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MP-01.01

Abiraterone Acetate Plus Low-Dose Prednisone Has a Favorable Safety Profile, Improves Survival and Produces PSA and Radiographic Responses in Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer: Results from COU-AA-301, a Randomized, Double-Blind, Placebo-Controlled, Phase III Study

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Introduction and Objective: Abiraterone acetate (AA) is an androgen biosynthesis inhibitor that selectively inhibits CYP17, blocking testicular, adrenal, and prostatic intratumoral androgen synthesis. Studies suggest that some metastatic castration-resistant prostate cancers (mCRPCs) remain dependent on androgen receptor (AR) signaling.

Methods: In COU-AA-301 patients (pts) with docetaxel-treated mCRPC were randomized 2:1 to AA (1000 mg) + prednisone (P) (5 mg BID) (n=797) or placebo + P (n=398) at 147 centers in 13 countries. The primary endpoint was overall survival (OS). PSA and radiographic assessments were adapted from PSAWG criteria (Bubley, JCO, 1999). Safety assessments were standard.

Results: Based on a pre-specified interim analysis, the IDMC recommended the study be unblinded. Efficacy results from 1195 enrolled patients are presented (Table 1). Grade 3/4 AEs occurred in 55% of pts with AA vs 58% with placebo. Frequently occurring (>5%) adverse events (AEs) with AA vs placebo were: fatigue (8% vs 10%), anemia (7.5% vs 7.4%), back pain (6% vs 10%), and spinal cord compression (3% vs 5%). The most common grade 3/4 laboratory-related AEs were decreased lymphocytes (21% vs 23%) and increased ALP (18% vs 13%).Grade 3/4 AEs of special interest (AA vs placebo) were: fluid retention (2.3% vs 1%), hypokalemia (3.8% vs 0.8%), LFT abnormalities (3.5% vs 3.0%), hypertension (1.3% vs 0.3%), and cardiac disorders (4.1% vs 2.3%). The cardiac disorders were predominantly arrhythmias; there was no imbalance in cardiac AEs with an outcome of death (1.1% vs 1.3% with AA vs placebo).

Conclusions: AA + P has a favorable safety profile and significantly improves OS, TTPP, rPFS, PSA response rate, and radiologic response rate in patients with mCRPC post docetaxel. This Phase III study confirms that AA provides clinical benefit following medical/surgical castration in post-docetaxel mCRPC.

MP-01.02

Prevention of Bone Loss Using Risedronate in Patients Starting Androgen Deprivation Therapy: Canadian Urologic Oncology Group (CUOG) Trial P-05

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Introduction and Objectives: Bone loss due to androgen deprivation therapy (ADT) is well established and has been implicated with a higher risk of fractures. Prevention of bone loss has been studied using various strategies using IV and oral bisphosphonates and more recently subcutaneous denosumab. The primary objective was to determine the feasibility and efficacy using weekly risedronate to prevent bone loss at 1 year in men beginning ADT. The primary endpoint of the study was change in lumbar spine (LS) BMD at 1 year.

Methods: Trial was begun in 2005 and ended in 2009. 140 patients starting ADT (less than 3 months prior to study entry) were randomized to receive weekly risedronate or placebo. BMD of the lumbar spine and hip was performed at baseline and at 1 year. Bone markers (Serum and urinary CTX, Bone Specific Alkaline phosphatise and osteocalcin) were obtained at baseline as well as at 3, 6, 12 months. Descriptive statistics were used to describe patient populations at baseline and changes from baseline. Analysis of covariance was used to test differences between treatment

Table 1. MP-01.01

Endpoint	AA (n=797)	Placebo (n=398)	HR (95% CI)	*p*
		Primary		
OS, median (months)	14.8	10.9	0.65 (0.54, 0.77)	<0.0001
		Secondary		
TTPP, median (months)	10.2	6.6	0.58 (0.46, 0.73)	<0.0001
rPFS, median (months)	5.6	3.6	0.67 (0.58, 0.78)	<0.0001
PSA response (%)	38	10	-	<0.0001
		Other		
Objective response rate (%)[a]	14.0 (n=55/392)	2.8 (n=5/181)	5.[1b] (2.1, 12.5)	<0.0001

a = RECIST in subjects with measurable disease at baseline; b = relative risk.

