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Research highlights of the 2020 society of urologic oncology young urologic oncologists' program

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The COVID-19 pandemic has not only changed the way we practice medicine, with increased reliance on video-conferencing and the practice of telehealth with the aim of maintaining social distancing. It has also necessitated adoption of virtual platforms for medical conferences. The Society of Urologic Oncology's 2020 winter annual program was no different, but this did not deter from an excellent general meeting and Young Urologic Oncologists (YUO) program. As part of the YUO program's mission to highlight cutting edge research, six exceptional abstracts were considered for the top research award. As follows is a summary of these abstracts, comprising the spectrum of bladder, prostate, and kidney cancer.

1. Bladder cancer

New therapies for Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) are needed given that patients in this disease space are often unfit or unwilling to undergo radical cystectomy. Nadofaragene firadenovec is a non-replicating recombinant type-5 adenovirus vector-based gene therapy that delivers a copy of the human IFNα2b gene. The single-arm, open-label, repeat-dose clinical trial of nadofaragene firadenovec for BCG-unresponsive NMIBC was recently published [1], investigating the safety and efficacy of intravesical nadofaragene firadenovec 75 mL once every 3 months in 157 patients with high-grade, BCG-unresponsive NMIBC. Patients free from high-grade recurrence were eligible for retreatment at 3-month intervals while they remained high-grade recurrence-free. The study met its primary endpoint with 53.4% of patients with carcinoma in situ (CIS) ±Ta/T1 achieving a complete response, all by 3 months, including 43.6% of these patients remaining free of high-grade recurrence at 15 months.

At this year's meeting, Dr. Vikram M. Narayan presented a *post hoc* analysis of this trial, assessing the impact of anti-adenovirus antibody response on efficacy of patients treated with nadofaragene firadenovec. Blood samples for anti-adenoviral antibody level assessments were collected between 24 and 1 hours prior to treatment on day 1, and at

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3, 6, 9, and 12 months after treatment or at a withdrawal-from-treatment study visit. A patient was considered to have a positive immunogenic response if a post-baseline anti-adenoviral antibodies titration demonstrated a > 2-fold dilution increase from baseline. Of the 151 patients included in the efficacy analysis, 129 had anti-adenoviral antibody titer results and were included in this analysis. Among the 55 patients who achieved a complete response in the CIS ± Ta/T1 cohort, significantly more patients had a positive post-baseline immunogenic response (43 vs. 8; $P = 0.003$). This was similarly observed in the high-grade Ta/T1 cohort where among the 34 patients who remained free of high-grade recurrence at 3 months, significantly more patients had a positive post-baseline immunogenic response (30 vs. 4; $P = 0.0003$). At 15 months of follow-up, the same trends were noted among patients who remained free of high-grade recurrence, with 19 vs. 3 ($P = 0.1032$) in the CIS ± Ta/T1 cohort and 17 vs. 2 ($P = 0.08$) patients in the high-grade Ta/T1 cohort who had a post-baseline immunogenic response. Based on these results, titer data suggests that a significant anti-adenovirus antibody response is associated with treatment response and may be used to identify responders to nadofaragene firadenovec.

Recurrence after BCG therapy for NMIBC occurs in approximately 40% of the cases at 5 years, therefore understanding the mechanisms of action of intravesical BCG may help in improving treatment outcomes. Dr. Jorge Daza presented results of their study describing changes in the tumor microenvironment after BCG therapy and biomarkers associated with worse oncological outcomes. Formalin-fixed and paraffin-embedded (FFPE) tissue sections before and after BCG therapy underwent differential gene expression analysis for both bulk targeted and single cell RNAseq. Dr. Daza and colleagues found that for patients undergoing BCG therapy, there was an upregulation of genes involved in B cell function, including a significant enrichment in genes associated with switched memory B cells and a downregulation in genes associated with marginal zone B cells uniquely found in post-BCG tumors. Additionally, *IGHA1* expression was significantly enriched in tumors that recurred in ≥ 6 months compared to those that recurred in ≤ 6 months. With the intermittent BCG shortages likely to continue, utilization of novel signatures in the bladder tumor microenvironment may aid in identifying patients that are likely to have an optimal response to BCG therapy, thus prioritizing BCG instillations for those patients likely to derive the greatest benefit.

2. Prostate cancer

Radiotherapy for biochemical recurrence after radical prostatectomy has historically been administered in the adjuvant setting for patients with high-risk pathologic features. However, 2020 saw the publication of three clinical trials (RADICALS-RT [2], GETUG-AFU 17 [3], and RAVES [4]), as well as a prospectively planned systematic review and meta-analysis of these three trials [5] that advocated for early salvage radiotherapy rather than adjuvant radiotherapy. The Genomics in Michigan ImpactiNg Observation or Radiation (G-MINOR) trial is the first prospective randomized trial assessing the impact of Decipher genomic classifier testing on adjuvant therapy use. Dr. Udit Singhal presented results of this study on behalf of his colleagues, assessing the impact of genomic classifier testing on patient-reported (PRO) quality of life outcomes in men at high-risk of post-prostatectomy recurrence. PROs were obtained using the Expanded Prostate Cancer Index Composite (EPIC-26) survey at baseline, 3, 6, 12, and 24 months after surgery. A total of 240 patients completed pre-radical prostatectomy baseline surveys prior to enrollment and were eligible for the PRO portion of this study. At 12 months follow up, those in the genomic classifier arm had no significant change in adjusted mean difference in domain score from baseline compared to those in the usual care arm for urinary irritative function (1.53, 95% CI -1.48 to 4.55), urinary incontinence (1.08, 95% CI -5.27 to 7.44), or sexual function (-2.26, 95% CI -8.85 to 4.33). This also remained true at 24 months for all three domains. Taken together, although the use of post-operative radiotherapy may be impacted by genomic classifier testing results, the authors did not observe any effect on recovery of patient-reported urinary or sexual function.

