

PROGRAMME SCIENTIFIQUE • SCIENTIFIC PROGRAM

Vendredi, le 14 novembre 2008

Session scientifique V

14 h 30 – 14 h 39

Frequency of cyclooxygenase-2 expression is increased in non-muscle invasive bladder tumours at higher risk of recurrence

Anis Aziz; Katherine Moore; F. Blackburn; Annie Lessard; Hélène Hovington; François Harel; Hélène Larue; Louis Lacombe; Yves Fradet

Centre de recherche en cancérologie, Pavillon HDQ; Faculté de Médecine, Université Laval, Québec, Quebec

Introduction: Nonsteroidal anti-inflammatory drugs (NSAID) users have been shown to reduce the incidence of bladder cancer by 20% in a large population-based case-control study (OR 0.81). Moreover selective COX-2 inhibitors have been shown to have an antitumour effect in vitro and in vivo in a study using a human TCC cell line (HT1376). To determine the potential utility of COX-2 inhibition in secondary prevention of bladder cancer recurrence, we evaluated the expression of COX-2 in non-muscle invasive bladder tumours (NMIBTs) in relation to known risk factors of recurrence and progression.

Methods: Our study population comprised 214 patients with initial NMIBT followed without previous BCG for a median time of 7 years, and 81 patients at high risk of recurrence treated with BCG and followed for a median time 4 years. COX-2 expression was evaluated immunohistochemically with a monoclonal anti-COX-2 antibody. Results were correlated with risk factors of recurrence. Immunoreactivity was categorized as positive if COX-2 staining was > 5% tumour cells.

Results: COX-2 was expressed in 52/214 patients (24.3%) with initial NMIBT. COX-2 was associated with increasing risk factors such as tumour stage (17% in Ta and 47% in T1), grade (14% in G1, 20% in G2 and 64% in G3), tumour diameter (19% in ≤ 3 cm and 32% in > 3 cm) and number of tumours (single 19% and multiple 34%). The expression of COX-2 was also increased in accordance with risk categories of recurrence: low 7.7%, intermediate 22% and high 45%. In this cohort, COX-2 expression was associated with an increased risk of recurrence ($p = 0.0051$). Among BCG treated patients, 27/81 (33%) had a positive COX-2 expression. In this cohort, there was no association of COX-2 expression with stage, grade, number of tumours and duration of BCG treatment nor with recurrence-free survival.

Conclusion: COX-2 expression on initial NMIBT does increase with increasing risk factors for tumour recurrence. However, in higher risk patients treated with BCG, no association was found with outcome. COX-2 inhibitors may be effective in reducing recurrence of NMIBT after transurethral resection.

14 h 39 – 14 h 48

Nephron sparing surgery for high grade renal tumours does not undermine cancer control: a matched analysis study

Sara Baillargeon-Gagné; Claudio Jeldres; Julien Letendre; Ahmed Al Asker; Pierre I. Karakiewicz

Cancer Prognostics and Health Outcomes Unit, CHUM-Pavillon, Saint-Luc, Université de Montréal, Montréal, Quebec

Background: Elective nephron-sparing surgery (NSS) for renal cell carcinoma is an alternative to radical nephrectomy (RN) for renal tumours up to 7 cm in diameter. No previous study addressed the effect of NSS on cancer-specific mortality in patients with high grade tumours (Fuhrman grade 3 and 4). We assessed this outcome in a large tertiary cohort.

Methods: The analyses relied on a cohort of 973 patients with high grade

renal cell carcinoma treated either with nephron-sparing surgery ($n = 158$) or radical nephrectomy ($n = 815$). Kaplan-Meier analyses and univariable and multivariable Cox regression models addressed cancer-specific survival in the overall cohort and in a cohort of 214 patients (72 NSS and 142 RN) that were matched for age, tumour size, Fuhrman grade, T stage and histological type.

Results: At 10 years after surgery, renal cancer-specific survival was 74.8% and 55.2% for, respectively, NSS and in RN patients. In univariable analyses, patients treated with RN demonstrated higher renal cell carcinoma-specific mortality than NSS patients (HR 2.25, $p = 0.003$). However, after adjusting for age, sex, tumour size, T stage, Fuhrman grade and histologic subtype, the type of surgery did not represent an independent prognostic factor ($p = 0.85$). Moreover, when the analyses were restricted to the matched cohort, no difference was observed in renal cancer-specific survival between NSS and RN patients ($p = 0.16$).

Conclusion: In patients selected for NSS, this approach does not compromise cancer control outcome relative to NSS.

14 h 48 – 14 h 57

Comparaison de 2 techniques de clampage du hile rénal dans les néphrectomies partielles par laparoscopie

Annie Imbeault; Frédéric Pouliot; Thierry Dujardin

CHUQ, Université Laval, Québec, Quebec

Objectif : La néphrectomie partielle laparoscopique (NPL) nécessite un contrôle du pédicule rénal afin d'assurer une exérèse tumorale dans de bonnes conditions. Toute modification technique visant à diminuer le temps d'ischémie chaude est primordiale. Lors de notre courbe d'apprentissage, nous avons raffiné notre contrôle pédiculaire en passant d'un clampage artériel isolé vers une prise en masse du pédicule rénal. Nous évaluons les implications de ces changements sur la fonction rénale et les paramètres péri-opératoires.

Méthode : Depuis mars 2003, 166 NPL furent pratiquées par voie transpéritonéale par un seul opérateur. Les 102 premières ont bénéficié d'un contrôle unique (CA) de l'artère rénale (bulldog) alors que les 64 dernières le furent sous contrôle en bloc (CB) du hile (clamp de satinsky). Les données pré-, per- et péri-opératoires de ces néphrectomies furent recueillies de manière prospective. Les paramètres rénaux sont évalués selon les variations de créatinine sérique, du débit de filtration glomérulaire estimé ainsi que sur la perte de la fonction rénale différentielle des reins opérés mesurée à J10 sur des scintigraphies rénales au MAG3-lasix. 53 des 166 patients avaient eu des scintigraphies rénales pré- et post-opératoires.

Résultats : L'âge, le sexe, le temps opératoire, le stade pathologique, la localisation et les dimensions de la masse sont comparables entre les 2 groupes. Le temps de clampage ainsi que l'augmentation de la créatinine post-opératoire sont moins élevés dans le groupe (CB), soit 28,6 minutes v. 23,5 minutes ($p = 0,004$) et 17 $\mu\text{mol/L}$ v. 10,1 $\mu\text{mol/L}$ ($p = 0,015$). Les données reliées au saignement opératoire, au temps d'hospitalisation et au taux de fuites urinaires sont non significatives. La perte de fonction différentielle du rein opéré est de 13,6 % (CA) et de 16,4 % (CB) ($p = 0,406$).

Conclusion : Le clampage en bloc du hile rénal n'est pas associé à une détérioration plus importante de la fonction rénale. Au contraire, cette technique nous permet de diminuer significativement le temps d'ischémie chaude, principal facteur prédictif de la perte de fonction rénale.

14 h 57 – 15 h 06**Ingénierie tissulaire pour la reconstruction d'équivalents urétraux auto-logues par la méthode d'auto-assemblage**

Gabrielle Ouellet; Martine Magnan; Stéphane Bolduc
LOEX, Hôpital du Saint-Sacrement, CHA, Université Laval, Québec, Quebec

Objectif : Chaque année, plusieurs maladies telles l'hypospadias et les sténoses sont à l'origine de désordres urétraux. Pour traiter ces troubles, des biomatériaux ou des tissus non-urologiques natifs sont utilisés et l'emploi de ces matériaux mènent fréquemment à des complications post-chirurgicales. Notre but est donc de reconstruire, à l'aide du génie tissulaire et par la méthode d'auto-assemblage, un modèle urétral autologue, greffable et viable.

Méthodes : Pour réaliser notre modèle urétral, des fibroblastes de la couche dermique et des cellules urothéliales de vessie porcine sont extraits. Les fibroblastes sont cultivés quatre semaines pour pouvoir sécréter assez de matrice extracellulaire et former un feuillet manipulable. Ce feuillet est ensuite enroulé autour d'un support cylindrique pour former un tube, puis gardé en culture pour maturation de trois semaines afin de permettre une bonne adhésion entre les couches. Avant de mettre le tube de fibroblastes en perfusion dans un bioréacteur, les cellules urothéliales sont ensemencées à l'intérieur. La perfusion est d'une durée d'une semaine pour stimuler la prolifération et la différenciation des cellules urothéliales. Dans le but de comparer l'équivalent urétral à l'urètre natif, des tests histologiques, de caractérisations en immunofluorescence et en Western blot (CK7, CK8/18, CK20, collagène I, UKIII), de viabilités cellulaires, de résistance mécanique par éclatement ainsi que de traction uniaxiale ont été effectués.

