Podium Session 1: Oncology
June 28, 2015, 1010-1110

POD-01.01

Developing a patient-derived xenograft model using the ex-ovo avian embryo to predict targeted therapy tumor resistance in renal cell carcinomas

Power, Nicholas E.[1]; Willie, Chantalle[1]; Mazzola, Clarisse R.[1]; Tailly, Thomas[1]; Sonke, Eric[1]; Pardhan, Siddika[1]; Tram, Ahn[2]; Brugarolas, James[2]; Sener, Alp[1]; Chambers, Ann F.[1]; Pautler, Stephen E.[1]; Leong, Hon[1]
[1]Surgery, Western University, London, ON, Canada; [2]Oncology, UT Southwestern Medical Center, Dallas, TX, United States

Introduction and Objectives: Optimizing targeted therapy in patients with metastatic renal cell carcinoma (RCC) would improve clinical outcomes but patient derived xenograft (PDX) models are lacking. We present a novel preclinical model that is superior to nude mice for accommodating RCC PDXs. This preclinical model implants RC PDXs into the chorioallantoic membrane (CAM) of avian embryos and is a patient-specific platform that could be advantageous for physicians in the future when deciding what treatment options are best for their patients. This drug panelling platform is rapid, cost-effective, and relies on the highly angiogenic CAM to support RCC PDXs.

Methods: Commercial and patient derived RCC cell lines, were grown to full confluence and transduced to generate fluorescently labeled versions of each cell line. Cells were implanted into the CAM. Tumors were treated every two days by applying 10 µL (10 µM) of indicated drug onto the tumor onplant. The drugs that were paneled include Sunitinib, Sorafenib, Pazopanib, Axitinib and a vehicle treatment. After 7-8 days of incubation post-implantation, tumor take rate was determined by the presence of tumor growth in the CAM using a fluorescent stereoscope.

Results: The highest tumor take rates were observed in the vehicle treatments of the embryos, ranging from 50-86%. Both commercial and primary cell lines saw a reduction in tumor take rate with the application of various anti-angiogenic drugs. Specifically, XP121 tumors were resistant to Sorafenib; 786-0, XP121; XP206 were resistant to Pazopanib; T258, XP121 were resistant to Sunitinib; and lastly, T258 tumors were resistant to Axitinib (Table 1).

Conclusions: RCC PDXs onplanted in the CAM of avian embryos offer a robust and cost-effective platform to predict sensitivity/resistance to targeted therapies. When evaluating several patient-derived RCC cell lines, drug paneling revealed other alternative treatment options for these PDXs. More importantly, RCC PDXs that were shown to be Sunitinib-resistant in both the patient and in mouse-based PDXs, also produced the same resistance phenotype in the CAM.

POD-01.02

Validation of a prediction model for the use of postchemotherapy retroperitoneal lymph node dissection in patients with metastatic nonseminomatous germ cell cancers

Punjani, Nahid[1]; Power, Nicholas E.[1]; Vanhie, James[2]; Winquist, Eric[3]
[1]Division of Urology, Western University, London Health Sciences Centre, London, ON, Canada; [2]Western University, London, ON, Canada; [3]Department of Medical Oncology, Western University, London Health Sciences Centre, London, ON, Canada

Introduction and Objectives: Men treated with chemotherapy for metastatic germ cell cancers (GCC) often have residual masses (PCRMs). These contain persistent GCC and/or teratoma in over 50% of patients (pts) with nonseminoma (mNSGCC). Retroperitoneal lymph node dissection (RPLND) identifies persistent GCC and cures teratoma, however, there is controversy about selection criteria for surgery. Ideally data from large datasets would be most informative. Vergouwe et al (2007) have validated a predictive model based on over 1000 pts, and we evaluated its utility in pts treated at our centre.

Methods: mNSGCC pts treated with RPLND for PCRMs were identified from an electronic database. The 2007 publication contained typographical errors, so the prediction formula published in Vergouwe 2003 was utilized with coefficients from the 2007 publication. Six clinical variables were included in the prediction model, and the probability of benign tissue at RPLND was generated and compared with actual pathological results for each pt. "Benign tissue only" was a positive test outcome in pts with a predicted probability of "benign tissue only" of >70%.

Results: 52 mNSGCC pts treated with RPLND for PCRMs between January 1980 and November 2014 were identified. Median age was 32 years (range 17-52). IGCCC prognostic stages were: good 46.2%, intermediate 32.7%, and poor 21.2%. Chemotherapy consisted of BEP in all but 3 pts. Surgery usually consisted of full bilateral RPLND +/- nerve sparing. Pathology showed residual GCC or teratoma elements in 31 pts (59.6%), and benign findings in 21 pts (40.6%). Positive & negative predictive values and accuracy of the predictive model were 100%, 69%, and 73%; respectively.