CUAJ • June 2011 • Volume 5(3Suppl1)

groups for the changes from baseline with the baseline value being the covariate.
Results: Baseline characteristics were balanced between groups. One year LS-BMD were available for 118 patients. Patients on placebo had a statistically significant bone loss at 1 year for LS-BMD (p=0.012) and LS-T-Scores (p=0.0003). LS-BMD and LS-T-Scores remained unchanged for patients treated with risedronate. The differences in the changes from baseline in LS-BMD and LS-T-Scores between two groups were significantly different. Changes from baseline for the Hip BMD and Hip T-Scores were not observed.
Conclusions: Risedronate was well tolerated and prevented bone loss of the LS at 1 year in patients initiating ADT.

MP-01.03
Urinary PCA3 and Cancer Progression under Active Surveillance of Prostate Cancer

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Introduction and Objectives: Active surveillance of low-risk prostate cancer is now routinely used in clinical practice. Yet, about 30-40% of patients will experience cancer progression over time and need treatment with curative intent. A biomarker predictive of cancer progression is lacking. In this retrospective cohort study, we sought to determine the clinical utility of the urinary PCA3 test.
Methods: Patients with Gleason 6 prostate cancer were enrolled in a IRB-approved phase II study of active surveillance complemented with prescription of a 5-alpha-reductase inhibitor (5ARi) drug (dutasteride or finasteride). Informed consent was obtained from each patient before enrolment. Repeat prostate biopsy was recommended after 6-12 months of surveillance, then yearly. All 84 patients in whom urine was collected after digital rectal examination of the prostate before the baseline diagnostic biopsy are reported here. Urinary RNA was stabilized with UTM buffer (GeneProbe). Urine was stored at -80C until PCA3 test was performed at GeneProbe central laboratory. Trends were tested using Mantel-Haenszel chi-square statistic. Cox regression models were fitted for time-dependent events.
Results: At baseline, mean age was of 63.8 (SD 7.0), mean PSA was of 5.5 (SD 2.6) and mean prostate volume of 42.3 mL (SD 20.2). Median follow-up time was 18.2 months and the median number of repeat prostate biopsies was 2. The median PCA3 score was of 13.4 (range 0-2123.3). PCA3 score did not differ across 5ARi drug type (p=0.40). PCA3 was categorized using cut-off values of 35 (high 14; low 70). The baseline PCA3 score was predictive of first repeat biopsy findings (trend p=0.01): of the 70 patients (83.3%) with PCA3 score <35, 44 patients (62.9%), 21 (30.0%) and 5 (7.1%) had no cancer, persistence of Gleason 6 and upgrade to Gleason 7 or more, respectively. Of the 14 patients (16.7%) with a PCA3 score ≤ 35, 4 patients (28.6%), 5 (35.7%) and 5 (35.7%) had no cancer, persistence of Gleason 6 and upgrade to Gleason 7 or more, respectively. The baseline PCA3 score was also predictive of the last repeat biopsy findings (trend p=0.013, not detailed). Patients with a PCA3 score ≤35, had an almost 4-fold greater risk of upgrade to Gleason 7 or more than patients with a PCA3 score <35 (Hazard Ratio 3.5; 95%CI: 1.4-8.9; p=0.009). No other clinical parameter (PSA, PSA density, gland volume, number of cores involved, age) was predictive of Gleason upgrade.
Conclusion: The urinary PCA3 test predicts cancer progression (or missed higher grade cancer at diagnosis) when under active surveillance. PCA3 test may help better select men for active surveillance or better adapt surveillance strategy.

MP-01.04
Safety Profile of Robot-Assisted Radical Prostatectomy: A Standardized Report of Complications in 3317 Patients

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Introduction and Objectives: Previous studies attempting to study complications after robot-assisted radical prostatectomy (RARP) are limited by small numbers, short follow-up, or lack of risk-factor analysis. The objective of this study was to document complications after RARP by strict application of standardized reporting criteria.
Material and Methods: Between January 2005 and December 2009, 3317 consecutive patients underwent RARP at a tertiary referral center. Median follow-up was 24.2 months (interquartile range: 12.4-36.9). Transperitoneal RARP was performed by one of five surgeons: two experienced, and 3 beginners. Complications were captured by exhaustive review of multiple datasets including our prospective prostate cancer database, claims data, electronic medical and institutional morbidity and mortality records, and reported according to the Martin-Donat criteria. Complications were stratified by type (medical / surgical), Clavien classification and timing of onset. Multivariable analysis of factors predictive of complications was performed.
Results: The median hospitalization was 1 d. There were 349 complications in 302 patients (9.1%), including a transfusion rate of 2.2%. We detected 81 medical complications in 801 patients (2.4%) and 268 surgical complications in 222 patients (6.7%). There were 223 minor (Clavien I- II) and 126 major (Clavien III-V) complications. 278 (79.7%) complications occurred within 30 d, 18 (5.2%) within 31-90 d, and 53 (15.2%) after 90 d from surgery. On multivariable analysis, only cardiac co-morbidity was predictive for medical complications whereas cardiac, hepatic, and gastrointestinal diseases and positive lymph node status were predictive for surgical complications. Limitations of this study are that it represents results from a single high volume referral center and does not include the learning curve of the two most experienced surgeons.
Conclusions: RARP was a safe operation with an overall complication rate of 9.1%. Most complications occurred within 30 days of surgery. On risk factor analysis, cardiac co-morbidity was predictive for both medical and surgical complications.

