

# NS-AUA 2023 Annual Meeting Abstracts – Oncology – Bladder, Renal, Testes

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## Abstract 25

### Variation in non-muscle-invasive bladder cancer recurrence after transurethral resection surgery between sites is independent of tumor factors: Results from the RESECT study (NCT05154084)

Fortis Gaba<sup>1</sup>, Kevin Gallagher<sup>2</sup>, Nikita Bhatt<sup>3</sup>, Keiran Clement<sup>4</sup>, Eleanor Zimmermann<sup>5</sup>, Sinan Khadhour<sup>6</sup>, Meghana Kulkarni<sup>7</sup>, Thines Anbarasan<sup>8</sup>, Alexander Ng<sup>9</sup>, Alexander Light<sup>10</sup>, Aqua Asif<sup>11</sup>, Vinson Chan<sup>12</sup>, Arjun Nathan<sup>11</sup>, Sabrina Rossi<sup>13</sup>, Tim O'Brien<sup>14</sup>, Steven MacLennan<sup>15</sup>, Matthew Nielsen<sup>16</sup>, Paramanathan Mariappan<sup>17</sup>, Veeru Kasivisvanathan<sup>11</sup>, RESECT study global collaborators (BURST)

<sup>1</sup>Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston, MA; <sup>2</sup>Department of Urology, Western General Hospital, Edinburgh, U.K.; <sup>3</sup>Department of Urology, Norfolk and Norwich University Hospital, Norwich, U.K.; <sup>4</sup>Department of Urology, NHS Greater Glasgow Clyde, U.K.; <sup>5</sup>University Hospitals Plymouth, U.K.; <sup>6</sup>University of Aberdeen, Health Services Research Unit, U.K.; <sup>7</sup>St. Georges University Hospital London, U.K.; <sup>8</sup>Department of Urology, Oxford University Hospitals NHS Foundation Trust, Oxford, U.K.; <sup>9</sup>University College London, Division of Surgery and Interventional Science, U.K. Royal Free London NHS Foundation Trust, U.K.; <sup>10</sup>Department of Surgery and Cancer, Imperial College London, London, U.K.; <sup>11</sup>University College London, Division of Surgery and Interventional Science, U.K.; <sup>12</sup>School of Medicine, Faculty of Medicine, University of Leeds, Leeds, U.K.; <sup>13</sup>Academic Department of Surgery, University of Cambridge, U.K.; <sup>14</sup>Guy's and St. Thomas' NHS foundation trust, London, U.K.; <sup>15</sup>Academic Urology Unit, University of Aberdeen, U.K.; <sup>16</sup>Department of Urology, University of North Carolina School of Medicine, Chapel Hill, NC; <sup>17</sup>Department of Urology, Edinburgh Bladder Cancer Surgery (EBCS), Western General Hospital, Edinburgh, U.K.

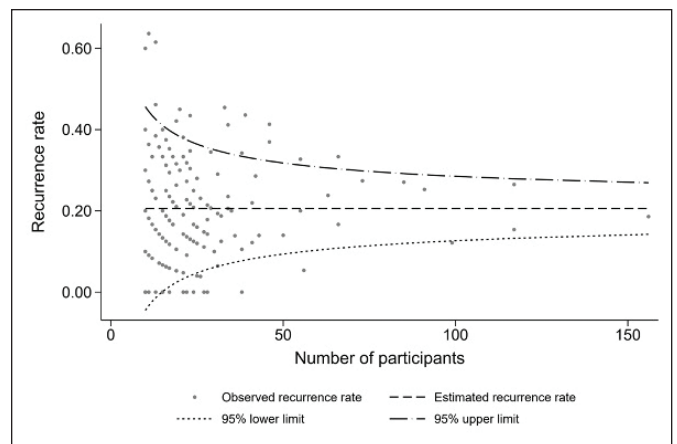
**Introduction:** We aimed to determine if there is significant variation in early recurrence after transurethral resection (TURBT) surgery between sites taking part in the RESECT study (NCT05154084) after accounting for tumor characteristics.

**Methods:** We conducted an international, multicenter, observational study. A mixed-effects logistic regression model with tumor size, tumor number; tumor grade, tumor stage as fixed effects, and site as a random effect was fitted. Cases with first, presumed non-muscle-invasive bladder cancer (NMIBC) undergoing TURBT were included. Cases were excluded if first check followup had not been completed. Sites were excluded if they did not have at least 10 cases with first check followup. Local and/or national approvals or ethical exemptions were obtained prior to commencing the study at participating sites.

**Results:** After exclusions, 186 sites (U.K: 80; Europe: 59; North America: 18; Asia: 17; Africa 7; South America: 3; Oceania: 2) contributing a total 4597 cases (average 25 cases) were included. Median recurrence rate per site was 12% (IQR 0–22) for low-grade tumors and 27% (IQR 13–42) for high-grade tumors (Figure 1). After controlling for tumor size, number, stage, and grade (all significantly and independently associated with early recurrence) (Table 1), there was significant residual variation attributable to site ( $p < 0.0001$ , intra-class correlation, 0.1). Adjustment for sites improved the regression model from an area under the receiver operating characteristic curve of 0.66 to 0.74. Initial analysis of surgical and perioperative practice showed wide variation; a mean of 75% (IQR 66–92) of cases per site had detrusor muscle resection and 42% (IQR 17–58) had use of single instillation of intravesical chemotherapy. Other differences in operative and perioperative practice were identified through surveys.

**Conclusions:** There is significant variation in the early recurrence rate of NMIBC after TURBT surgery between sites that could not be explained by currently understood tumor features. We have identified differences in surgical technique and perioperative practice that may impact this, and further investigation is warranted to understand how these factors impact recurrence rates.

**Funding:** The RESECT study is supported by unrestricted grants from Karl Storz, Photocure, and Medac Pharma.



Abstract 25. Figure 1. Median recurrence rate per site.

Abstract 25. Table 1. Mixed effects logistic regression for early recurrence after first TURBT for NMIBC

Tumor feature	OR	p	95% CI
<b>Diameter(cm)</b>			
<1	1.00		
1-3	1.63	<0.001	1.29–2.08
3-7	2.55	<0.001	1.94–3.33
>7	2.42	0.003	1.34–4.38
<b>No.</b>			
1	1.00		
2-3	1.49	<0.001	1.24–1.81
>3	1.92	<0.001	1.56–2.36
<b>Stage</b>			
Ta	1.00		
Tis	2.00	0.015	1.15–3.50
T1	1.90	<0.001	1.57–2.30
<b>Grade</b>			
Low	1.00		
High	1.44	<0.001	1.19–1.73
<b>Constant</b>	0.07	<0.001	0.06–0.09
<b>Random intercept - site</b>	0.36	<0.001	0.23–0.57

**Abstract 26**

**Intravesical contrast-enhanced magnetic resonance imaging (ICE-MRI) of superficial and invasive bladder cancer**

Pradeep Tyagi, Marc Connell, Chan-Hong Moon, Biatta Sholosh, Christopher Chermansky, Rajiv Dhir, Jodi Maranchie  
University of Pittsburgh, Pittsburgh, PA

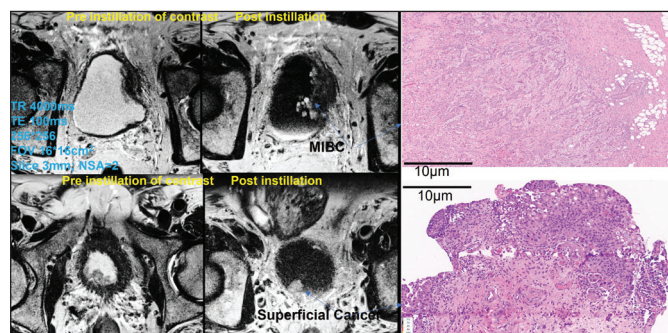
**Introduction:** The critical role of staging in bladder cancer prognosis and higher rates of understaging with traditional imaging and transurethral resection (TUR) propels the search for alternatives. Here, we describe the premise and promise of ICE-MRI to discriminate superficial from invasive bladder cancer and inflammatory lesions.