Résultats : Macroscopiquement, le modèle urétral est uniforme, résistant aux sutures et aux manipulations. Histologiquement, une épaisse couche de fibroblastes dans une matrice extracellulaire ainsi qu'un urothélium similaire à l'urètre natif sont observés. La caractérisation cellulaire du modèle urétral indique la présence d'un urothélium bien différencié et pseudo-stratifié aussi bien en immunofluorescence qu'en Western blot. Pour le test de viabilité cellulaire, les cellules urothéliales et fibroblastiques ont pu être à nouveau extraites et cultivées avec un taux de mortalité de seulement 2 %, ce qui est normalement constaté en culture cellulaire. Pour les tests de résistance mécanique par éclatement et de traction uniaxiale effectués, les résultats sont supérieurs à ceux retrouvés chez l'urètre native de porc.

Conclusion : L'équivalent urétral développé dans notre laboratoire est un modèle innovateur qui offre une alternative idéale pour le remplacement ou la reconstruction urétral puisqu'il utilise les cellules du patient ce qui atténue les réactions inflammatoires par matrices exogènes.

15 h 06 – 15 h 15**Seladin-1 in the prostate: a potential protector against cancer progression**

Meng Guan; Marie-Claude Battista; Véronique Robert; Claude Roberge; Alexandre Ali Doueik; Nicole Gallo-Payet; Robert Sabbagh
Centre Hospitalier Universitaire de Sherbrooke, Québec, Quebec

Background: In cancer, abnormal cholesterol metabolism favours tumour cell growth. Recently, overexpression of Seladin-1 (a protein involved in cholesterol synthesis) has been reported in prostate cancer. Seladin-1 also belongs to a subgroup of androgen-dependant genes associated with antiproliferative, pro-differentiation and pro-apoptotic functions. In fibroblasts, Seladin-1 was shown to offer a protection against oncogenic stress. The objective of this study was to examine the localization, expression and role in proliferation of Seladin-1 in normal and malignant human prostatic tissue at different Gleason scores. The hypothesis is that Seladin-1 offers protection against prostate cancer progression.

Methods: Tissue localization of Seladin-1 was determined by immunofluorescence performed on human prostate biopsies. Expression of Seladin-1 was assessed in normal and malignant prostatectomy specimens by Western blot. Primary cell cultures were provided from fresh radical prostatectomy specimens. The effects of Seladin-1 on proliferation were assessed

by counting the cells after 5 days of culture following treatment with the Seladin-1 specific inhibitor, U18666A.

Results: Western blot results show that Seladin-1 is highly expressed in low risk prostate cancer tissues (Gleason score 6) compared to noncancerous prostate tissues. Its expression is much lower in advanced prostate cancers (Gleason score 8–10) than compared to the normal prostate tissue. Immunofluorescence on prostate biopsies show that in both normal and cancer specimens, Seladin-1 is localized in the glandular tissues rather than in the fibromuscular stroma. Also, Seladin-1 is more localized on the luminal side of the glandular tissue in low grade (Gleason 3) prostate cancer. In contrast, in both normal and high grade (Gleason 4 to 5) prostate biopsy specimens, Seladin-1 is localized evenly throughout the glandular tissues. In primary prostate cell cultures, the specific inhibitor of Seladin-1, U18666A, increased the normal prostate cell proliferation to levels seen in prostate cancer cell cultures.

Conclusion: Our results are in agreement with our hypothesis that Seladin-1 seems to offer protection against prostate cancer progression. In low to intermediate grade prostate cancer, the expression of Seladin-1 seemed to be increased to protect the cells against anarchic proliferation thus helping to slow down progression of the cancer. When the expression of Seladin-1 can no longer be maintained, the cells lose complete control on proliferation leading to more invasive forms of cancer. Confirmation of the role of Seladin-1 would open new horizons in the treatment of prostate cancer.

15 h 15 – 15 h 24**Early induction of erectile dysfunction by angiotensin II in rats**

R. Segal¹; Frederic Mampouma²; Taben M. Hale²; Serge Carrier¹; Denis deBlois²

¹Jewish General Hospital, McGill University, Montréal, Quebec; ²Department of Pharmacology, Université de Montréal, Montréal, Quebec

Objective: Erectile dysfunction (ED) is an early indicator of cardiovascular disease, of which a major contributing factor is hypertension. Furthermore, there is evidence to suggest that angiotensin II (AngII) receptor (AT1) blockers improve erectile function in hypertensive patients. The aim of this study is to determine whether the development of ED precedes systemic cardiovascular damage after a continuous infusion of AngII in rats.

Methods: Sprague Dawley rats (250 g) were randomized to receive a continuous infusion of either AngII (200 ng/kg/min s.c., $n = 5$) or saline ($n = 6$) by osmotic minipumps implanted subcutaneously for a total of 7 days. The mean arterial pressure (MAP) and intracavernous pressure (ICP) were measured simultaneously, and erectile function was estimated by the ICP/MAP ratio measured in response to electrical stimulation of the cavernosal nerve (1–5.5 V) in the anesthetized rats. At the end of this procedure, the rats were sacrificed, the hearts excised and the ventricles separated and weighed. The aorta and penis were also excised and cleaned, and a section of each was fixed in formalin for histological analysis. Aortic rings were used to evaluate vascular relaxations induced by acetylcholine or sodium nitroprussiate (SNP).

Results: A continuous infusion of AngII for 7 days did not significantly affect the MAP (saline 97, SD 9, mm Hg, v. AngII 86, SD 4, mm Hg, [NS] prior to stimulations and 118, SD 7, mm Hg, v. 109, SD 10, mm Hg, [NS], after) heart/body weight ratio (saline 1.94, SD 0.07, mg/g, v. AngII 1.95, SD 0.22, mg/g, NS), aortic cross-sectional area (saline 0.47, SD 0.020, mm², v. AngII: 0.48, SD 0.061, mm², NS) or aortic cell number (saline: 174, SD 32.4, cells/μm, v. AngII: 177, SD 38.9, cells/μm, NS). The ratio ICP/MAP, on the other hand, was significantly diminished in the group treated with AngII in a voltage-dependent manner (at 5.5 V, saline 26, SD 9, v. AngII 57, SD 6, $p = 0.003$). Functional studies showed no evidence of endothelial dysfunction in the aorta.

Conclusion: This study, the first to examine the impact of chronic AngII administration on erectile function, suggests that ED precedes the development of arterial hypertension and left ventricular hypertrophy at 7 days of infusion. Our results support the hypothesis that erectile function is an early gauge of cardiovascular complications.

15 h 24 – 15 h 33

Extended lymphadenectomy in radical prostatectomy: a multicentre study

Michele Lodde¹; Hélène Hovington¹; François Harel¹; Michael J. Harris²; David P. Wood³; Louis Lacombe¹; Yves Fradet¹

¹Université Laval, CHUQ-Hotel-Dieu de Québec, Québec, Quebec; ²Northern Institute of Urology, Traverse City, Michigan; ³University of Michigan, Department of Urology, Ann Arbor, Michigan

Objective: The aim of this study was to analyse the impact on PSA failure (PSAF) of extended lymphadenectomy (PNLD) with particular sampling of the internal iliac chain versus standard and no PLND.

Methods: The databases of 3328 radical prostatectomies (RP) from 3 different urological departments, A, B and C, have been retrospectively compared. 552 patients that received neoadjuvant therapy have been excluded since only group B and C performed it and pathological stage and Gleason could have been down staged. Then, 2776 patients left for the analysis. Group A performed only perineal RP and no PNLD, group B a retropubic RP and standard PNLD and group C a retropubic RP and extended PLND. For the statistical analysis patients have been stratified according to preoperative PSA < 10 ng/mL or PSA > 10 in 2 different groups. PSAF was defined for centre and A and B as 0.2 ng/mL and for centre C 0.3 ng/mL or in case of salvage radiotherapy or hormone therapy the date of therapy begin was considered as a PSA failure.

Results: The analysed cohort consist on 2776 patients, 667 for group A, 1229 group B and 870 group C. Median follow-up was 4, 3.13 and 6.28 years for groups A, B and C, respectively. Group C had consisted of patients with higher pathological characteristics compared to group B and C. Extended PNLD retrieved a median of 14 (IQ 10–18) nodes compared to the 5 (IQ 3–9) of the standard PNLD and pathological positive nodes were 2% and 12% for groups B and C, respectively. The Cox regression analysis adjusted for age, initial PSA, clinical and pathological variable, surgical variable as well as the use of adjuvant androgen deprivation therapy or adjuvant radiotherapy in patients with PSA < 0.10 and PSA > 10 shows for patients with PSA < than 10 ng/mL a 25% risk reduction of PSAF for for the group with extended PNLD which was not statistically significant. For patients with a PSA > 10 ng/mL extended PNLD (HR 0.41, 95% CI 0.23–0.73, $p = 0.002$) but not standard PNLD (HR 0.93, 95% CI 0.53–1.6, $p = 0.8$) reduced the risk of biochemical recurrence compared to group A (no PNLD).