MP-01.05
Impact of Prevalent Vertebral Fracture on Overall Survival in Men Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer

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Introduction and Objective: Androgen deprivation therapy (ADT) is well-established for treating prostate cancer, and is complicated by bone loss and increased fracture risk, including vertebral fracture. In non-cancer-populations, vertebral fractures may be asymptomatic or have functional consequences (eg, loss of height, kyphoscoliosis, and impaired respiratory mechanics), and are prognostic for subsequent fractures and increased long-term mortality (Hasserius et al, Osteoporos Int 2003; Bliuc et al., JAMA 2009). As there are no data available on this association in men with prostate cancer, we performed an analysis of overall survival (OS) and prevalent vertebral fracture (PVF) at baseline in 1468 men with non-metastatic prostate cancer on ADT enrolled in a phase 3, randomized, placebo-controlled study of denosumab.

Methods: OS during 36 months of treatment was analyzed by presence or absence of radiographically-confirmed PVFs in the overall population (median age: 75 years; median ADT duration: 20.5 months), and was adjusted for stratification factors of age (<70 vs ≥70 years) and ADT treatment duration (≤6 vs >6 months). We also analyzed OS by placebo treatment (n=734; mean age: 76 years; median prior duration of ADT: 20.4 months) or denosumab treatment (n=734; mean age: 75 years; median prior duration ADT: 20.8 months). PVFs were assessed by lateral spine radiographs of T4–L4 vertebrae at baseline in a blinded fashion by a central reader using the Genant vertebral fracture scoring system.
Results: PVFs were present in 22% (329/1468) of subjects enrolled at baseline. The on-study death rate was higher for subjects with PVFs compared with those without PVFs, 7.6% (25/329) vs 5.1% (53/1035; HR=1.57; p=0.062). After adjusting for age group and ADT duration, the death rate remained higher in subjects with PVFs compared with those without PVFs (HR=1.55; p=0.07). Within each treatment arm, on-study death rate for subjects with PVFs compared with those without PVFs was 9.2% (16/174) vs 4.6% (23/504) with HR=2.14, p=0.019 for placebo, and 5.8% (9/155) vs 5.7% (30/531) with HR=1.09, p=0.81 for denosumab. The hazard ratio (PVF: without PVF) adjusted for age group and ADT duration was placebo: HR=2.13, p=0.021; denosumab: HR=1.08, p=0.84.
Conclusions: Men with prostate cancer on ADT who had PVF at baseline appeared to have shorter overall survival.

MP-01.06
The Impact of Nerve-Sparing on Capsular Incision into Tumor during Radical Prostatectomy

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Introduction and Objective: Capsular incision (CI) into tumor during radical prostatectomy (RP) has a detrimental effect on recurrence-free survival. However, factors influencing the likelihood of CI are largely unknown. Our objective was to evaluate the impact of nerve-sparing RP on CI into tumor.
Methods: A retrospective review was conducted of 9915 consecutive patients with prostate cancer treated at the Ottawa Hospital and at Memorial Sloan–Kettering Cancer Center, both tertiary academic centers, between 1985 and 2010. All patients underwent an open, laparoscopic or robotic RP. Our primary endpoint was the presence of capsular incision (positive margins with no extraprostatic extension). The effect of nerve-sparing on capsular incision was determined using univariate and multivariate logistic regression analyses adjusting for age, prostate specific antigen (PSA), Gleason sum, clinical stage, RP modality, and RP date in the multivariate model. Patients who received pre-operative hormones (n=369) or had incomplete data (n=3456) were excluded.
Results: Patients underwent open (n=4067), laparoscopic (n=1519) or robotic (n=504) prostatectomy. Approximately 6.1% (370/6090) of patients had CI. On univariate analysis, patients undergoing bilateral nerve-sparing were significantly more likely to have CI (OR 2.89 (1.36, 6.16), p=0.006) than those who had a nerve resection. Patients who underwent unilateral nerve-sparing had similar rates of CI as did those with nerve resection (OR 1.09 (0.43, 2.77), p=0.85). On multivariate analysis, patients undergoing bilateral nerve-sparing were significantly more likely to have CI (OR 2.21 (1.02, 4.75), p=0.04) than those who had a nerve resection. Capsular incision was significantly more likely in patients treated with robotic prostatectomy than either open (OR 1.69 (1.15, 2.56), p=0.009) or laparoscopic RP (OR 1.92 (1.27, 2.86), p=0.002). There were similar CI rates between open and laparoscopic RP within this analysis. CI was more likely in patients with Gleason 7 disease than with Gleason 8-10 (OR 2.53 (1.32, 4.87), p=0.005) but less likely with more recent date of surgery (OR 0.92 (0.88, 0.96), p<0.0001). Age, clinical stage, PSA, and unilateral nerve sparing were not significantly associated with CI.
Conclusions: Bilateral nerve-sparing during RP significantly increases the likelihood of capsular incision into tumor during radical prostatectomy. This data highlights the challenges of radical prostatectomy in balancing oncologic and functional outcomes in addition to the learning curve associated with technologic advancement.