Conclusions: Benign tissue only was found in 100% of pts in whom this was predicted. This study involved a limited number of pts, but confirms the findings of Vergouwe et al. Routine use of this prediction rule in clinical practice should be considered for mNSGCC pts with PCRMs.

Table 1. POD-01.01. Drug paneling data for RCC PDX tumor take rates (%) ($p<0.05$)

Cell lines	Sorafenib	Pazopanib	Sunitinib	Axitinib	Vehicle
ACHN	**4.5% (1/22)**	**7.10% (1/14)**	**4.80% (1/21)**	15.4% (2/13)	53.3% (8/15)
786-0	9.10% (1/11)	18.2% (2/11)	10.0% (1/10)	**11.8% (2/12)**	50.0% (7/14)
XP158c4.7257	53.8% (7/13)	**20.0% (3/15)**	**14.3% (3/21)**	**0.00% (0/15)**	78.6% (11/14)
ZP127c11.5711	**47.7% (7/16)**	**37.5% (6/16)**	**35.7% (5/14)**	**35.3% (6/17)**	86.7% (13/15)
T258cc	**0.00% (0/10)**	**20.0% (2/12)**	61.1% (11/18)	37.5% (3/8)	66.7% (8/12)
XP121c7.8481	66.7% (6/9)	12/5% (1/8)	53.3% (7/12)	0.00% (0/6)	50.0% (4/8)
XP206c5.535	0.00% (0/7)	16.7% (1/6)	0.00% (0/8)	0.00% (0/8)	50.0% (3/6)

Bold numbers represent statistically significant reduction in tumour size compared with vehicle.

POD-01.03

Lymph node counts are valid indicators of the quality of surgical care in bladder cancer: A population-based study

Siemens, D. Robert[1,2]; William, Mackillop[2]; Wei, Xuejiao[2]; Peng, Paul[2]; Booth, Christopher M.[2]
[1]Urology, Queen's University, Kingston, ON, Canada; [2]Oncology, Queen's University, Kingston, ON, Canada

Introduction and Objectives: To describe lymph node counts at cystectomy for muscle invasive bladder cancer (MIBC) in routine clinical practice. We also evaluate their association with outcomes to explore its utility as a quality indicator.

Materials and Methods: Electronic records of treatment and surgical pathology reports were linked to the population-based Ontario Cancer Registry to identify all patients who underwent cystectomy between 1994-2008. Temporal trends were described over three periods: 1994-1998, 1999-2000, 2004-2008. Multivariate generalized linear regression analysis was used to determine the factors associated with the utilization of pelvic lymph node dissection (PLND). A Cox proportional hazards regression model was used to explore the associations between PLND and survival.

Results: The study population included 2802 patients. Utilization of PLND (50, 62, 85%), median node yield (5, 6, 9), and node density (56, 50, 39%) all improved over the study periods (p<0.001). In multivariate analysis, factors associated with not having PLND include advanced age, female gender, lower socio-economic status, low surgeon volume, and partial cystectomy. In adjusted analyses patients who did not receive a PLND had inferior overall (HR 1.26, 95%CI 1.15-1.38) and cancer-specific (HR 1.23, 95%CI 1.11-1.36) survival. Node yield, as well as density, was also associated with long-term survival.

Conclusions: There is significant variation in utilization and quality of PLND at cystectomy in routine practice. Node counts are independently associated with long-term survival, and this association is persistent despite adjustment for provider-related variables. These results suggest that lymph node counts are a valid quality indicator of surgical care of MIBC.

POD-01.04

An overview on risk factors, treatment patterns and outcomes in primary urethral cancer: Results of the international collaboration on primary urethral carcinoma

Gakis, Georgios[1]; Morgan, Todd[7]; Daneshmand, Siamak[3]; Keegan, Kirk[8]; Clayman, Rebecca[6]; Mischinger, Johannes[1]; Zaid, Harras[8]; Hrbacek, Jan[4]; Ali-El-Dein, Bedeir[5]; Galland, Sigolene[6]; Olugbade Jr., Kola[7]; Rink, Michael[9]; Fritsche, Hans-Martin[2]; Burger, Maximillian[2]; Chang, Sam[8]; Babjuk, Marko[4]; Thalmann, George[10]; Stenzl, Arnulf[1]; Efstathiou, Jason[6]
[1]Department of Urology, University Hospital Tuebingen, Tuebingen, Germany; [2]Department of Urology, University Hospital Regensburg, Regensburg, Germany; [3]Institute of Urology, USC, Norris Comprehensive Cancer Center, Los Angeles, CA, United States; [4]2nd Department of Urology, Charles University, Prague, Czech Republic; [5]Urology and Nephrology Center, Mansoura University, Mansoura, Egypt; [6]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; [7]Department of Urology, University of Michigan, Ann Arbor, MI, United States; [8]Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, United States; [9]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [10]Department of Urology, University of Bern, Bern, Switzerland