Conclusion: In this study extended PLND compared to standard PLND

increased the number of LN removed and the detection of positive N+. Extended PNLD but not standard PNLD could reduce the risk of PSAF in 60% of the cases.

15 h 33 – 15 h 42

Phase II study of treatment with 5- α reductase inhibitors (5ARIs) in low risk prostate cancer

Jérôme Lévesque; Michele Lodde; Thierry Dujardin; Louis Lacombe; Yves Fradet

Université Laval, CHUQ, L'Hôtel Dieu de Québec, Québec, Quebec

Objective: The PCPT trial showed a 25% reduction of prostate cancer (PCA) incidence in men treated with 5ARIs. We studied the impact of a treatment of low risk PCA patients with 5ARIs on follow-up biopsy outcome.

Materials and methods: Patients with a low risk PCA (Gleason < 7, PSA < 10 ng/mL, < 3 biopsy cores) on 12 cores TRUS biopsy were offered a treatment with 5ARIs. Patients were followed with PSA, digital rectal examination and a first follow-up TRUS biopsy after 6 to 12 months of therapy and yearly thereafter. The presence of cancer, Gleason score, high grade PIN and ASAP was recorded at diagnosis and at each successive biopsy.

Results: We recruited 77 patients (median age 64, SD 4, yr) with a median PSA of 5.52 ng/mL and median follow-up 20 months. All patients had a first follow-up biopsy at a median of 8.5 months and 20 patients had a second follow-up biopsy on average a year later. For the total length of the study, Gleason score up grading was seen in 14 cases (18.2%, 10 = G7, 4 = G > 7); 7 (9%) had definitive treatment (2 radiotherapy, 4 radical prostatectomy and 1 hormonotherapy). At the first follow-up biopsy patients still positive for cancer were 30 (39%). Of the 20 patients with a second follow-up biopsy 14 (70%) remained negative, 5 had a Gleason 6 and 1 increased to Gleason 7. The percentage of specimens positive for high grade PIN and ASAP changed little. Compared to pre-treatment biopsy, the percentage at first follow-up biopsy of high grade PIN went from 18.4% to 15.2% and ASAP from 6.8% to 9.4%.

Conclusion: Treatment of low risk PCA with 5ARIs resulted in a negative first follow-up biopsy in 61% providing a positive reinforcement to expectant management. Indeed, 91% of patients are still under surveillance after 20 months of average follow-up, which is slightly higher than average expectant management series (76%–80%). Gleason score upgrade occurred in 18.2% at first follow-up biopsy, selecting out early those patients requiring definitive treatment.

PROGRAMME SCIENTIFIQUE • SCIENTIFIC PROGRAM

Samedi, le 15 novembre 2008

Session scientifique VIII

8 h 00 – 8 h 09

Radical cystectomy treatment delays in the province of Quebec: an update

Nader Fahmy; Moamen Amin; Suganthiny Jeyaganth; Wassim Kassouf; Simon Tanguay; Jordan Steinberg; Armen Aprikian
Montreal General Hospital, McGill University Health Centre, Montréal, Quebec

Introduction: Invasive bladder cancers have a rapidly progressing nature. We have shown that delay to radical cystectomy is associated with increased mortality in Quebec. The aim of the current study was to examine the delay to RC in more recent years in Quebec and compare to our original study of 1990–2002.

Methods: We obtained the billing records of all patients treated with RC for bladder cancer across Quebec from 2003 to 2005. Collected information included age, sex, dates of urologists visits, cystoscopy, TURBT and CT scanning, hospital type (academic or not) and volumes and dates of death. Data were then compared to the previously obtained billing records from 1990 to 2002.

Results: A total of 610 RC were included in this study. Median recent (2003 to 2005) diagnostic delays from urologist to cystoscopy, then to TURBT have increased significantly when compared to earlier (1990 to 2002) delays, going from 11 to 43 and 4 to 21 days respectively. TURBT to CT or to RC delays have also increased, going from 14 to 22 and 33 to 55 days, respectively. Finally median urologist to RC delays have increased from 69 to 134 days. Interestingly, hospital case-load has increased significantly during the same time period. Although recent mean caseload/year was significantly greater in academic institutions when compared to nonacademic (11 v. 31 cases/yr, $p = 0.02$), the former tended to have shorter delays ($p = 0.09$).

Conclusion: Recent treatment delays have significantly increased when compared to earlier periods. Although academic centres had significantly higher caseload/year when compared to non academic institutions, they did not demonstrate longer delays.

8 h 09 – 8 h 18

Analyse des mécanismes d'inhibition de la croissance induite par la toxine botulinique dans les cancers prostatiques

J. Cury¹; Gilles Karsenty²; C. Andrieu²; P. Rocchi¹; F. Bladou¹; S. Chevallier¹; J. Iovanna¹; Jacques Corcos¹

¹Université McGill, Montréal, Quebec; ²Marseille, France

Objectif : Plusieurs études cliniques ont montré que l'injection de toxine botulinique A (TBA) dans la prostate humaine améliore les troubles mictionnels liés à l'hypertrophie bénigne de prostate. Dans ce contexte nous étudions l'effet potentiel de la TBA sur des foyers de cancer de prostate infracliniques coexistants. Nous avons préalablement montré que la TBA inhibe la prolifération du modèle hormonosensible de cancer de la prostate (CaP) humain LNCaP in vitro et in vivo et qu'elle est sans effet sur le modèle hormonorésistant PC-3. Le but de ce travail était d'élucider le mécanisme d'action de la TBA dans ces deux modèles.

Matériels et méthodes : Le récepteur de la toxine botulinique SV2 a été évalué sur les lignées LNCaP et PC-3 ainsi que sur des prélèvements de CaP humain par techniques de Western blot, immunocytochimie, immunohistochimie et microscopie à fluorescence. Des cultures cellulaires de lignée LNCaP et PC-3 ont été exposées à des doses croissantes de TBA. L'apoptose évaluée par la technique de cytométrie de flux a été comparée entre cellules traitées et contrôle.

Résultats : Par technique de Western blot, le récepteur SV2 était significativement surexprimé dans la lignée sensible à la TBA (LNCaP) comparée à la lignée insensible (PC-3). Par immunofluorescence et immunocytochimie SV2 a été mis en évidence au niveau membranaire et cytoplasmique dans les deux lignées. L'intensité du marquage a confirmé la surexpression de SV2 dans la lignée LNCaP. Le récepteur est présent dans les tumeurs humaines peu différenciées son expression est superposable à celle du marqueur neuroendocrine chromogranine A. Le traitement des cellules LNCaP par BTA augmente significativement l'apoptose comparée au contrôle (ratio 3/1) $p < 0,001$

Conclusion : La surexpression de SV2 dans la lignée LNCaP comparée à la lignée PC-3 pourrait permettre d'expliquer l'action directe de la toxine botulinique sur les cellules LNCaP. L'inhibition de la croissance de la lignée LNCaP induite par la TBA est associée à une augmentation de l'apoptose. Ces observations montrent que la TBA peut agir par effet direct sur les cellules épithéliales prostatiques.

8 h 18 – 8 h 27

A simple and accurate model for prediction of cancer specific mortality in patients treated with surgery of a primary penile squamous cell carcinoma

Vincent Cloutier^{1,3}; Laurent Zini^{1,2}; Paul Perrotte³; Umberto Capitanio^{1,4}; Claudio Jeldres¹; Shahrokh F. Shariat¹; Fred Saad³; Alain Duclos³; Philippe Arjane³; Hugues Widmer³; Francesco Montorsi⁴; Pierre I. Karakiewicz^{1,3}

¹Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montréal, Quebec; ²Department of Urology, Lille University Hospital, Lille, France; ³Department of Urology, University of Montréal, Montréal, Quebec; ⁴Department of Urology, Vita-Salute San Raffaele, Milan, Italy

Background: Even after stratification for stage, the cancer specific mortality of patients with penile squamous cell carcinoma (SCC) may be quite variable. Recently a nomogram was developed to provide standardized and individualized predictions of cancer specific survival (CSS) after removal of the primary tumour. Unfortunately, it relies on a large number ($n = 8$) of specific variables that are unavailable in routine clinical practice. This important limitation limits the usefulness of this nomogram.