**Methods:** Twenty-one subjects in the age range of 62–90 years with the suspicion of bladder cancer on cystoscopy were recruited for NCT04369560 and 13 (12 males and one female) subjects consented for ICE-MRI prior to TUR or cystectomy. Bladder was scanned before and after instillation via 14 Fr urethral straight tip catheter of 50 mL gadobutrol (20mM) and ferumoxylol (0.1mM) using T2-weighted turbo spin echo and 3D T1-weighted fast low-angle shot (FLASH) at Siemens Biograph 3T.

**Results:** Multislice T-weighted ICE-MRI over 92s (repetition/echo time [TR/TE] 4000/100 ms) in voxel volume of 0.625\*0.625\*3 mm<sup>3</sup> with slice thickness 3 mm and number of signal averages (NSA=2) produced dark lumen with clear demarcation of enhanced regions of interest (ROI) in seven quadrants of bladder wall, and then 3D-FLASH acquisition over 23.30 s at each flip angle of 3° to 22°, with constant TR/TE of 5.24/1.86 ms mapped T1 of ROIs in voxel volume of 0.67\*0.67\*1 mm<sup>3</sup>. Larger extracellular space and lower cellularity of inflammatory lesions (3/13) than the histopathologically proven superficial, urothelial cancer lesions (9/13) elicited higher contrast-enhancement from instilled gadobutrol diffusing down the concentration gradient passively along tight junctions (paracellularly) and exclusively into extracellular space available in ROI. Deeper submucosal enhancement predicted MIBC, later confirmed by histopathology of cystectomy specimen. While catheterization evoked brief discomfort in all subjects, no one complained of any additional discomfort from luminal retention of the contrast mixture for ~30 min in ICE-MRI.

**Conclusions:** ICE-MRI capitalizes on the differences in perturbed tight junctions, cellularity, and extracellular space modifying gadobutrol diffusion for differential enhancement of superficial, MIBC and inflammatory lesions. Further studies are warranted to determine if ICE-MRI can be a non-surgical surveillance tool for indolent cancer in older patients and reduce the time to correct treatment by stratifying suspected MIBC patients without TUR.

Funding: CA252590



**Abstract 26. Figure 1.**

**Abstract 27**

**Pharmacologic inhibition of endogenous hydrogen sulfide production in an intravesical murine model of bladder cancer**

Sydney Relouw<sup>1,2</sup>, George Dugbartey<sup>2,3,4</sup>, Natasha Knier<sup>5,6</sup>, Francisco Martinez Santiesteban<sup>5</sup>, Melissa Huynh<sup>4,7</sup>, S. M. Mansour Haeryfar<sup>1,4,7,8</sup>, Alp Sener<sup>1,2,4,7</sup>

<sup>1</sup>Department of Microbiology & Immunology, Western University, London, ON, Canada; <sup>2</sup>Matthew Mailing Center for Translational Transplant Studies, Western University, London Health Sciences Center, London, ON, Canada; <sup>3</sup>Department Pharmacology Toxicology, School of Pharmacy, College of Health Sciences, University of Ghana, Legon, Accra; <sup>4</sup>Department of Surgery, Western University, London, ON, Canada; <sup>5</sup>Department of Medical Biophysics, Western University, London, ON, Canada; <sup>6</sup>Robarts Research Institute, Western University, London, ON, Canada; <sup>7</sup>Lawson Health Research Institute, London, ON, Canada; <sup>8</sup>Division of Clinical Immunology & Allergy, Department of Medicine, Western University, London, ON, Canada

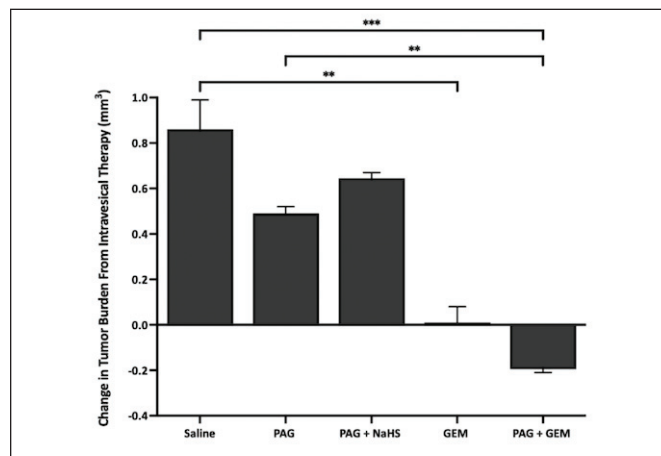
**Introduction:** Current intravesical bladder cancer treatment paradigms have limited therapeutic impact, requiring investigation of novel therapies. Recent evidence suggests hydrogen sulfide (H<sub>2</sub>S), an endogenous gaseous signaling molecule, mediates cancer progression. Preliminary in-vitro data demonstrated significant attenuation of mouse and human bladder cancer cell viability by an H<sub>2</sub>S-producing enzyme inhibitor and significant potentiation by an H<sub>2</sub>S donor, alluding to a role of H<sub>2</sub>S in the progression of bladder cancer. Thus, this study investigates the effect of inhibiting endogenous H<sub>2</sub>S production on bladder cancer tumor progression with or without chemotherapy in-vivo.

**Methods:** A murine intravesical bladder cancer model was subjected to mono- and dual intravesical therapies consisting of an H<sub>2</sub>S donor, an H<sub>2</sub>S-producing enzyme inhibitor, and conventional chemotherapy. Magnetic resonance imaging (MRI) depicted tumor burden prior to and subsequent to intravesical therapy, and these images were used to evaluate tumor progression.

**Results:** Current findings, as portrayed in Figure 1, demonstrate a noticeable reduction in tumor growth following treatment with the H<sub>2</sub>S inhibitor. This effect was partially abrogated by H<sub>2</sub>S donor administration compared to the control. Furthermore, dual therapy with the H<sub>2</sub>S inhibitor and chemotherapy demonstrate a downward trend in tumor growth compared to chemotherapy alone and significantly suppressed tumor growth compared to H<sub>2</sub>S inhibitor monotherapy (p<0.001) and the control (p<0.0001), resulting in tumor regression.

**Conclusions:** These findings suggest that inhibition of endogenous H<sub>2</sub>S production shows antineoplastic effects and H<sub>2</sub>S inhibition together with conventional chemotherapy produces a synergistic effect. Thus, H<sub>2</sub>S could be a potential therapeutic target in bladder cancer treatment.

Funding: Canadian Urological Association Scholarship Foundation



**Abstract 27. Figure 1.** Change in bladder cancer tumor burden, represented by change in bladder wall area (mm<sup>3</sup>) from MRI prior to and subsequent to intravesical therapy. Intravesical therapy consisted of mono and dual therapies of the H<sub>2</sub>S donor, sodium hydrosulfide (NaHS), the H<sub>2</sub>S-producing enzyme inhibitor, DL-propargylglycine (PAG), and chemotherapy, gemcitabine (GEM). Data (n=3) are expressed as mean ± standard error of the mean.