Introduction and Objectives: The aim of the study was to investigate the impact of risk factors and treatment patterns on survival in patients with primary urethral cancer (PUC) in a large international cohort.

Methods: A series of 154 patients (109 men, 45 women; median age: 66, IQR: 58-76; N=125 with cM0) were diagnosed with PUC in ten referral centers between 1993 and 2012. Kaplan-Meier analysis with log-rank was used to estimate recurrence-free (RFS) and overall survival (OS). The median follow-up was 21 months (mean: 32 months; IQR: 4-48).

Results: The modality of primary treatment was open surgery in 88 (57.1%), transurethral resection in 39 (25.3%) and radiotherapy and/or chemotherapy in 25 (16.2%) patients, respectively. Clinical tumor and nodal stage correlated highly with pathological tumor and nodal stage (both p<0.001). Patients with synchronous bladder cancer (BC) exhibited inferior 3-year RFS compared to patients with no BC/metachronous BC (63.2% vs. 34.4%; p=0.026). Receipt of neoadjuvant chemotherapy (NAC)/neoadjuvant chemoradiotherapy (N-CRT) was associated with clinically node-positive disease (cN+; p=0.033) and lower utilization of cystectomy at surgery (p=0.015). The overall response rate to NAC and N-CRT was 50% and 50%, respectively. Response to neoadjuvant treatment tended to be associated with improved 3-year OS (100% vs. 37.5%, p=0.08). The 3-year OS for the locally advanced subset of patients (≥cT3 and/or cN+) who received NAC (N=5), N-CRT (N=3), surgery only (N=10) and surgery plus adjuvant chemotherapy (AC; N=8) was 100%, 100%, 50% and 20%, respectively (p=0.016). Patients who underwent salvage surgery/radiotherapy (N=50) for local/urethal recurrence had superior 3-year OS compared to patients who did not undergo salvage therapy (N=32; 95.1% vs. 68.2%; p=0.032).

Conclusions: Nodal stage is a critical parameter in PUC. Patients who receive NAC/N-CRT for cT3 and/or cN+ PUC appear to demonstrate improved survival compared to those who undergo upfront surgery with or without AC. With regard to the high degree of concordance between clinical and pathological staging, multimodal treatment should be strongly considered for these patients. Salvage therapy is of prognostic importance in patients with local/urethral recurrence after primary treatment.

POD-01.05

Pathological upstaging of clinical T1 renal cell carcinoma: A multi-institutional analysis of outcomes

Nayak, Jasmir G.[1,2]; Patel, Premal[1]; Saarela, Olli[4]; Liu, Zhihui[3]; Kapoor, Anil[5]; Tanguay, Simon[8]; Finelli, Antonio[6]; Rendon, Ricardo A.[7]; Moore, Ronald[12]; Breau, Rodney H.[10]; Kawakami, Jun[11]; Black, Peter C.[9]; Drachenberg, Darrel E.[1]
[1]University of Manitoba, Winnipeg, MB, Canada; [2]University of Washington, Seattle, WA, United States; [3]CancerCare Ontario, Toronto, ON, Canada; [4]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [5]McMaster University, Hamilton, ON, Canada; [6]University of Toronto, Toronto, ON, Canada; [7]Dalhousie University, Halifax, NS, Canada; [8]McGill University, Montreal, QC, Canada; [9]University of British Columbia, Vancouver, BC, Canada; [10]University of Ottawa, Ottawa, ON, Canada; [11]University of Calgary, Calgary, AB, Canada; [12]University of Alberta, Edmonton, AB, Canada

Objectives: It has been suggested that the survival among those with clinical T1 renal cell carcinoma (RCC) is unaffected by pathological upstaging and perhaps nephron-sparring surgery should not be dissuaded by concerns for this occurrence. We evaluated the early oncological outcomes for patients upstaged from cT1 to pT2/T3a RCC treated by partial (PN) or radical nephrectomy (RN).