Objective: To develop a simple and accurate nomogram predicting cancer specific mortality after surgical removal of primary penile SCC.

Design, setting and participants: The predictive model was developed on a cohort of 420 patients and externally validated using a cohort of 436 patients identified in the 1988–2004 Surveillance, Epidemiology and End Results (SEER) database. The predictors consisted of age, race, stage, grade, type of surgery and lymph node status.

Measurements: A nomogram based on Cox regression model-derived coefficients was used for prediction of cancer-specific mortality (CSM) and its accuracy was tested using the area under the receiver operating characteristics (ROC) curve.

Results and limitations: Of all candidate predictors, stage and histological grade variables qualified for inclusion in the final nomogram. In the external validation cohort, the nomogram achieved 77% accuracy for prediction of CSM at 5 years after resection of primary penile SCC.

Conclusion: Our model is more accurate (77% v. 73%) and substantially less complex (2 v. 8 variables) than the previously published model. In

consequence, we strongly advocate the use of our tool to predict cancer specific mortality after surgery of primary penile SCC.

8 h 27 – 8 h 36

Immunosuppression dans le cancer la prostate : régulation androgénique de l'expression des arginases

Philippe O. Gannon; Jessica Godin-Ethier; Matthew Hassler; Benjamin Péant; Alexis Poisson; Megan Aversa; Réjean Lapointe; Anne-Marie Mes-Masson; Fred Saad

Hôpital Notre-Dame, Insitut du cancer de Montréal, CR-CHUM, Montréal, Quebec

Objective: The significant immunological boost following androgen deprivation therapy (ADT) illustrates the immunosuppressive potential of androgens in prostate cancer. The expression of arginase II (ArgII) appears to be one possible mode of immunosuppression in prostate cancer. Therefore, it is of interest to determine whether the expression of ArgII, and of arginase I (ArgI), is regulated by androgens in prostate cancer. Our objectives are to evaluate the in vitro and in vivo expression of ArgII and ArgI in prostate cancer cell lines and primary tumours and determine their role in the immunosuppressive potential of prostate cancer cells.

Methods: The regulation of the in vitro expression of ArgI and ArgII was evaluated in LNCaP cells stimulated for 72 hours with R1881 by real-time PCR and Western blots. The activation of immune cells was studied using PBMCs from healthy donors, which were stimulated with OKT3 (anti-CD3) in the presence of conditioned media from LNCaP expressing a siRNA against ArgI or ArgII. PBMCs activation was monitored by ELISA against IFN γ . The androgen-regulated expression of ArgII was evaluated in vivo by immunohistochemistry on duplicate tissue micro-array containing cores from a cohort of 40 control patients (radical prostatectomy only) and 36 ADTx patients (ADT prior to radical prostatectomy). Two independent observers scored ArgII expression based on staining intensity and percentage of stained cells.

Results: By real-time PCR, LNCaP stimulated with R1881 expressed > 6x more ArgII than control LNCaP ($p < 0.01$, Mann-U, $n = 6$). Western blot revealed an androgen-dependant upregulation of ArgI and ArgII protein expression. This increased in arginase expression was associated with a decreased in L-arginine in the media (HPLC). The androgen-dependent expression of ArgI was dependent on the presence of the androgen receptor, but not that of Arg II. PBMCs activated in the presence of conditioned media of LNCaP + SiArgII secreted more IFN γ (537 pg/mL with LNCaP+SiCtrl v. 1681 pg/mL with LNCaP+SiArgII) ($p < 0.05$, Mann-U, $n = 4$). In vivo expression of ArgII in ADTx patients was 2x lower in normal adjacent tissues ($p < 0.001$, t test) and was 1.3x lower in tumour tissues ($p = 0.024$, t test) compared to control patients.

Conclusion: Our results demonstrate that the presence of androgens favors the expression of ArgII both in vitro and in vivo. Our data supports the notion that, in the presence of androgens, prostate cancer cells are directly involved in the development of an immunosuppressive tumour environment through the up-regulation of ArgI and ArgII.

8 h 36 – 8 h 45

Increasing tumour size is associated with higher rates of high Fuhrman nuclear grade in patients with renal cell carcinoma

Rupinder Johal; Claudio Jeldres; Pierre I. Karakiewicz
Cancer Prognostics and Health Outcomes Unit, CHUM-Pavillon, Saint-Luc, Université de Montréal, Montréal, Quebec

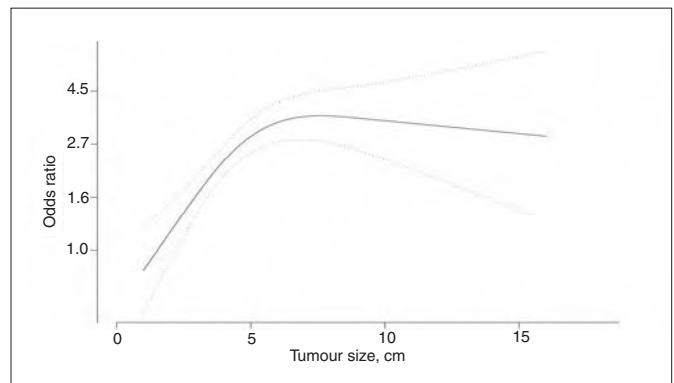
Introduction: Active surveillance as been used in selected patients with small localized renal masses. Since high Fuhrman nuclear grade defined as grade III or IV is associated with unfavorable outcomes, we assess the effect of tumour size on the rate of Fuhrman grade III-IV in patients who underwent nephron-sparing surgery (NSS) and radical nephrectomy (RN) for renal cell carcinoma.

Materials and methods: Between 1984 and 2001, 2476 patients were treated for renal cell carcinoma in 13 academic centres in Europe. Univariable and multivariable logistic regression analyses addressed the presence of Fuhrman grade III-IV at final pathology according to the tumour size. Covariates consisted of age, T stage and symptoms

at diagnosis. Tumour size was coded as cubic splines (to allow nonlinear effect).

Results: The age mean and median were 60 years and 61 years, respectively, (range 18–93 yr). Of all, 1991 (80.4%) patients were T1 stage and 485 (19.6%) patients were T2 stage tumours. Mean and median tumour size values were 5.2 cm and 4.5 cm, respectively, (range 0.5–21.0 cm). Of all, 1625 (65.6%) were male. At diagnosis, 1776 (71.7%) patients were asymptomatic. The rate of Fuhrman grade III-IV increased with tumour size, where tumours ≤ 1 cm, 1–2 cm, 2–3 cm, 3–4 cm, 4–5 cm, 5–6 cm, 6–7 cm and > 7cm were associated with rates of Fuhrman grade III-IV of 0.4%, 3.7%, 11.2%, 14.8%, 15.9%, 12.5%, 11.2% and 30.3%, respectively. In univariable and multivariable analyses increasing tumour size was associated with higher risk of Fuhrman grade III-IV at final pathology. The multivariable cubic spline analyses showed that the rate of Fuhrman grade III-IV markedly increased up to a tumour size of 7 cm ($p < 0.001$) and then flattened.

Conclusion: Tumour size predicts the rate of Fuhrman grade III-IV up to 7 cm and may be used as an indicator of nuclear grade. (Fig. 1)

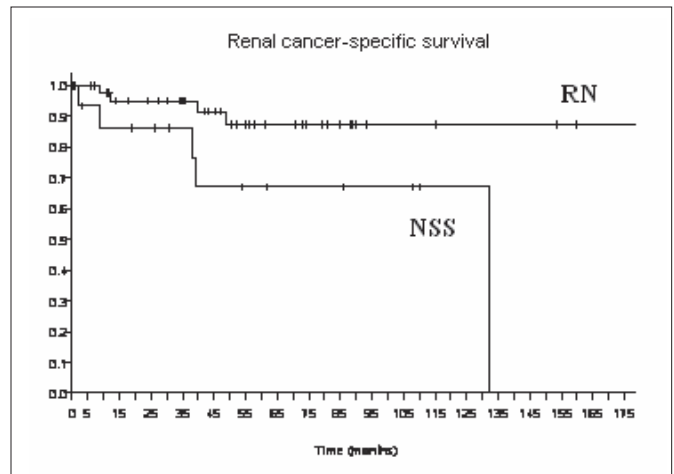


8 h 45 – 8 h 54

Nephron-sparing surgery v. radical nephrectomy in patients with renal cell carcinoma > 7 cm with no evidence of nodal or distant metastasis

Julien Letendre; Claudio Jeldres; Sara Baillargeon-Gagné; Ahmed Al-Asker; Quoc Dien-Trinh; Naeem Bhojani; Paul Perrotte; Pierre I. Karakiewicz
Cancer Prognostics and Health Outcomes Unit, CHUM-Pavillon Saint-Luc, Université de Montréal, Montréal, Quebec

Introduction: Nephron-sparing surgery (NSS) may be associated with higher rate of renal cell carcinoma cancer-specific mortality in patients with tumours > 7cm.