**Abstract 28**

**Assessing health disparities in non-muscle-invasive bladder cancer through the Ontario Marginalization Index**

Maximiliano Ringa<sup>1</sup>, Jethro C.C. Kwong<sup>2,3</sup>, Amna Ali<sup>1</sup>, Yashan Chelliahpillai<sup>4</sup>, Hafsa Khurram<sup>5</sup>, Soomin Lee<sup>4</sup>, Nicole Bodnariuc<sup>4</sup>, Vereena Andrawes<sup>5</sup>, Andrew Feifer<sup>1,2,6</sup>

<sup>1</sup>Institute for Better Health, Trillium Health Partners, Mississauga, ON, Canada; <sup>2</sup>Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada; <sup>3</sup>Temerty Centre for AI Research and Education in Medicine, University of Toronto, Toronto, ON, Canada; <sup>4</sup>Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; <sup>5</sup>Research Internship, Trillium Health Partners, Mississauga, ON, Canada; <sup>6</sup>Carlo Fidani Regional Cancer Centre, Trillium Health Partners, Mississauga, ON, Canada

**Introduction:** Socio-economic levels have shown association with diagnostic cancer stage, treatment patterns and overall mortality; however, the impact of marginalization status on NMIBC outcomes remains unclear. The Ontario Marginalization Index (ON-Marg) is a tool for studying health inequality using four dimensions: residential instability, material deprivation, dependency, and ethnic concentration. This study aimed to assess the association between marginalization and non-muscle-invasive bladder cancer (NMIBC) outcomes for patients treated at a Canadian center that serves one of the most diverse communities worldwide, with >50% of its constituents identifying as immigrants.

**Methods:** An ongoing retrospective chart review (2005–2022) of NMIBC patients from a regional cancer center in Ontario was conducted; with preliminary analysis of 154 patients. Marginalization status, clinical and disease features, treatment compliance, and recurrence, progression, and overall survival (OS) were collected. Marginalization status was calculated using ON-Marg. Grouping as follows: G1=low marginalization (ON-MARG levels 1–2); G2=high marginalization (ON-Marg level 3–5). Differences in tumor stage at diagnosis and treatment compliance were assessed using Chi-squared tests. Time to event analysis were assessed by Kaplan-Meier curve analysis.

**Results:** Sixty-one patients (40%) were G1 and 93 (60%) were G2. At diagnosis, pT1 was present in 36% and 41% of G1 and G2 (p=0.8), respectively, and high-grade tumor in 71% of G1 and 80% of G2 (p=0.2). Rates of recurrence were 53% vs. 71% (p=0.09), high-risk recurrence 48% vs. 56% (p=0.5), and any progression 28% vs. 42% (p=0.08) for G1 vs. G2, respectively (Figure 1). No differences observed in treatment compliance, OS, or cancer-specific survival.

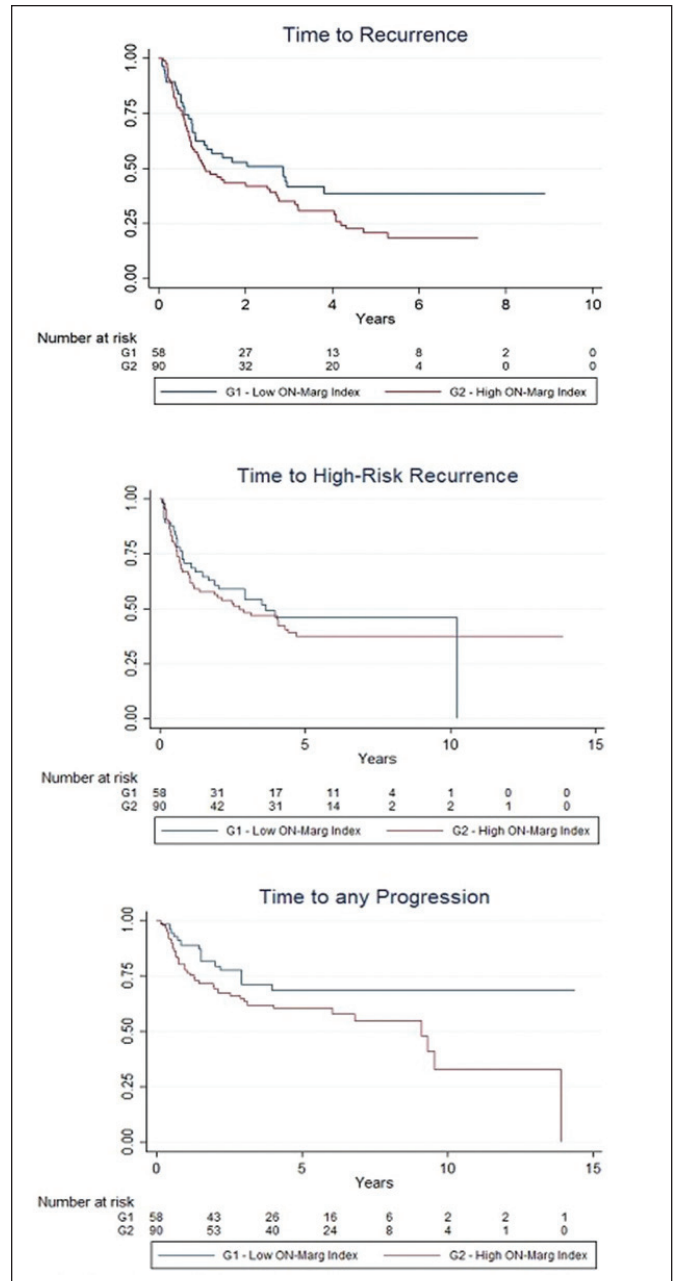
**Conclusions:** In a marginalized patient population, higher grade and stage tumors were more common. This may be associated with delayed presentation, or other mitigating non-measured factors. Further investigation with a larger cohort is ongoing to fully understand the relationship between marginalization, social determinants of health, and prognosis in NMIBC patients.

**Abstract 29**

**First results from SunRISe-I in patients with bacillus Calmette-Guérin unresponsive, high-risk non-muscle-invasive bladder cancer receiving TAR-200 in combination with cetrelimab, TAR-200, or cetrelimab alone**

Joseph Jacob<sup>1</sup>, Siamak Daneshmand<sup>2</sup>, Michiel S. van der Heijden<sup>3</sup>, Andrea Necchi<sup>4</sup>, Evangelos Xylinas<sup>5</sup>, David S. Morris<sup>6</sup>, Philipp Spiegelhalder<sup>7</sup>, Daniel Zainfeld<sup>8</sup>, Taek Won Kang<sup>9</sup>, Justin T. Matulay<sup>10</sup>, Laurence H. Belkoff<sup>11</sup>, Karel Decaestecker<sup>12</sup>, Harm Arentsen<sup>13</sup>, Shalaka Hampras<sup>14</sup>, Shu Jin<sup>15</sup>, Christopher J. Cutie<sup>15</sup>, Hussein Sweitj<sup>16</sup>, Katherine Stromberg<sup>14</sup>, Jason Martin<sup>17</sup>, Giuseppe Simone<sup>18</sup>

<sup>1</sup>Upstate Medical University, Department of Urology, Syracuse, NY; <sup>2</sup>Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA; <sup>3</sup>Netherlands Cancer Institute, Department of Medical Oncology, Amsterdam, the Netherlands; <sup>4</sup>Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy; <sup>5</sup>Department of Urology, Bichat-Claude Bernard Hospital, Assistance-Publique-Hôpitaux de Paris, Université de Paris Cité, Paris, France; <sup>6</sup>Urology Associates, Nashville, TN; <sup>7</sup>Urologie Neandertal, Gemeinschaftspraxis für Urologie, Mettmann, Germany; <sup>8</sup>Urology San Antonio, San Antonio, TX; <sup>9</sup>Department of Urology, Chonnam National University Medical School, Chonnam National University Hospital, Gwangju, Korea; <sup>10</sup>Atrium Health Levine Cancer Institute, Charlotte, NC; <sup>11</sup>MidLantic Urology/Solaris Health, Bala Cynwyd, PA; <sup>12</sup>Department of Urology, Ghent University Hospital, Ghent, Belgium; <sup>13</sup>AZ Sint-Jan Hospital Brugge-Oostende, Bruges, Belgium; <sup>14</sup>Janssen Research Development, Clinical Oncology, Raritan, NJ; <sup>15</sup>Janssen Research Development, Clinical Oncology, Lexington, MA; <sup>16</sup>Janssen Research Development, Spring House, PA; <sup>17</sup>Janssen Research Development, High Wycombe, U.K.; <sup>18</sup>Regina Elena National Cancer Institute, Department of Urology, Rome, Italy



**Abstract 28. Figure 1.** Time from first treatment to recurrence, high-risk recurrence, and any specific progression, stratified by ON-Marg Index groups.