Methods: The Canadian Kidney Cancer Information System is a prospectively maintained database for patients diagnosed with RCC from 15 Canadian institutions. Patients surgically treated for non-metastatic, cT1 RCC between 2009-2014 were evaluated. Upstaging was defined as pT2/T3a disease on final pathology. Our primary outcome was disease progression (recurrence or metastatic disease). Multi-variate Cox regression analysis (MVA) identified predictors for progression while logistic regression was used to predict upstaging. Kaplan-Meir methods estimated survival.

Results: Of 1187 patients with cT1 disease, 862 (73%) underwent PN and 325 (27%) RN. Median follow up was 18 months. 121 (10%) patients were upstaged; 55 (6%) treated by PN and 66 (20%) treated by RN. The 24-month progression-free survival (PFS) was 88% in those upstaged compared with 95% in those not upstaged (p<0.001). Sub-stratifying by surgical approach, upstaged compared with non-upstaged patients had lower PFS rates for both PN (90% vs. 95%, P<0.001) and RN (86% vs. 95%, p=0.001). The difference in 24 month PFS among upstaged patients treated by PN compared with RN was not significant. The median time to progression was 48 months in upstaged patients and not-reached in those without upstaging. Controlling for age, gender, year of surgery, histology, tumor size and surgical approach, pathological upstaging was

independently associated with PFS (HR 2.4, 95% CI 1.2-4.7). Increasing age (OR 1.03, 95% CI 1.01-1.05) and tumor size (OR 1.87, 95% CI 1.62-2.15) were associated with a risk of pathological upstaging.
Conclusions: Pathological upstaging is associated with inferior oncological outcomes at short-term follow-up, irrespective of surgical approach. These findings highlight the importance of accurate clinical staging to facilitate informed decision making among patients with clinical T1 RCC considering treatment options.

POD-01.06

Is re-resection necessary? Re-resection of non-muscle invasive bladder cancer at a tertiary care centre

Matta, Rano[1]; Al Matar, Ashraf[1]; Bhindi, Bimal[1]; Zlotta, Alexandre[1]; Fleshner, Neil[1]; Jewett, Michael[1]; Hamilton, Robert J.[1]; Finelli, Antonio[1]; Kulkarni, Girish S.[1]
[1]Division of Urology, University Health Network, University of Toronto, Toronto, ON, Canada

Introduction: Re-staging transurethral resection (re-TUR) of T1 bladder tumors provides more accurate staging, and is associated with better local control. Re-TUR has been included in guidelines for management of non-muscle invasive bladder cancer since 2008. However, in practice, re-TUR has been questioned in the setting of perceived complete resection at initial TUR, amongst other patient and surgeon specific factors. We aimed to describe re-TUR of T1 urothelial carcinoma and associated outcomes at a Canadian tertiary care center.
Methods: We retrospectively identified 245 patients with T1 urothelial carcinoma of the bladder who were treated at the University Health Network, University of Toronto from 2000 to 2012. We compared re-TUR rates in the pre- (2000-2008) and post-guideline (2009-2012) era. End points, assessed by Kaplan-Meier estimates, were time to recurrence, time to progression (defined as stage T2 or higher), and mortality. Univariate analyses were used to determine any significant effect of patient specific factors (age, gender) and disease specific factors (associated CIS, tumor mass, immediate chemotherapy) on re-TUR. We also analysed the effect of re-TUR on BCG Treatment and stage of first recurrence.
Results: The median age of the cohort was 70.9 years (18.3-96.5) with a male:female ratio of 3.9:1 and a median follow up 2.7 years (0.08-17.9). Re-TUR was performed in 91 patients (37.1%). The average re-TUR rate during the period from 2000-2008 was 28.9% (20.1-37.8) versus 47.8% (30.1-65.6) during 2009-2012 (p=0.052). On re-TUR there was residual T1 tumor in 41.8% but no cases of upstaging. There were no significant patient specific factors or disease specific factors that affected re-TUR rate. There was no significant difference in mortality, with median survival of 10.3 years for patients receiving re-TUR vs. 9.54 years for patients without re-TUR (p=0.25). There were also no significant differences in time to recurrence (4.53 vs. 4.99 years; p=0.52) or time to progression (10.5 vs. 11.1 years; p=0.92) estimates.
Conclusions: With the introduction of current guidelines, re-TUR of T1 bladder cancer has increased, but the majority of T1 bladder cancers are still not re-resected. We found no evidence of upstaging on re-TUR. Furthermore there was no effect on time to recurrence or progression. There was a trend towards decreased mortality in patients being re-resected. Nevertheless, these results bring into question the need for re-TUR in all T1 bladder cancer.