Material and methods: Between 1984 and 2001, 4669 patients were treated for renal cell carcinoma. Of all, 925 (19.8%) were > 7 cm without nodal or distant metastasis. Of these tumours, 72 (3.1%) underwent NSS and 789 (96.9%) had radical nephrectomy (RN). Multivariable and matched analyses were performed for age, gender, tumour size, Fuhrman grade, T stage and histology, which resulted in 2 comparable groups. Up to 3 RNs were matched with one NSS case. Life tables, Kaplan-Meier and Cox regression analyses addressed RCC-specific survival (RCC-SS) according to the type of surgery (NSS v. RN).

Results: Of 29 NSS cases, 17 were matched with 45 of 896 RN cases. At 2 and 5 years, RCC-SS rates in men treated with NSS v. RN were 86.2% versus 95.0% and 67.0% versus 87.2%, respectively. In the matched analyses, after adjusting for age, gender, tumour size, Fuhrman grade, T stage and histology, RN was associated lower rate of RCC-SM (RR 0.2, $p = 0.02$).

Conclusion: Our data indicate that better cancer control might be achieved with RN, when tumour size exceeds 7 cm. (Fig. 1)

8 h 54 – 9 h 03

A comparison between composix-based slings, tension-free vaginal tapes (TVT) and transobturator tapes (TVT-O): median follow-up of 24 months

Nadim Haïdar; Mireille Grégoire; Katherine Moore
CHUQ-L'Hôtel-Dieu de Québec, Québec, Québec

Objective: Suburethral synthetic sling procedures have become widely used as surgical treatment for female urinary stress incontinence. However synthetic slings are expensive. Since 2002, we have used in a nonrandomized fashion, Composix-based slings, tension-free vaginal tapes TVT and transobturator tapes TVT-O.

Methods: Among the 103 women suffering from stress incontinence, 60 were assigned to Composix, 28 to TVT and 15 to TVT-O. Only patients presenting a complete set of data were included in the analysis. Preoperative workups included medical history, clinical examination, a 24-hour pad test, FPSUND (symptom score), and satisfaction and impact incontinence quality of life (I-QOL) questionnaires. Objective changes in SUI were the primary end point, whereas other outcome variables such as symptoms, quality of life questionnaires and satisfaction scale were our secondary end points. Clinical check-ups were conducted at 3 months, every 6 months for 2 years and then annually for up to 5 years. The objective result was considered successful when the absolute value of incontinence after treatment was ≤ 2 g per 24 hours.

Results: The median follow-up of the cohort was 24 months. The median I-QOL scores for the Composix, TVT and TVT-O prior to surgery were 57, 55 and 49, respectively, and 106, 106 and 109 at 24 months. Similarly, the FPSUND scores were initially 12, 11, 12 and 4, 1, 2 at follow-up, whereas the 11 point-scale satisfaction score improved from 2 to 9 for all groups. The median pad weight was 26 g, 66 g and 20 g prior to surgery; only 4 patients had persistent urinary stress incontinence following surgery.

Conclusion: This study did not detect a significant difference between the Composix, TVT and TVT-O slings for the cure of female stress incontinence at a mean follow-up of 24 months. The effect of the all procedures on cure of incontinence and improvement in quality of life is maintained over at least 2 years. The Composix sling was significantly cheaper but the product is no longer available.

9 h 03 – 9 h 12

Novel biomimetic angiogenic acellular urinary bladder for urinary bladder tissue engineering in small and large animal models

Katherine Moore; Jennifer Haig; Herman Yeager; Roula Antoon; Walid A. Farhat
Division of Urology, Centre Hospitalier Universitaire de Québec (CHUQ), Université Laval, Québec, Québec

Objective: Successful organ tissue engineering requires timely vascularization and recellularization. Herein, we assess the regenerative potential of newly developed hybrid constructs of porcine bladder acellular matrix (ACM) incorporated with hyaluronic acid (HA) and vascular endothelial growth factor (VEGF) matrix in both murine and porcine models.

Methods: Using a nude mice model we initially investigated the maximum angiogenic effects of incorporated VEGF into the construct. HA-ACM was lyophilized then rehydrated in different concentrations of VEGF. Different VEGF concentrations of 1 ng, 2 ng, 3 ng, 10 ng and 50 ng of tissue were incorporated intraperitoneally in nude mice. Implants were left in situ for 1 week and upon explantation, angiogenesis was detected by immunohistochemistry using endothelial cell markers (CD31 and Factor VIII). Microvascular density was measured using commercially available software. The VEGF concentration that induced the maximum amount of normal vascularization was then used to augment urinary bladder implants in a porcine model (Control ACM, ACM/HA and ACM/HA/VEGF). Using histology and immunohistochemistry (uropodins, SMA, CD31 and Factor VIII) regenerative capacity of the different groups was then assessed.

Results: In the mice, using statistically significant differences in microvascular density were demonstrated in the 2 ng group. This concentration was used in the porcine model, where there was pronounced cellularization (urothelial and smooth muscle cells) of the matrix, both in the centre and periphery. In addition, vascular in growth was potentiated in the HA and HA-VEGF grafts.

Conclusion: We have demonstrated statistically significant differences in microvascular density in vivo when 2 ng of VEGF is incorporated in the ACM. Other growth factors, which also play a role in angiogenesis and cellularization warrant further investigation.

9 h 12 – 9 h 21

Role of mTOR inhibitors in bladder cancer cells treated with radiation therapy

Roland Nassim; J. Mansure; Fabio Cury; Françoise DeBlois; Simone Chevalier; Wassim Kassouf

Urologic Oncology Research Group, McGill University Health Centre Research Institute, Montreal General Hospital, Montréal, Québec

Introduction: Radiation therapy for invasive bladder cancer allows for organ preservation but systemic toxicity and local control remains problematic. As such, there is a need to increase radiosensitization of tumour cells to improve efficacy. The aim of this study was to investigate if mTOR (mammalian target of rapamycin), a downstream kinase of the phosphatidylinositol 3-kinase/Akt survival pathway, may be a target for bladder cancer therapy.

Methods: A panel of 9 representative human urothelial carcinoma cell lines reflecting different stages of bladder cancer (from superficial to invasive and metastatic) was screened for their sensitivity to the mTOR inhibitor, RAD001. Growth inhibition was monitored by MTT assays. Effects on cell cycle and apoptosis were ascertained by FACS analysis. Clonogenic assays were used to analyze the response of RAD001-resistant and RAD001-sensitive cell lines alone and in combination with different doses (1 Gy–6 Gy) of gamma radiation. The expression of Akt and mTOR as well as the mTOR substrate, S6, was assessed by Western blots, including in their phosphorylated state.

Results: RAD001 was a very potent growth inhibitor for the 9 screened bladder cancer cell lines, causing a G0/G1 phase arrest but not significantly affecting cell death. From the established dose-response curves, IC50 values ranging from 0.1 nM to 100 nM were found, thereby reflecting striking differences in RAD001 cell sensitivity. Western blots revealed expression of activated key signalling molecules of the mTOR pathway. Moreover RAD001 effectively inhibited the mTOR downstream signal in the subset of cell lines tested. Dose response to gamma radiation alone was determined in 3 cell lines. UM-UC3 (IC50 = 3 Gy) were considered to be the most resistant to radiation, followed by KU7 and 253-JP (IC50 = 2 Gy). More importantly, a significant decrease in colony formation was observed in KU7 and 253-JP in the combined treatment when compared to RAD001 or radiation alone. These findings point to an additive or synergistic effect between the 2 treatments.

Conclusion: The inhibition of mTOR signalling appears promising as therapeutic modality for bladder cancer, especially in the context of combination with radiation therapy.

9 h 21 – 9 h 30

Analyse rétrospective des cas de carcinomes rénaux/surrénaux avec thrombus dans la veine cave inférieure s'étendant en supra-diaphragmatique

Alexandre Saourine; François Dagenais; Louis Lacombe
Hôpital Laval et HDQ, Québec, Québec

Objectif : La néphrectomie radicale avec exérèse de thrombus dans la veine cave inférieure s'étendant en supra-diaphragmatique sous circulation extra-corporelle est une chirurgie rarissime. Nous avons donc révisé notre expérience pour cette chirurgie, ainsi que la survie à long terme de ces patients.