**Introduction:** Patients with high-risk non-muscle-invasive bladder cancer (HR NMIBC) unresponsive to intravesical bacillus Calmette-Guérin (BCG) have limited treatment options. TAR-200 is a novel intravesical drug delivery system that provides sustained local release of gemcitabine into the bladder. Cetrelimab is an anti-PD1 agent. SunRISe-I is an ongoing phase 2 study (NCT04640623) evaluating efficacy and safety of TAR-200 + cetrelimab (cohort 1 [C1]), TAR-200 alone (C2), or cetrelimab alone (C3) in patients with BCG-unresponsive HR NMIBC (carcinoma in situ [CIS]) who are ineligible/decline radical cystectomy. We report preliminary results from SunRISe-I, providing data from C2 and C3.

**Methods:** Patients ≥ 18 years with histologically confirmed CIS ± papillary disease (T1, high-grade Ta) who completed adequate BCG ≤ 12 months before enrollment and with ECOG performance status 0–2 were randomized to C1, C2, or

C3. TAR-200 was dosed Q3W through week 24, then Q12W until week 96. Cetrelimab was dosed through week 78. Cystoscopy, centrally read urine cytology, CT/MRI, and centrally read TURBT (bladder biopsy) were performed at baseline and prespecified time points to assess disease response. The primary endpoint is overall complete response (CR) rate. Secondary endpoints include duration of response, overall survival, pharmacokinetics, quality of life, safety, and tolerability. **Results:** As of May 25, 2022, 13 patients in C2 and 13 in C3 (median age 71.5 years [range 51–88]) received treatment. The efficacy evaluable set comprised eight patients in C2, and eight in C3. Centrally confirmed CR by urine cytology and/or biopsy was 88% (95% CI 47–100) in C2 and 38% (9–76) in C3. Median CR duration of response for C2 and C3 was not reached after median followup of 13.6 and 12.0 weeks, respectively. At data cutoff, 7/8 patients in C2 remained CR, with three ongoing responses  $\geq 6$  months (range 7.7–9.4 months). Eleven patients (85%) in C2 and eight (62%) in C3 had treatment-emergent adverse events (TEAEs); most were grade 1–2. Most common TEAEs were pollakiuria (39%), micturition urgency (39%), and non-infective cystitis (39%) in C2; fatigue (23%) and lipase increased (23%) in C3. One patient (8%) in C2 and two patients (15%) in C3 had treatment-related Gr  $\geq 3$  TEAEs. One serious TEAE (myocarditis) occurred in C3.

**Conclusions:** First results from SunRISe-1 show promising CR rate and safety profile with TAR-200 monotherapy. Cetrelimab results are consistent with other anti-PD(L)1 treatment in this setting. Preliminary efficacy and safety data support the continued study in NMIBC.

Funding: Janssen Research Development

### Abstract 30

#### Does betulinic acid, a natural anti-cancer agent, target metabolic programming in bladder cancer?

Anirban Ganguly, Stephanie Daugherty, Keara Healy, Jonathan Beckel, Anthony Kanai, Pradeep Tyagi

University of Pittsburgh, Pittsburgh, PA

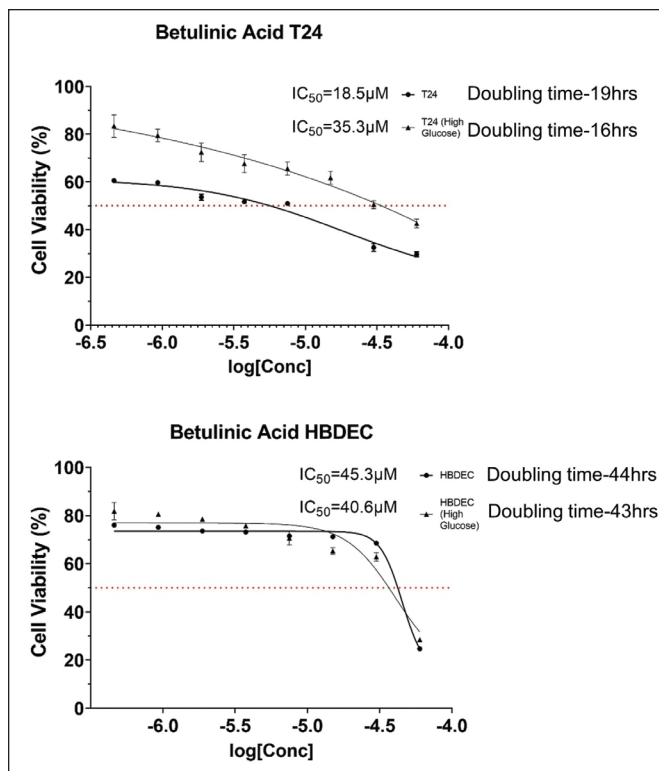
**Introduction:** Betulinic acid (ALS 357) obtained from the bark of white birch (*Betula alba*), is a well-known tumor-selective drug, which underwent phase I clinical testing for melanoma (NCT00346502). Betulinic acid is known to affect mitochondrial potential but the mechanism for its tumor selectivity is unknown. While rapid proliferation consumes glucose at higher rate, cancer cells also rewire their metabolism amid nutrient scarcity to metabolize fatty acids and cholesterol for proliferation. Hence, we reasoned that the structural similarities with cholesterol may underlie the tumor selectivity of betulinic acid and accordingly examined the effect of glucose supplementation on the antiproliferative effect of betulinic acid on bladder cancer.

**Methods:** Cell culture: T24 bladder transitional carcinoma cells and non-cancerous, non-immortalized human urothelial cells (HBDEC) were procured from ATCC. T24 cells were cultured in McCoy's 5a medium supplemented with 10% FBS, whereas HBDEC cells were maintained in bladder epithelial cell basal medium supplemented with the bladder epithelial growth kit (both purchased through ATCC). In addition, both cell lines were also grown in respective media after supplementation with 10% glucose. MTT assay: Cells were plated on 96 well plates at a concentration of 5000 cells/well and allowed to grow overnight. The cells were then treated with increasing amounts of betulinic acid for 18 hours both in normal and high glucose media.  $IC_{50}$  was determined by MTT assay.

**Results:** The  $IC_{50}$  of betulinic acid on T24 cancer cells was nearly two-fold lower than on HBDEC cells without glucose supplementation. While the doubling time of HBDEC and  $IC_{50}$  of betulinic acid was only slightly reduced with 10% glucose supplementation, T24 cells become resistant to the cytotoxic effect of betulinic acid, and  $IC_{50}$  nearly doubled to affirm the role of Warburg effect and higher glucose consumption for fueling the rapid proliferation of T24 relative to HBDEC cells. Taken together, metabolic reprogramming of cancer appears central to the tumor selective action of betulinic acid.

**Conclusions:** These findings support the anti-cancer action of betulinic acid on bladder cancer and implicate the role of metabolic reprogramming in the tumor selective action of betulinic acid in melanoma and other cancers. Findings warrant future testing in mouse models of superficial bladder cancer.

Funding: NIH R01DK117884, NCI RA263243, NCI R01 CA251341



Abstract 30. Figure 1.