Abiraterone acetate (AA) is a pregnenolone analogue approved for use for men with locally advanced, metastatic hormone-sensitive, and metastatic castration-resistant prostate cancer. Given its activity on adrenal steroid precursors, AA is consequently administered with an oral corticosteroid to combat the adverse effects associated with mineralocorticoid excess. Perhaps secondary to the physiology of AA, clinical trial adverse events have suggested an increased cardiac risk among patients receiving AA. [6] Given this side effect and adverse event profile, Dr. Marybeth Hall presented results of a meta-analysis focusing on side effects of patients receiving AA, including hypokalemia and fluid retention. Among six studies comparing AA to ADT alone in advanced prostate cancer (phase II/III studies), 3,178 patients were included. In the AA versus the control group, respectively, hypokalemia was observed in 16.7% vs 6.0% (OR 3.01, 95% CI 1.71-5.30, $I^2 = 87\%$), fluid retention in 33.2% vs 24.7% (OR 1.51, 95% CI 1.22-1.87, $I^2 = 49.5\%$), hypertension in 24.6% vs 14.7% (OR 1.85, 95% CI 1.39-2.45), and cardiac events in 25.4% vs 15.9% (OR 1.77, 95% CI 121-2.58, $I^2 = 84\%$). As such, this data suggests there is increased cardiotoxicity with the administration of AA with ADT versus ADT alone. Although these results are hypothesis-generating and require further validation, patients should be counselled appropriately and understand the associated risks of AA with ADT.

3. Kidney cancer

Financial distress among cancer patients includes out-of-pocket expenditures relative to income and assets, loss of work, and household debt. There is increasing evidence that financial toxicity is associated with primary cancer treatment [7] and is likely being exacerbated by the COVID-19 pandemic [8]. Specific to small renal masses, treatment may ultimately be utilized in the setting of a benign mass, resulting in unnecessary cost, morbidity, and mortality, as well as substantial decisional regret. To assess these concerns in more detail, Dr. Neil Mendhiratta presented results of his study assessing decisional regret and financial toxicity among patients with benign renal masses.

Among 70 members of a support group in the United States who had been diagnosed with benign renal tumors, survey data reveal that most patients were young (mean 48.0 +/- 12.6 years), female (89%), and Caucasian (86%). The most common histology was oncocytoma (47%) and 49 patients (70%) received active treatment. Decisional regret was expressed by 49% of patients and was associated with older age ($P = 0.037$) on multivariable analysis. With regards to financial toxicity, younger patients ($P < 0.001$) and a diagnosis of angiomyolipoma ($P = 0.047$) were associated with greater financial toxicity. This study highlights many opportunities for improving patient care, including improved counseling and diagnostic tools to limit the psychological and financial burdens in select populations with benign renal masses.

Despite kidney cancer being the sixth and ninth most common malignancies in males and females, respectively, in the United States [9], there is a paucity of non-syndromic risk factors associated with developing renal cell carcinoma (RCC). Obesity and diabetes have been suggested as modifiable risk factors for developing RCC [10], however the degree to which modifiable risk factors explain the interstate variation in kidney cancer incidence within the United States is unknown. Dr. Abhishek Venkataramana and colleagues presented results of their study assessing these relationships by associating longitudinal variations in the prevalence of obesity, diabetes, smoking, and alcohol consumption. Using data from the North American Association of Central Cancer Registries (2001−2016), survey-weighted state-wide annual prevalence estimates for modifiable RCC risk factors (obesity, smoking, diabetes, and alcohol consumption) were extracted from the Behavioral Risk Factor Surveillance System. They found that both kidney cancer incidence and obesity are increasing in the US, but with variation for both between states. Furthermore, in this epidemiological study, obesity and diabetes prevalence were significantly associated with RCC incidence, whereas smoking or alcohol consumption had no association. Using random effects linear regression modelling, the increased age-adjusted RCC incidence per 100,000 people was related to the increased prevalence of those with a BMI of 30 kg/m^2 to 35 kg/m^2 (regression coefficient 24.4, $P < 0.001$), BMI 35-40 kg/m^2 (41.4, $P < 0.001$), BMI 40+ kg/m^2 (72.2, $P < 0.001$), and diabetes (8.4, $P = 0.291$). After adjusting for obesity, diabetes was no longer a significant variable for RCC incidence. Overall, obesity explained 52% of variation in renal tumor incidence within states over time and 62% of variation between states. With a United States age-adjusted prevalence of obesity in adults of 42.4% [11], this data strengthening the epidemiologic evidence linking obesity to RCC are relevant to every day clinical practice.

Among these six excellent abstracts submitted to the YUO program, the two winners selected by the YUO committee were Dr. Mendhiratta for “Decisional regret and financial toxicity among patients with benign renal masses”, and Dr. Vikram Narayan for “Significant anti-adenovirus antibody response positively correlates with efficacy in patients treated with nadofaragene firadenovec for high-grade BCG-unresponsive NMIBC”. In a challenging year both personally and professionally, the YUO congratulates and is grateful for the continued research and clinical excellence put forth by our colleagues across the country.

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