Methodes : Entre mars 1999 et mai 2008, 18 patients ont subi une néphrectomie radicale avec exérèse de thrombus dans la veine cave inférieure sous circulation extra-corporelle. Tous les patients avaient un envahissement de la veine cave inférieure supra-diaphragmatique, dont 9 avaient un thrombus s'étendant jusque dans l'oreillette droite. La durée moyenne de la circulation extra-corporelle était de 96,3 minute, avec abaissement de la température ad 22°C chez 71,4 %. La durée moyenne de cette chirurgie était de 255 minutes.

Resultats : Notre cohorte est composée de 11 hommes et de 7 femmes. L'âge des patients varie entre 28 ans et 79 ans, avec une moyenne de 59,8 ans. La perte sanguine moyenne a été de 3543 mL. La pathologie a révélé un carcinome à cellules claires chez 76,4 %. La durée de séjour à l'hôpital a été de 5 à 34, médiane de 9 jours. Une patiente est décédée en post-op immédiat d'une tamponnade cardiaque. La durée du suivi s'étend de 1 à 75 mois, 10 patients (66,7 %) sont actuellement vivants avec un suivi moyen de 9,75 mois. 5 patients (33,7 %) sont décédés avec suivi moyen de 23,5 mois. La proportion de patients décédés était plus élevée dans le groupe où le thrombus s'étendait dans l'oreillette droite (60 % v. 40 %).

Conclusion : La néphrectomie radicale avec exérèse de thrombus dans la veine cave inférieure s'étendant en supra-diaphragmatique sous circulation extra-corporelle demeure une chirurgie rarissime. L'extension de thrombus dans l'oreillette droite semble diminuer la survie à long terme de ces patients. L'augmentation de nombre de patients dans notre série pourra peut-être confirmer cette hypothèse.

9 h 30 – 9 h 39

Outcome of patients who had unresectable bladder cancer upon exploratory laparotomy

Faysal A. Yafi¹; Marie Duclos¹; José A. Correa²; Simon Tanguay¹; Armen G. Aprikian¹; Luis Souhami¹; Raghu Rajan¹; Jeremy Sturgeon¹; Wassim Kassouf¹

¹Divisions of Urology, Radiation Oncology and Medical Oncology, McGill University Health Centre, Montréal, Québec; ²Department of Mathematics and Statistics, McGill University, Montréal, Québec

Objective: Abortion of a cystectomy due to unresectable disease is not uncommon in patients with bladder cancer. Our aim was to review the outcome of these patients and evaluate various prognostic variables.

Methods: From 1993 to 2007, a total of 31 patients with bladder cancer underwent exploration for radical cystectomy which was aborted due to fixation to the pelvis and rectum or presence of grossly palpable nodes. Collected variables included presence of hydronephrosis, concomitant carcinoma in situ, clinical stage, variant histology, ECOG performance, Charlson comorbidity score, history of superficial tumours, reason for abortion, pelvic lymph node dissection, postoperative chemotherapy/radiation, recurrence and salvage cystectomy. Survival data were analyzed using Kaplan–Meier method and Cox regression analysis.

Results: Mean age of patients was 66 years with a median follow-up of patients alive 10 months. The 2-year and 5-year overall survival (OS) was 41% and 0%, respectively. 17 cases were aborted due to tumour fixation to the pelvis or rectum and 14 due to gross palpable nodes. 20 had a pelvic lymph node dissection and 11 had no lymph node dissection or just nodal sampling. 23 patients received postoperative therapy, of which 8 received chemotherapy alone and 15 a combination of chemoradiation. OS was not significantly associated with hydronephrosis, concomitant carcinoma in situ, clinical stage, histology,

performance, comorbidities, history of superficial tumours, postoperative therapy or salvage cystectomy. However, gross palpable nodes showed a worse outcome than fixation to sidewalls ($p = 0.0325$) with shorter median OS (13 v. 17 mo). Patients who underwent a pelvic lymph node dissection were associated with prolonged OS compared to those who did not (24 v. 10 mo, $p = 0.09$).

Conclusion: Outcome of patients with unresectable disease is dismal. Patients who had an aborted cystectomy due to unresectable disease may benefit from a pelvic lymph node dissection prior to chemoradiation. Further refinements of clinical staging to better identify these patients pre-operatively and offer them upfront chemotherapy are needed.

9 h 39 – 9 h 48

The effect of androgen deprivation therapy on the rate of subsequent noncancer morbidities

Claudio Jeldres; Quoc-Dien Trinh; Naeem Bhojani; Vincent Cloutier; Julien Letendre; Sara Baillargeon; Ahmed Al Asker; Rupinder Johal; Paul Perrotte; Pierre I. Karakiewicz
University of Montréal, Montréal, Québec

Introduction: Androgen deprivation therapy (ADT) is widely utilized for the treatment of prostate cancer patients. This treatment modality exposure has been shown to be associated to a subsequent increase in the rate of other comorbidities. We examined the effect of ADT exposure time on the rate of 12 different comorbidities in a large administrative database.

Methods: The study population consisted of 28 510 prostate cancer patients diagnosed between 1983 and 2004. Of these, 10 787 (37.8%) were treated with androgen deprivation therapy according to medication codes. Exposure to more than 1.5 year was recorded in 6437 patients (59.7%). The addressed comorbidities consisted of: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebro-vascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, moderate to severe renal disease, diabetes, mild liver disease and moderate to severe liver disease. Univariable and multivariable Cox regression analyses were performed. Covariates included age, anti-androgen therapy exposure and comorbidities acquired prior to the date of the diagnosis of the comorbidity of interest. Each comorbidity was addressed in a separate analysis and was excluded from the list of covariates. Comorbidities were coded as cubic splines, to account for nonlinear effect.

Results: In univariable analyses, the rates of myocardial infarction (HR 1.24, $p < 0.001$), congestive heart failure (HR 1.49, $p < 0.001$), peripheral vascular disease (HR 1.13, $p = 0.002$), dementia (HR 1.98, $p < 0.001$), cerebro-vascular disease (HR 1.22, $p < 0.001$), chronic pulmonary disease (HR 1.18, $p < 0.001$), moderate to severe renal disease (HR 1.53, $p < 0.001$) and diabetes (HR 1.19, $p < 0.001$) were elevated in ADT exposed patients relative to unexposed ones. In multivariable analyses, after adjusting for age and anti-androgen therapy exposure, virtually all rates of these morbidities were increased in ADT exposed individuals. Interestingly, after controlling for other comorbidities using the time-dependent covariate approach and after coding other comorbidities as cubic splines, only the rates of dementia ($p = 0.02$) and of chronic pulmonary disease ($p = 0.01$) maintained their independent predictor status.

Conclusion: Exposure to ADT is associated with an increased risk of developing dementia and chronic pulmonary disease. Lack of detailed control for the confounding effect of comorbidities and of variable ADT exposure time may falsely exaggerate the strength of the association between ADT and other morbidities.

9 h 48 – 9 h 57

Suspected clinical T3 prostate cancer is associated with high rate of negative extended biopsies: clinical implications

Daniel Liberman; Claudio Jeldres; Quoc-Dien Trinh; Naeem Bhojani; Vincent Cloutier; Julien Letendre; Sara Baillargeon; Ahmed Al Asker; Rupinder Johal; Paul Perrotte; Pierre I. Karakiewicz
University of Montréal, Montréal, Québec

Introduction: The presence or even the suspicion of clinical T3 prostate

cancer (PCa) discourages many urologists from considering surgical management, due to potentially high rate of treatment failure. However, patients with suspected clinical T3 PCa may do well clinically. Many may have a more favourable pathological stage than T3 disease. Others may have a favorable Gleason grade. Finally, some patients with suspected clinical T3 disease may not even be found to have PCa at needle biopsy. We decided to explore the hypothesis that clinical T3 stage may not be a reliable indicator of true disease extent. To test this hypothesis, we assessed the rate of negative biopsy in patients with suspected clinical T3 PCa. A substantial rate of negative needle biopsy in patients with suspected clinical T3 PCa can be interpreted as evidence for unreliability of clinical stage assignment in this patient category, whereby clinical stage may overestimate the true extent of the disease.

Methods: We examined the rate of PCa detection in 340 consecutive patients with suspected clinical T3 prostate cancer who underwent a biopsy at our institution, between 1992 and 2007.

Results and limitations: Of these, 81.5% had cancer, but the others (28.5%) did not. Among these 340 patients, we reassessed the PCa detection rate in 83 patients who underwent an extended biopsy (≥ 10 cores) and detailed clinical information. Of these 83 patients, 20 (24.1%) had no PCa at biopsy. Only prostate volume distinguished patients according to biopsy outcome: patients with negative biopsies had significantly larger prostates than patients with PCa.