### Abstract 31

#### Large opioid prescription following cystectomy increases the risk of chronic opioid use

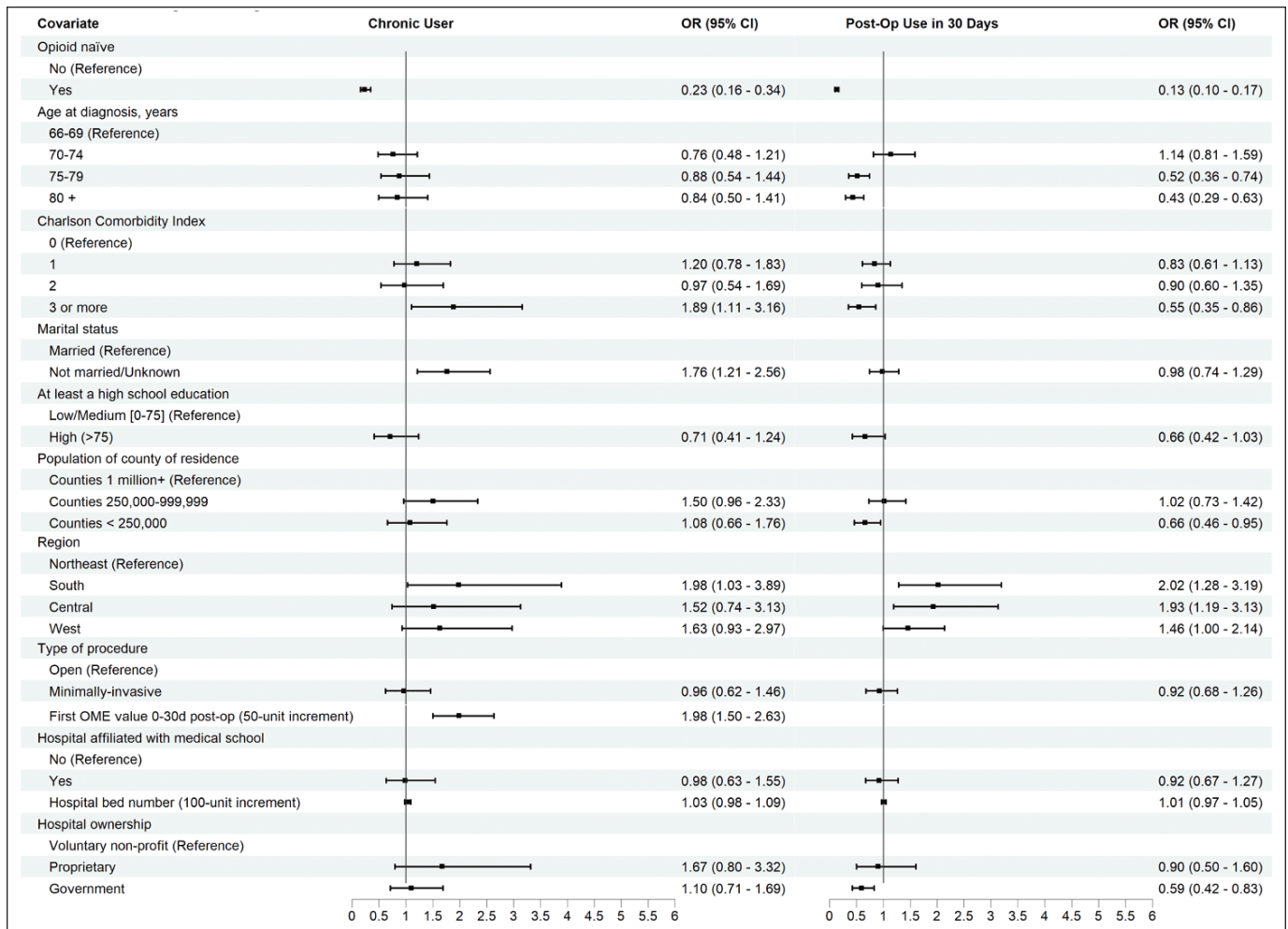
Christopher Stanjorski<sup>1</sup>, Michelle Yu<sup>1</sup>, Danielle Sharbaugh<sup>1</sup>, Michael Stencel<sup>1</sup>, John Myrka<sup>1</sup>, Benjamin Davies<sup>1</sup>, Jonathan Yabes<sup>2</sup>, Bruce Jacobs<sup>1</sup>

<sup>1</sup>Division of Health Services Research, Department of Urology, UPMC, Pittsburgh, PA; <sup>2</sup>Division of Internal Medicine, Department of Medicine, UPMC, Pittsburgh, PA

**Introduction:** Chronic opioid use following any urologic procedure is known to be as high as 10.8%. Identifying patients at highest risk for chronic use, especially following major surgery, can direct further attention to helping combat this issue. This study aims to evaluate both patient and hospital factors predisposing to persistent opioid use following cystectomy using the Surveillance, Epidemiology, and End Results (SEER) Program.

**Methods:** We identified patients who underwent cystectomy between July 2007 and December 2015 using SEER. The primary outcomes were postoperative opioid use and chronic opioid use, defined as an opioid prescription filled 0–30 days and 90–180 days after surgery, respectively. Multivariable logistic regressions evaluated patient and hospital factors for their contribution to chronic opioid use, as well as opioid prescription postoperatively.

**Results:** A total of 1774 patients were identified who underwent cystectomy during the study period. The majority were opioid-naïve at the time of surgery (70.9%). Procedures were performed at 349 different hospitals. Most were associated with a training program (53.3%) and voluntary non-profit facilities (72.2%), with a median capacity of 361 beds (IQR 234–517). Of patients who filled a postoperative prescription, the median oral morphine equivalent filled during the first month following surgery was 40.0 equivalents (IQR 30.0–60.0). Younger, healthier patients who were exposed to opioids preoperatively were more likely to be prescribed an opioid. Government hospitals were associated with lower likelihood of an opioid prescription; 10.2% of patients in the cohort developed chronic use. Opioid-naïve patients were less likely to develop chronic opioid use relative to non-opioid-naïve patients (OR 0.23,  $p < 0.001$ ). Additionally, an increase in initial opioid prescription by 50 morphine milligram equivalents nearly doubled the risk of developing chronic opioid use (OR 1.98,  $p < 0.001$ ).



Abstract 31. Figure 1. Multivariable analysis of predictors of opioid prescription and chronic use following cystectomy.

Hospital size, ownership, and affiliation with a medical school were not predictive of chronic use (Figure 1).

**Conclusions:** Even when controlling for preoperative opioid use, larger prescriptions postoperatively were predictive of chronic opioid use after cystectomy. While opioid prescription may be necessary after major procedures, efforts to reduce the amount prescribed may help to prevent the development of chronic use.

Funding: ShadySide Hospital Foundation

### Abstract 32 Prebiotics improve the efficacy of anti-PD1 immunotherapy in bladder cancer by modulating the gut microbiota

Jalal Laaraj<sup>1,2,3</sup>, Gabriel Lachance<sup>1,3</sup>, Prisca Nadège Kone<sup>1,3</sup>, Typhaine Gris<sup>1</sup>, Afshin Jamshidi<sup>1,3</sup>, Paul Toren<sup>1,2</sup>, Yves Fradet<sup>1,2</sup>, Alain Bergeron<sup>1,2</sup>, Karine Robitaille<sup>1,3</sup>, Vincent Fradet<sup>1,2,3</sup>

<sup>1</sup>Laboratoire d'Uro-Oncologie Expérimentale, Oncology Axis, Centre de recherche du CHU de Québec-Université Laval and Centre de Recherche sur le Cancer de l'Université Laval, Québec, QC, Canada; <sup>2</sup>Faculty of Medicine, Department of Surgery, Université Laval, Québec, QC, Canada; <sup>3</sup>Institut sur la nutrition et aliments fonctionnels (INAF) et centre NUTRISS, Université Laval, Québec, QC, Canada

**Introduction:** In multiple cancers, the anti-tumor activity of the immune checkpoint blockade immunotherapies (ICB), such as anti-PD1, is modulated by the gut microbiota. Accordingly, microbiome-based interventions are emerging strategies to modulate the gut microbiota of non-responding patients and enhance the

efficacy of ICB. Here, we assessed the modulatory effect of promising prebiotics on the gut microbiota and on improving the efficacy of anti-PD1 in a syngeneic bladder cancer (BCa) mouse model.

