomas at baseline, all (100%) were graded as showing improvement. The most common adverse events were anemia (in 90% of the patients) and fatigue (in 66%). Seven patients discontinued treatment: four patients voluntarily discontinued, one discontinued owing to a treatment-related adverse event (grade 1 dizziness), one discontinued because of disease progression as assessed by the investigator, and one patient died (of acute toxic effects of fentanyl).
Conclusions: Belzutifan was associated with predominantly grade 1 and 2 adverse events and showed activity in patients with renal cell carcinomas and non-renal cell carcinoma neoplasms associated with VHL disease. (Funded by Merck Sharp and Dohme and others; MK-6482-004 ClinicalTrials.gov number, NCT03401788.).

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. Choueiri TK et al. 2021 N Engl J Med. Aug 19;385(8):683-694.
Methods: In a double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with clear-cell renal-cell carcinoma who were at high risk for recurrence after nephrectomy, with or without metastasectomy, to receive either adjuvant pembrolizumab (at a dose of 200 mg) or placebo intravenously once every 3 weeks for up to 17 cycles (approximately 1 year). The primary end point was disease-free survival according to the investigator's assessment. Overall survival was a key secondary end point. Safety was a secondary end point.
Results: A total of 496 patients were randomly assigned to receive pembrolizumab, and 498 to receive placebo. At the prespecified interim analysis, the median time from randomization to the data-cutoff date was 24.1 months. Pembrolizumab therapy was associated with significantly longer disease-free survival than placebo (disease-free survival at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P = 0.002 [two-sided]). The estimated percentage of patients who remained alive at 24 months was 96.6% in the pembrolizumab group and 93.5% in the placebo group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96). Grade 3 or higher adverse events of any cause occurred in 32.4% of the patients who received pembrolizumab and in 17.7% of those who received placebo. No deaths related to pembrolizumab therapy occurred.
Conclusions: Pembrolizumab treatment led to a significant improvement in disease-free survival as compared with placebo after surgery among patients with kidney cancer who were at high risk for recurrence. (Funded by Merck Sharp and Dohme, a subsidiary of Merck; KEYNOTE-564 ClinicalTrials.gov number, NCT03142334.).

The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group. Franzese C. Clin Exp Metastasis. 2021 Dec;38(6):527-537.
Abstract: Although systemic therapy represents the standard of care for polymetastatic kidney cancer, stereotactic body radiation therapy (SBRT) may play a relevant role in the oligometastatic setting. We conducted a multicenter study including oligometastatic kidney cancer treated with SBRT. We retrospectively analyzed 207 patients who underwent 245 SBRT treatments on 385 lesions, including 165 (42.9%) oligorecurrent (OR) and 220 (57.1%) oligoprogressive (OP) lesions. Most common sites were lung (30.9%) for OR group, and bone (32.7%) for OP group. Among 78 (31.8%) patients receiving concomitant systemic therapy, sunitinib (61.5%) and pazopanib (15.4%) were the most common for OR patients, while sunitinib (49.2%) and nivolumab (20.0%) for OP patients. End points were local control (LC), progression free survival (PFS), overall survival (OS), time to next systemic therapy (TTNS) and toxicity. Median follow-up was 18.6 months. 1, 2 and 3-year LC rates were 89.4%, 80.1% and 76.6% in OR patients, and 82.7%, 76.9% and 64.3% in those with OP, respectively. LC for OP group was influenced by clear cell histology (p = 0.000), total number of lesions (p = 0.004), systemic therapy during SBRT (p = 0.012), and SBRT dose (p = 0.012). Median PFS was 37.9 months. 1, 2- and 3-year OS was 92.7%, 86.4% and 81.8%, respectively. Median TTNS was 15.8 months for OR patients, and 13.9 months for OP patients. No grade 3 or higher toxicities were reported for both groups. SBRT may be considered an effective safe option in the multidisciplinary management of both OR and OP metastases from kidney cancer.

Counterbalancing COVID-19 with Cancer Surveillance and Therapy: A Survey of Patients with Renal Cell Carcinoma. Staehler M et al. Eur Urol Focus. 2021 Nov;7(6):1355-1362.
Background: While providers are challenged with treatment decisions during the coronavirus disease 2019 (COVID-19) crisis, decision making ultimately falls in the hands of patients-at present, their perspective is poorly understood.
Objective: To ascertain renal cell carcinoma (RCC) patients' perspectives on COVID-19 and understand the associated implications for treatment.
Design, setting, and participants: An online survey of RCC patients was conducted from March 22 to March 25, 2020, disseminated through social media and patient networking platforms. The survey comprised 45 items, including baseline demographic, clinicopathologic, and treatment-related information. Patients were additionally queried regarding their anxiety level related to COVID-19 and associated implications for their cancer diagnosis.
Intervention: An online survey study.
Outcome measurements and statistical analysis: Descriptive statistics with graphical outputs were used to characterize survey results.
Results and limitations: A total of 539 patients (male:female 39%:58%) from 14 countries responded. Of them, 71% felt that their risk of COVID-19 infection was higher than the general population, and 27% contacted their physician to establish this. Among patients with localized disease (40%), most (42%) had scheduled surveillance scans within 6 wk-65% were unwilling to delay scans. Among patients with metastatic disease, 76% were receiving active therapy. While most patients preferred not to defer therapy (51%), patients receiving immune therapy regimens were less amenable to deferring therapy than those receiving targeted treatment (20% vs 47%).
Conclusions: Despite high levels of anxiety surrounding COVID-19, many patients with RCC were inclined to adhere to existing schedules of surveillance (localized disease) and systemic treatment (metastatic disease).
Patient summary: The coronavirus disease 2019 (COVID-19) pandemic has prompted many doctors to develop different treatment strategies for cancer and other chronic conditions. Given the importance of the patient voice in these strategies, we conducted a survey of patients with kidney cancer to determine their treatment preferences. Our survey highlighted that most patients prefer to continue their current strategies of kidney cancer treatment and monitoring.