Conclusion: These data indicate that not all men with suspected clinical T3 PCa have voluminous cancers, since such cancers should clearly not escape any method of detection. Instead, as many as 24.1% of men had no evidence of PCa at initial extended biopsy, which implies that clinical stage suggestive of extracapsular extension (clinical T3 PCa) is a poor indicator of true disease extent in at least 24.1% of such men.

9 h 57 – 10 h 06

Applicability of dorsal lumbotomy for pyeloplasty in older kids: How far can we push the limits?

Jonathan Cloutier; Nadim Haïdar; Stéphane Bolduc
CHUL, CHUQ, Université Laval, Québec, Quebec

Objective: Dismembered pyeloplasty performed through a dorsal lumbotomy incision for the correction of ureteropelvic junction obstruction is mainly performed successfully in the paediatric population for children less than 5 years old for technical reasons. We compared the records of 78 children who had undergone dorsal lumbotomy by age group (< 5 v. > 5 yr) to determine if the surgical success and long term results were comparable in both.

Methods: We retrospectively reviewed the records of 78 consecutive children undergoing dismembered pyeloplasty by a single paediatric urologist from 2002 to 2007. The study population was divided into 2 groups. Group 1 which consisted of the children < 5 years old ($n = 48$) and group 2 consisted of the older children, > 5 years old ($n = 30$). Patients' characteristics, intra- and postoperative variables as well as all pre- and postoperative renal radiographic and scintigraphic parameters were compared. Success was defined as an objective ultrasound improvement in the anteroposterior renal pelvis diameter and grade of hydronephrosis and a scintigraphic improvement of the drainage half time (T1/2) when indicated. Data were obtained from hospital records and both groups were compared with the 2-tailed *t* test. Univariate and multivariate analysis were performed to check for independent risk factors predicting the percentage of improvement in renal radiographic parameters.

Results: The main mode of presentation in group 1 was prenatal diagnosis (80%), whereas renal colic (64%) was the one in group 2. The mean age at surgery was 0.9 year and 10.3 year in group 1 and group 2, respectively; 64% were males in both groups, left kidney was involved in 62% of group 1 population versus 46% in group 2. The mean operative time and the mean blood loss were 106 minutes and 7 mL versus 126 minutes and 20 cc for group 1 and 2, respectively. The mean hospitaliza-

tion time was 2.8 days for both groups and opioids analgesia requirement was 10% higher in group 2. A Pippi-Salle stent was used in 92% ($n = 72$) of cases while double J stent in 6% ($n = 5$), they were kept for 11 and 48 days, respectively. In our study population, intraoperative and postoperative complications were non significant. The mean follow-up time was 554 days and our success rate as defined above was 93% for both groups.

Conclusion: The dorsal lumbotomy pyeloplasty is a safe and efficacious approach in both age groups and may be more cost-effective than laparoscopy in older kids before teenage years. In our series, our preliminary results show that a dismembered pyeloplasty by dorsal lumbotomy has a comparable outcome in both age groups with regard to intraoperative and postoperative complications, surgical success as well as the maintenance of long term results.

10 h 06 – 10 h 15

Tumour-specific fusion RNA as noninvasive new markers for diagnosis and prognosis of prostate cancer

Junjian Z. Chen; Baoying Gu; Sam Chan; Annie Giannatselis;
Armen Aprikian

Department of Surgery, Division of Urology, McGill University Health Centre, Montréal, Quebec

Many prostate tumours are slow-growing and may pose little threat to health. Only certain prostate tumours require treatment. At present, there is no reliable method to identify cancers that are beginning to spread and require aggressive treatment. As a recent groundbreaking discovery, many prostate tumours contain a specific genetic change that involves fusion of 2 different genes. The most common fusion places oncogenic *ERG* gene under the androgen-regulated transcriptional control of *TMPRSS2*, a very specific event in prostate cancer. Thus the fusion-mediated *ERG* over-expression may be a causative change in early prostate tumorigenesis, and its tumour-specificity may offer a new venue for noninvasive cancer detection in bodily fluid. The objective of current study focuses on its clinical applications as a noninvasive marker for early detection of clinically aggressive prostate cancer. We hypothesize that diverse *TMPRSS2:ERG* fusion gene subtypes can be detected in exfoliated prostate tumour cells in urine, and early detection of specific fusion subtypes may have prognostic utility to identify aggressive forms of cancer. In an initial analysis, we have successfully adopted a whole-transcriptome-amplification (WTA) strategy to amplify ng amount of degraded urine RNA into μ g of WTA cDNA fragments, which allowed sensitive detection of less than 0.1% of fusion positive RNA from a cancer cell line in a background of normal urine RNA. The WTA cDNA fragments then served as substrates for "unlimited" qPCR of multiple fusion isoforms. To do so, we have developed and validated a new panel of isoform-specific fusion probes targeting the common fusion isoform (I) and 7 additional isoforms (II-VIII) including several implicated in aggressive prostate cancer. In a pilot analysis, 8 of 20 (40%) urine samples from men with prostate cancer were detected with at least one fusion isoform, among which 4 samples were each detected with 2 or more fusion isoforms. Moreover, none of the fusion isoforms was detected in 16 urine samples from noncancer control subjects, suggesting their high specificity to prostate cancer. In comparison, *PCA3*, a commonly used prostate cancer-specific marker, was detected in 10 of 20 (50%) urine samples from the same cancer subjects. However, *PCA3* was also detectable in several urine samples from the control subjects. Based on these progresses, we are currently evaluating the sensitivity and specificity of a combined urine test using fusion RNA, *PCA3* and other cancer-specific markers in early detection of prostate cancer, and correlating specific fusion gene subtypes to cancer progression in a watchful waiting cohort in prospective studies. Sensitive detection of tumour-specific fusion genes in bodily fluids may provide mechanism-based diagnostic and prognostic markers that can be used in clinical management of prostate cancer.

PROGRAMME SCIENTIFIQUE • SCIENTIFIC PROGRAM

Dimanche, le 16 novembre 2008

Session scientifique XIII

8 h 57 – 9 h 06

Number and sites of bone lesions and history of skeletal-related events (SREs): Do these parameters correspond with skeletal morbidity and mortality in patients with bone metastases (mets) from hormone-refractory prostate cancer (HRPC)?

Fred Saad¹; Pierre P. Major²; D. Habr³; Richard J. Cook⁴

¹Centre Hospitalier de l'Université de Montréal, Montréal, Quebec;

²McMaster University, Juravinski Cancer Centre, Hamilton, Ontario;

³Novartis Pharmaceuticals Corporation, East Hanover, New Jersey;

⁴University of Waterloo, Waterloo, Ontario

Background: Bone mets are common in HRPC, and baseline (BL) risk factors for SREs and death have been studied. However, potential risk factors during zoledronic acid (ZOL) therapy have not been evaluated.

Methods: Exploratory univariate analyses were performed using data from the placebo-controlled trial of ZOL in HRPC patients with bone mets (Saad et al. *J Natl Cancer Inst* 2002). ZOL-treated patients with data on SRE history, lesion number (< or ≥ 4), and lesion site (weight-bearing [WB] v. non-WB bone) were included ($n = 376$ at BL). At BL, 6 months and 12 months, patients were recategorized, and relative risks (RRs) for SREs and death throughout the remaining on-study period were estimated by Cox regression.

Results: **SRE history:** Having ≥ 1 v. no prior SRE was a risk factor for SREs throughout treatment (BL: RR = 1.429, $p = 0.0338$; 6 mo: RR = 1.892, $p = 0.0018$; 12 mo: RR = 2.080; $p = 0.0259$). Although not a prognostic factor at baseline, ≥ 1 v. no prior SRE correlated with RR of death in on-study assessments (6 mo: RR = 1.449, $p = 0.0124$; 12 month: RR = 2.135, $p = 0.0006$). **Bone lesion number:** For each timepoint, ≥ 4 v. < 4 bone lesions correlated with ~2-fold increased risks of death (BL: RR = 2.115, $p < 0.0001$; 6 mo: RR = 2.131, $p < 0.0001$; 12 mo: RR = 2.100; $p = 0.0003$) and with increased risks of SREs during the 6 months of treatment (BL: RR = 1.953, $p < 0.0001$; 6 mo: RR = 1.572; $p = 0.0267$); however, no significant effect was observed at 12 months. **Lesion site:** Lesions on WB bones were not a significant risk factor for SRE or death at any assessment.

Conclusion: In patients with bone mets from HRPC, prior SRE and ≥ 4 bone lesions correlate with increased risk for SREs and death throughout the course of ZOL treatment, and the association seems to be as high in post-BL assessments. These data support ongoing monitoring of skeletal health in patients with bone mets from HRPC. Multivariate analyses to place these parameters in context with other prognostic variables are underway.