**Methods:** Six- to eight-week-old C3H mice were subcutaneously injected with MBT-2 syngeneic tumor cells of BCa and daily fed with eight promising prebiotics. After tumor implantation, mice were injected intraperitoneally with anti-PD1 or an isotype control intraperitoneally, and tumor growth was regularly monitored. To assess the modulatory effect of prebiotics on gut microbiota, mice fecal samples were collected throughout the experiment and subjected to 16S rRNA gene sequencing to profile the gut microbiota composition. Short-chain fatty acids (SCFAs) analysis was performed at sacrifice from mice cecum using gas chromatography coupled with flame ionization detection to assess the impact of prebiotic supplementation on the production of gut microbial-derived metabolites. Finally, peripheral blood mononuclear cells (PBMC) and tumors were collected at sacrifice to assess the immunomodulatory effect of prebiotic supplementation by flow cytometry analysis.

**Results:** Prebiotics A and B (pre\_A and pre\_B) significantly reduced tumor growth and improved survival of MBT-2-injected mice. The combination of pre\_A with anti-PD1 also enhanced anti-PD1 efficacy. Mice treated with pre\_A displayed an enrichment of the Bacteroides genus, while mice that received pre\_B showed enrichment of Faecalibaculum genus and the Lachnospiraceae family. SCFAs analysis showed that pre\_B increased the production of iso-butyric and iso-valeric acids, suggesting a potential mechanism of action in this BCa mouse model. Flow cytometry analysis of PBMC demonstrated that pre\_A increased

the proportion of circulating CD8<sup>+</sup>T lymphocytes, supporting a strong antitumor immune response. Similarly, the administration of antibiotics in combination with pre\_A reduced its anti-tumor activity and decreased the proportion of circulating CD8<sup>+</sup>T lymphocytes, confirming that pre\_A activity is gut microbiota dependent. **Conclusions:** Taken together, our findings suggest that the modulation of gut microbiota with a diet-based strategy can reduce tumor growth and improve the efficacy of anti-PD1 immunotherapy in BCa. Translation of these findings into clinical practice could potentially overcome the resistance to ICB in BCa patients.

### Abstract 33

#### Enrichment for adverse pathology in resected small renal masses that meet objective progression criteria during active surveillance

*Muammer Altok, Arun Menon, Ahmed Aly, Tashionna White, James Gaybrielle, Bo Xu, Michael Petroziello, Charles Roche, Eric Kauffman*

Roswell Park Comprehensive Cancer Center, Buffalo, NY

**Introduction:** Active surveillance (AS) is increasingly used in small renal mass (SRM) patients; however, there is no uniform agreement on specific tumor progression criteria to trigger delayed intervention (DI). Ideal progression criteria for intervention (PCI) would selectively treat SRM with adverse pathology (15–25% of all SRM); however, patient factors (e.g., anxiety) have been the most common trigger for DI to date, which has challenged studying the efficacy of specific PCI thresholds. Recently, we described our AS experience prospectively using predefined PCI to almost exclusively trigger DI. The current study aimed to characterize pathologic outcomes of DI resection cases to assess the efficacy of these PCI thresholds for selecting SRM with adverse pathology.

**Methods:** From January 2013 to April 2021, all patients with SRM seen at a cancer center were recommended AS if predefined PCI were absent, and DI was recommended only upon new PCI development. PCI was defined prospectively as any SRM-related symptoms, unfavorable biopsy histology, cT3a stage, or any of the following without benign neoplastic biopsy histology: longest tumor diameter (LTD) >4 cm; growth rate (GR) >5 mm/year for LTD ≤3 cm or >3 mm/year for LTD >3 cm. Rates of adverse pathology were retrospectively assessed in DI resections and stratified by specific PCI thresholds met.

**Results:** Of 255 SRM patients with 42 months median followup on AS, there were no metastases and new PCI was diagnosed in 70 (28%), of which 49 (70%) underwent DI, including 44 resections (42 partial, two radical). Only one DI resection was due to patient factors alone. All DI resections were malignant and most (60%) had adverse pathology, including 54% high-grade and 19% pT3a. Rapid GR was the most common trigger of DI (alone=73% of DI cases; concomitant with LTD >4 cm=17% of DI cases), while LTD >4 cm alone was responsible

**Abstract 33. Table 1. Pathologic outcome of 44 DI resected tumors (stratified by PCI)**

	Overall	LTD >4 cm	GR >5 mm/year for LTD ≤3 cm	GR >3 mm/year for LTD >3 cm
<b>Total n</b>	44	13	17	24
<b>Histologic subtype, n (%)</b>				
Clear-cell RCC	37 (84.1)	12 (92.3)	14 (82.4)	20 (83.3)
Non-clear-cell RCC	5 (11.4)	1 (7.7)	2 (11.8)	3 (12.5)
Unknown	2 (4.5)	0 (0)	1 (5.9)	1 (4.2)
<b>Grade, n (%)</b>				
Low-grade (1-2)	19 (43.2)	6 (46.2)	7 (41.2)	11 (45.8)
High-grade (3-4)	22 (50.0)	6 (46.2)	9 (52.9)	11 (45.8)
Not applicable	1 (2.3)	1 (7.7)	0 (0)	1 (4.2)
Unknown	2 (4.5)	0 (0)	1 (5.9)	1 (4.2)
<b>pT stage, n (%)</b>				
pT1a-b	34 (77.3)	9 (69.2)	14 (82.4)	18 (75.0)
PT3	8 (18.2)	4 (30.8)	2 (11.8)	5 (20.8)
Unknown	2 (4.5)	0 (0)	1 (5.9)	1 (4.2)
<b>Any adverse pathology, n (%) (high-grade and/or pT3a)</b>	25 (59.5)	8 (61.5)	10 (62.5)	12 (52.2)

for only 10% of DI cases. Biopsy histology, cT3a upstaging, and symptoms were uncommonly met PCI thresholds (n=3) that were always accompanied by rapid growth and had adverse pathology in most (n=2) cases.

**Conclusions:** Prospectively applied PCI thresholds defined herein effectively identified aggressive SRM cases for DI conversion, given notably higher rates of adverse pathology at DI compared to those historically reported for SRM resections.

### Abstract 34

#### Outcomes of active surveillance for young and healthy patients with small renal masses

*Muammer Altok, Arun Menon, Ahmed Aly, Tashionna White, James Gaybrielle, Bo Xu, Michael Petroziello, Charles Roche, Eric Kauffman*

Roswell Park Comprehensive Cancer Center, Buffalo, NY

**Introduction:** Reported outcomes for active surveillance (AS) in patients with small renal masses (SRM) are heavily biased towards older and unhealthier patients. The safety, tolerability, and delayed intervention (DI) rates for AS in younger and healthier SRM patients remain largely unexplored. Here, we report outcomes at a single center for SRM patients with estimated life expectancy (LE) >20 years who were managed with AS ± DI.

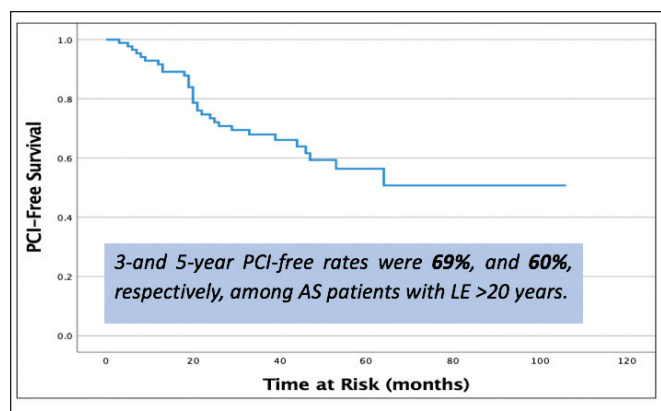
**Methods:** From January 2013 to April 2021, all patients with non-hereditary SRM presenting to a single urologic oncologist at a National Comprehensive Cancer Network institute were recommended AS if predefined progression criteria for intervention (PCI) were absent at presentation. PCI was defined prospectively as any SRM-related symptoms, unfavorable biopsy histology, cT3a stage, or either of the following without benign neoplastic biopsy histology: longest tumor diameter (LTD) >4 cm; growth rate >5 mm/year for LTD ≤3 cm or >3 mm/year for LTD >3 cm. DI was considered during AS only upon PCI development. Patients with LE >20 years were retrospectively reviewed. LE was estimated using social security LE estimations adjusted by age, gender, and Charlson comorbidity index. The three- and five-year rates of PCI-freedom and DI-freedom were determined.

**Results:** Among 98 consecutive SRM patients with LE >20 years, 97 (99%) patients (110 SRMs) did not meet PCI at presentation (median age 57, IQR 47–61) and underwent AS. With median followup of 47 months, 31/97 (32%) AS patients developed PCI, of whom 25/31 (81%) underwent DI (all surgery). One (1%) AS patient crossed over to DI without PCI development. three- and five-year PCI-free rates were 69% and 60%, respectively, and three- and five-year DI-free rates were 76% and 65%, respectively. No patient developed metastasis.

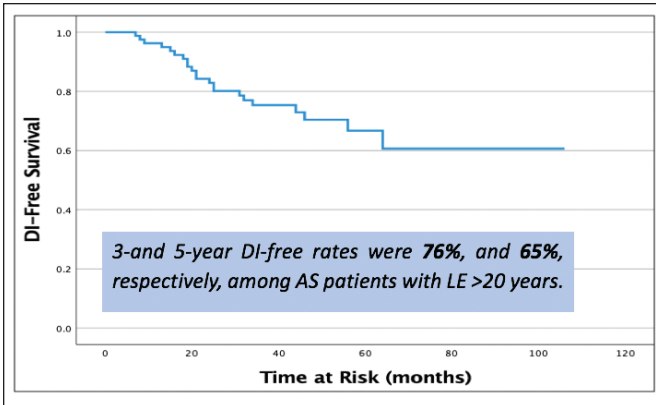
**Conclusions:** AS using predefined PCI in otherwise unselected SRM patients is well-tolerated and allows most SRM patients with >20 years LE to avoid treatment beyond five years. Long-term DI rates and oncologic safety in younger/healthier patients require further study.

### Abstract 35

#### Partial nephrectomy drives the association between high-volume



**Abstract 34. Figure 1A.** PCI-free survival.



Abstract 34. Figure 1B. DI-free survival.

**centers and decreased mortality**

Michael Stencel<sup>1</sup>, Liam MacLeod<sup>2</sup>, Daisy Obiora<sup>1</sup>, Jonathan Yabes<sup>3</sup>, Michelle Yu<sup>1</sup>, Benjamin Davies<sup>1</sup>, Bruce Jacobs<sup>1</sup>  
<sup>1</sup>UPMC, Pittsburgh, PA; <sup>2</sup>Asante Rogue Medical Center, Medford, OR; <sup>3</sup>University of Pittsburgh, Pittsburgh, PA

**Introduction:** We aimed to better understand the association between high-volume surgical kidney cancer centers and decreased mortality and to identify quality metrics that mediate this association.

**Methods:** We designed a cohort of 14 044 patients who were diagnosed with kidney cancer between 2004 and 2013 and underwent a partial or radical nephrectomy. Hospitals were divided into quartiles based on their total nephrectomy volume for the study period. We investigated six quality metrics as potential mediators of the association between hospital volume and mortality using a mediation model.

**Results:** At the highest-volume centers, survival was higher at one-, three-, five-, and 10-year time intervals (91% vs. 89%, 80% vs. 76%, 70% vs. 66%, and 45% vs. 38%, respectively,  $p < 0.001$ ) compared to the lowest quartile nephrectomy centers. Receipt of partial nephrectomy for stage  $\leq T1a$  tumors explains 52.3% of the total association between hospital nephrectomy volume and mortality. Additionally, patients at the highest-volume centers were more likely to be younger ( $\leq 80$  years old, 20% vs. 26%,  $p < 0.001$ ), White (82% vs. 78%,  $p < 0.001$ ), reside in more densely populated counties ( $\geq 1$  million residents, 62% vs. 42%,  $p > 0.001$ ), have a shorter mean length of stay (5.03 vs. 5.88 days,  $p < 0.001$ ) when compared to those in the lowest-volume quartile.

**Conclusions:** This analysis of SEER-Medicare data is the first to suggest that partial nephrectomy in the setting of T1a tumors mediates the association between hospital volume and mortality. Quality metrics that reduce mortality should be harnessed to develop more efficient and higher quality health systems.

**Abstract 36**

**Investigating the role of SLURP-2 in bladder cancer**

Anirban Ganguly, Stephanie Daugherty, Keara Healy, Pradeep Tyagi, Jonathan Beckel  
 University of Pittsburgh, Pittsburgh, PA

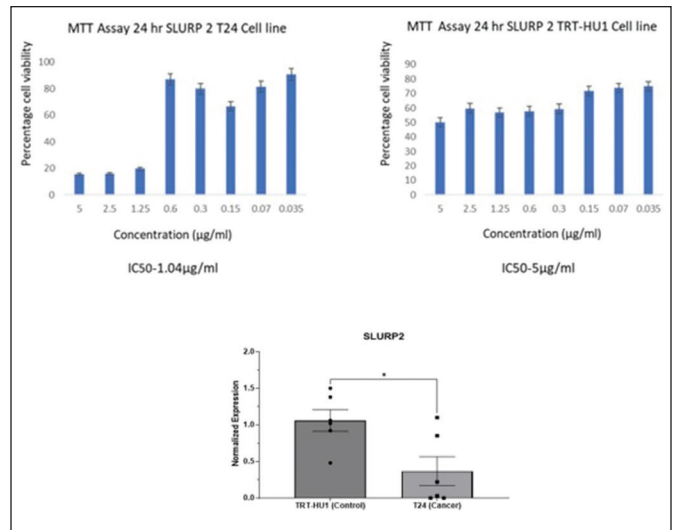
**Introduction:** The treatment of bladder cancer involves a partial or complete resection of the urinary bladder, which can lead to serious quality of life issues for bladder cancer patients. Hence, better treatment options are needed. Smoking is a major risk factor for bladder cancer, as cigarettes contain nicotine and its metabolites. Nicotinic acetylcholine receptors (nAChRs) play a significant role in bladder cancer development. The urothelium expresses two main types of nAChRs:  $\alpha 3$  heteromeric receptors and  $\alpha 7$  homomeric receptors. The third type, heteromeric  $\alpha 4$  receptors, are also expressed in urothelial cancer. Hence, role of endogenous nAChR modulators known as the human-secreted Ly-6/uPAR-related proteins (SLURPs) deserve special importance. Among the SLURPs, SLURP-2 is antagonist for  $\alpha 3/\alpha 4$  receptors. Herein, we investigate the role of SLURP-2 as an inhibitor in the progression of bladder cancer.

**Methods:** Cell culture: T24 bladder transitional carcinoma cells and TRT-HU1 non-cancerous human urothelial cells were cultured in McCoy's 5a medium supplemented with 10% FBS and K562 media supplemented with bovine pituitary extract and epidermal growth factor, respectively. MTT assay: Cells were plated on 96 well plates at a concentration of 5000 cells/well and allowed to grow overnight. The cells were then treated with increasing amounts of recombinant SLURP-2 for 24 hours.  $IC_{50}$  was determined by MTT assay. qPCR: mRNA was extracted from T24 and TRT-HU1 cells. Following reverse transcription, qPCR was performed to compare expression levels of SLURP-2 between the two cell types. SLURP-2 expression was normalized to the expression of a housekeeping gene (18S rRNA) and relative expression calculated using the  $2^{-\Delta\Delta Ct}$  method.

**Results:** MTT assay: The  $IC_{50}$  for SLURP-2 was five times lower in T24 bladder cancer cell lines (1.04  $\mu g/ml$ ) compared to the TRT-HU1 cell lines (5  $\mu g/ml$ ). qPCR: SLURP-2 expression was found to be downregulated in T24 bladder cancer cell lines by 50%.