9 h 06 – 9 h 15

CUOG phase II randomized study of custirsens (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within 6 months of first-line docetaxel therapy

Fred Saad¹; Sébastien J. Hotte²; Scott North³; Bernie Eig⁴; K. Chi⁵; P. Czaykowski⁶; M. Pollak⁷; L. Wood⁸; Eric Winquist⁹

¹Université de Montréal, Montréal, Quebec; ²Juravinski Cancer Centre, Hamilton, Ontario; ³Cross Cancer Institute, Edmonton, Alberta; ⁴Tom Baker Cancer Centre, Calgary, Alberta; ⁵BC Cancer Centre, Vancouver, British Columbia; ⁶CancerCare Manitoba, Winnipeg, Manitoba; ⁷Jewish General Hospital, Montréal, Quebec; ⁸Queen Elizabeth II Health Sciences

Centre, Halifax, Nova Scotia; ⁹London Health Sciences Centre, London, Ontario

Objective: There is no standard of care when patients with metastatic HRPC manifest disease progression (PD) after first-line docetaxel. Custirsens is an antisense oligonucleotide targeting clusterin which in preclinical studies increased response of taxane-resistant cell lines to chemotherapy. This study evaluated the safety and efficacy of custirsens in combination with either docetaxel or mitoxantrone as second-line therapy (Rx).

Materials and methods: Patients were eligible if they had PD while receiving or within 6 month of discontinuing first-line docetaxel. All patients received 640 mg of weekly IV custirsens following 3 loading doses. Patients were randomized to standard doses of docetaxel/prednisone (DPC) or mitoxantrone/prednisone (MPC) on a 21-day cycle for up to 9 cycles. Protocol defined PD was based on RECIST, pain and performance score but not solely on PSA.

Results: Analysis as of Jan. 3, 2008; median follow-up: 13.3 (8.4–17.1) months. Forty-two patients received at least 1 cycle of combined therapy (DPC-20, MPC-22). Prior outcomes with first-line docetaxel were similar in both arms. The median time to PD for all patients was 1.8 months; 16 (38%) patients had PD while receiving first-line Rx. Following custirsens therapy: median number of cycles delivered: DPC-7.5, MPC-6.0; 40% of patients completed 9 cycles. Best PSA response (≥ 90, ≥ 50, ≥ 30%): DPC-20/40/55%, MPC-0/27/32%. Predetermined pain response: DPC-8/12 (67%), MPC-7/14 (50%); median duration in both arms: 6 months. KM estimate of PFS: DPC-4.7, MPC-2.6 months. At a median follow-up of 13.3 months, 60% of patients are still alive in both arms. Both regimens were well tolerated; there were more grade 3/4 AEs with MPC (68%) than DPC (50%) + 1 patient died of CHF following 8 cycles of MPC.

Conclusion: In patients who progressed during or soon after first-line docetaxel, both custirsens combination regimens were well tolerated and associated with impressive PSA + pain responses and better than expected survival. Custirsens/docetaxel/prednisone appeared superior to custirsens/mitoxantrone/prednisone in both efficacy and safety. Phase 3 studies are planned utilizing chemotherapy plus custirsens as second-line therapy in patients progressing after a first-line docetaxel regimen.

9 h 15 – 9 h 24

Permanent seed prostate brachytherapy (PB) at the CHUM: early toxicity results

Daniel Taussky; Sandrine David; Yannick Hervieux; Renée Larouche; Stephanie Lassalle; Jean-Paul Bahary; David Donath

Radiation Oncology, Department of Radiation Oncology, CHUM, Hôpital Notre-Dame, Montréal, Quebec

Introduction: To report our early results in the first 195 patients treated with permanent seed prostate brachytherapy (PB).

Methods: We started our PB program in July 2005. 195 patients were treated until May 2008. Because of the short follow-up, we report only urinary toxicity results. AUA-scores were measured in all patients before the implant and then 1 month later. Most patients had additional measurements 4 months after the implant and then every 4 months for the first year. Urinary catheters were removed immediately after the implant. If patients were unable to urinate spontaneously, a catheter was reinserted and if possible taken out the day after the implant.

Results: Most patients had low risk cancer. 10.3% had a Gleason 7 (3 + 4 only) cancer and 8% had a PSA > 10. Median age was 65 (range

50–78) years. Median prostate volume was 38.2 (range 15–74.4) mL. Of the first 195 patients treated, 50.8% never needed a catheter after the procedure and 32.3% for 1 day, 13.3% had a catheter for 2–21 days and 7 (3.6%) needed self catheterization. In 5 patients it resolved spontaneously. One patient needed a TURP after 1 year and a second patient still catheterized himself after about 6 months. One patient had a rectourethral fistula. Median preimplant AUA score was 3 (range 0–24). Median values after 1 and 4 months were 8 (0–29) and 7 (0–29), respectively. After 8 and 12 months AUA scores were 4 (0–18) and 2 (0–17), respectively. Severe urinary symptoms, arbitrarily defined as a AUA score of ≥ 15 were present in 21%, 13%, 2.5% and 2% of patients after 1, 4, 8 and 12 months, respectively.

Conclusion: In our first nearly 3 years of experience, acute and chronic urinary retention was low when compared to the literature. Other more severe urinary symptoms usually resolve after 8 months.

9 h 24 – 9 h 33

RAD001 v. placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: results from a randomized, double-blind, multicentre phase-III study

Pierre I. Karakiewicz¹; Robert J. Motzer²; Bernard Escudier³; Stéphane Oudard⁴; Camillo Porta⁵; Thomas E. Hutson⁶; Sergio Bracarda⁷; Norbert Hollaender⁸; Gladys Urbanowitz⁹; Andrea Kay¹⁰; Alain Ravaud¹¹

¹Université de Montréal, Montréal, Quebec; ²Memorial Sloan-Kettering Cancer Center, New York, New York; ³Institut Gustave Roussy, Villejuif, France; ⁴Georges Pompidou European Hospital, Paris, France; ⁵San Matteo University Hospital, Pavia, Italy; ⁶US Oncology, Baylor-Sammons Cancer Center/TOPA, Dallas, Texas; ⁷Azienda Ospedaliera, Perugia, Italy; ⁸Novartis Oncology, Florham Park, New Jersey; ⁹Novartis Oncology, Florham Park, New Jersey; ¹⁰Novartis Oncology, Florham Park, New Jersey; ¹¹Department of Medical Oncology, Hôpital Saint André, Bordeaux, France

Background: RAD001 (everolimus) is an oral inhibitor of mTOR, an intra-

cellular kinase that regulates cell proliferation and angiogenesis. Antitumour activity has been shown in a single-arm phase-II trial in pretreated mRCC with continuous daily therapy (*JCO* 2007;25[18S]:261s Abs 5107).

Methods: Patients with RCC with a clear-cell component progressing on or $<$ 6 months after VEGFr-TKI therapy (sorafenib, sunitinib, or both) were randomized 2:1 to RAD001 (10 mg/d po) or placebo, both with best supportive care. Patients were stratified by MSKCC risk criteria and prior VEGFr-TKI therapy (1 v. 2). Progression-free survival (PFS), documented using RECIST and assessed via blinded, independent review, was the primary endpoint. At progression, treatment was unblinded and patients on placebo offered open-label RAD001. Based on a sample size of 362 patients, the trial had 90% power to detect a 33% risk reduction (HR 0.67), with a median exponential PFS improvement from 3.0 to 4.5 months (stratified log-rank test). Results of a planned interim analysis are presented as these met prespecified criteria for a positive trial, the Independent Data Monitoring Committee stopped the study to allow remaining patients on placebo to receive RAD001.

Results: From September 2006 to October 2007, 272 patients were randomized to RAD001 and 138 to placebo. Demographics were well balanced (pooled median age 60 yr) as was prior VEGFr-TKI therapy (sunitinib 71%, sorafenib 55%, sunitinib+sorafenib 26%). 191 PFS events (47% of 410 patients) were reported by central review: 101 (37%) and 90 patients (65%) on RAD001 and placebo, respectively. Most common AEs (all grades/grade 3–4) were stomatitis (RAD001 36/4%, placebo 7/0%), anemia (28/7% v. 15/5%), and asthenia (28/2% v. 20/4%). 10% of patients had AEs leading to discontinuation with RAD001 v. 4% with placebo whereas dose reductions were required by 4% v. $<$ 1%. 68 deaths were observed, and study follow-up is ongoing to assess the secondary endpoint of overall survival.

Conclusion: RAD001 resulted in a statistically and clinically significant improvement in PFS over placebo with a favourable safety profile in patients with mRCC after progression on other targeted therapies.