**Conclusions:** Preliminary results suggest a cytotoxic role for SLURP-2 in bladder cancer. Future mechanistic as well as in-vivo studies on the role of SLURP-2 in mouse models of bladder cancer are required.

Funding: NIH R01DK117884



Abstract 36. Figure 1.

**Abstract 37****Genitourinary malignancy in patients presenting with microscopic hematuria: Northwestern Ontario study**

Vahid Mehmoush, Moustafa Fathy, *Shahrazad Keramati Moezabad*, Mark Tatangelo, Prashidhi Pathak, Parsa Nikoufar, Waleed Shabana, Ahmed Kotb, Ahmed S. Zakaria, Walid Shahrouf, Owen Prowse, David Marsh, Hazem Elmansy  
Northern Ontario School of Medicine, Thunder Bay, ON, Canada

**Introduction:** This study aimed to determine the incidence and characteristics of genitourinary (GU) malignancy in patients that presented with microscopic hematuria (MH) at our tertiary center. Our institution is the only facility providing urologic care to the region of Northwestern Ontario (land area=526 417.35 km<sup>2</sup>, population=232 299).

**Methods:** We conducted a retrospective cohort study of all patients that presented to our center with MH from March 2017 to March 2021. The inclusion criteria included patients aged >40 years, with two microscopic urine analyses at referral showing >3 RBCs/HPF, that had at least a single cystoscopy and imaging of the upper urinary tract at, or, before the first urology visit.

All patients were followed for a minimum of six months with repeat microscopic urine analyses. Low- and high-grade MH were defined as <25 RBCs/HPF and >25 RBC/HPF, respectively.

**Results:** A total of 2545 patients (49.1% males) aged 63.1±17.4 years were included. During the entire study period, the incidence of GU malignancy was 5.2%, including bladder (4.3%), kidney (0.7%), and ureteric (0.2%) cancer. During the initial evaluation, the incidence of GU cancer was 4.2%. Forty patients (1.7%) underwent ureteroscopy after initial evaluation due to positive urine cytology and/or suspicious upper tract imaging, of which, five patients (0.2%) were found to have ureteric tumors. When stratified by the grade of MH at initial evaluation, 3.1% and 10.3% of patients in the low- and high-grade MH groups were found to have GU malignancy, respectively (p=0.0006). Our study identified 1812 patients that were followed up for three years. The rate of GU malignancy among this cohort was 4.5% and 12.5% in patients with low- and high-grade MH, respectively. Interestingly, only two-thirds (59 patients) of individuals in the low-grade MH group that were cancer-positive had a GU malignancy diagnosis during the initial workup.

**Conclusions:** The prevalence of GU malignancy in patients with MH is currently underestimated in the Canadian guidelines. Among our patients, 5.2% were diagnosed with GU malignancy over the study period. Repeat workup is specifically recommended for individuals with low-grade MH, as we found that one-third of cancer-positive patients had a missed cancer diagnosis during the initial workup.

**Abstract 38****Patient characteristics associated with genitourinary tract malignancies in microscopic hematuria cases: A single Canadian center experience**

Shahrazad Keramati Moezabad, Vahid Mehmoush, Moustafa Fathy, Parsa Nikoufar, Mark Tatangelo, Prashidhi Pathak, Ahmed Kotb, Waleed Shabana, Walid Shahrouf, Owen Prowse, Ahmed S. Zakaria, David Marsh, Hazem Elmansy  
Northern Ontario School of Medicine, Thunder Bay, ON, Canada

**Introduction:** The aim of our study was to investigate the characteristics of patients with and without genitourinary malignancy who were referred to the urology service with microscopic hematuria.

**Methods:** We conducted a retrospective data analysis for all patients who presented to the urology service of Thunder Bay Regional Health Science Centre with microscopic hematuria (MH) over the last five years. Inclusion criteria were patients over 40 years old, with microscopic urine analysis at referral (>3 RBCs/HPF), that had at least a single cystoscopy and imaging to the upper urinary tract at or before the first urology visit and were followed for at least six months

with repeat microscopic urine analysis. Low- and high-grade MH was described as <25 RBCs/HPF and >25 RBC/HPF, respectively. Logistic regression models were fit for baseline clinical characteristics and care level characteristics, with reporting in odds ratios and 95% confidence intervals. Outcome measures were binary occurrences of any genitourinary malignancy, and a separate analysis was performed on the outcome of malignancy grade (low/high).

**Results:** The retrospective analysis included 2545 patients referred for urology services included in the study, with 1102 (43.3%) males and a mean age of 66.48 (SD 12.82). Genitourinary cancers were detected in 129 (5.1%) of patients, with 43 (29.9%) patients with high-grade cancer. Covariates that reached statistical significance for increased odds of genitourinary cancers in logistic regression models were age (OR 1.03, p<0.01), gender (male) (OR 2.96, p<0.01), previous gross hematuria (OR 3.46, p<0.01), lower urinary tract symptoms (OR 0.08, p=0.013), and high grade of MH (> 25RBC/HPF) (OR 2.97, p<0.01). For the grade of cancer outcome, male gender (OR 5.66, p<0.01), previous gross hematuria (OR 3.87, p<0.01), and family history of GU cancer (OR 6.54, p=0.02) were associated with an increased odd of high-grade GU cancers.

**Conclusions:** The prevalence of genitourinary malignancy in patients presenting with MH is currently underestimated. Along with age, male gender, previous family history of GU cancer, and previous history of gross hematuria, we highlight the association of high grade of MH (RBC > 25 RBC/HPF).

**Abstract 39****Clinical practice patterns and genitourinary tract malignancies in microscopic hematuria patients: A Northwestern Ontario perspective**

Shahrazad Keramati Moezabad, Vahid Mehmoush, Moustafa Fathy, Mark Tatangelo, Parsa Nikoufar, Prashidhi Pathak, Ahmed Kotb, Waleed Shabana, Walid Shahrouf, Ahmed S. Zakaria, David Marsh, Hazem Elmansy  
Northern Ontario School of Medicine, Thunder Bay, ON, Canada

**Introduction:** Microscopic hematuria (MH) can be the earliest sign of genitourinary (GU) cancers. Therefore, the early detection of GU cancers hinge on patient flow in the healthcare system. This study's goal was to investigate the association of clinical practice patterns (i.e., time to access health services) with the GU cancer in patients referred for MH.

**Methods:** We conducted a retrospective chart review of patients presented to the urology service at Thunder Bay Regional Health Science Centre with MH from 2017–2022. The differences between the time points in the patient evaluation were reported as follows: T1=date of first UA-date of consultation received; T2=date of urology first visit-date of consultation received; T3=date of cystoscopy–date of urology first visit.

**Results:** The retrospective analysis included 2545 patients referred for urology services included in the study, with 1102 (43.3%) males and a mean age of 66.48 (SD 12.82). Statistically significant associated factors with genitourinary cancer detection rate were age (OR 1.03, p<0.01), male gender (OR 2.42, p<0.01), cytology results (OR 3.25, p<0.01), urinalysis high-grade MH (OR 2.80, p<0.01), and other imaging (OR 7.97, p<0.01). For the grade of cancer outcomes, associated factors included male sex (OR 15.9, p<0.01), number of ordered cytology (OR 6.10, p=0.04), cytology results (OR 8.03, p<0.01), and urinalysis very high-grade MH (OR 0.05, 0.04). We found that time points in patient evaluation, longer T1, T2, and T3 were associated with more cancer detection rates and worse outcomes. When it comes to the grade of cancer, those who were living further had higher grades of cancer.

**Conclusions:** Both patient- and system-level factors interact to provide high-quality of care in GU cancers among patients with MH. Our findings highlight the primary care practice in tandem with urology healthcare services at higher levels (hospital) can affect the detection rate and grade of GU cancers in MH patients.