MP-01.07
Uniform Anatomic Template for Pelvic Lymph Node Dissection during Radical Prostatectomy: Comparison of Open, Laparoscopic and Robot-Assisted Procedures

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Introduction: To compare outcomes of pelvic lymph node dissection (PLND), with inclusion of the hypogastric nodal region, in patients undergoing a radical prostatectomy (RP) performed by differing surgical approaches—open radical retropubic (ORP), laparoscopic (LRP) or robot-assisted laparoscopic prostatectomy (RALP)— in a concurrent contemporaneous series with standardized indications and uniform templates.
Methods: From January 1 – September 1, 2010 we analyzed all patients who underwent primary RP regardless of surgical approach. PLND was performed on almost all patients with ≥2% nomogram predicted risk of PLND (high risk) and at the surgeon's discretion in all others. A standardized template including the external, obturator, and hypogastric node packets was used, regardless of approach. Differences in lymph node yield between surgical approaches were compared using multivariable linear regression with adjustment for clinical stage, biopsy Gleason grade, PSA, and age.
Results: In this analysis 475 patients were included (187 ORP, 114 LRP, 174 RALP) and 399 (84%) underwent PLND. There were no differences in oncologic characteristics between surgical approaches. The median yield for ORP, LRP and RALP were 18, 17, and 16, respectively. Adjusted differences between groups were significant (p=0.036). Rates of LNI were high (14% ORP, 6% LRP and 12% RALP) with no significant difference in LNI between approaches (p=0.11). PLND was performed in 98% (n=314) of high risk patients, regardless of approach. Variations in individual surgeons median LNY were greater (10–28) than variations in median LNY between surgical approaches (16-18).
Conclusions: PLND, including the hypogastric nodal packet, can be performed by any approach with slightly different yield but similar pathologic outcomes. High LNY and LNI relative to prior series are commensurate with standardization to a uniform template which includes hypogastric nodes and is particularly evident among higher risk patients.

MP-01.08
Reverse Stage Shift at a Tertiary Care Center: Escalating Risk in Men Undergoing Radical Prostatectomy

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Purpose: To evaluate changes in clinical and pathological characteristics of prostate cancer in patients treated surgically at a large tertiary care center in the context of increased use of active surveillance (AS) and minimally invasive surgery (MIS).
Materials: We performed retrospective review of 6,624 patients with localized prostate cancer who underwent radical prostatectomy from 2000–2010 at Memorial Sloan-Kettering Cancer Center. Patients were stratified by surgical approach (open, laparoscopic or robotic) and risk categories (low, intermediate, or high). Patients with low-risk disease, without intervention and minimum followup of 6 months were considered to have elected AS.
Results: AS cases increased from <20 per year between 2000–2004 to ≥100 per year between 2007–2009. Over the same decade MIS cases (laparoscopic or robotic) increased from zero to 63% of all surgical

cases. The percentage of patients in intermediate- and high-risk categories increased over time, while the percentage in the low-risk category decreased (OR per year 0.91, 95% CI 0.89, 0.92, $p<0.0005$). The proportion of surgery patients with Gleason 6 tumors decreased over time (OR per year 0.87, 95% CI 0.85, 0.88; $p<0.0005$) while pathologic stage and Gleason score increased ($p<0.0005$). The proportion of low-risk cases decreased across all types of surgery, with the largest decrease in robotic surgery ($p<0.0005$).

Conclusions: We observed a reverse stage shift in patients undergoing radical prostatectomy since 2000 despite the introduction and rapid proliferation of MIS. These findings may be due to increased use of AS and institutional focus on treatment of higher-risk disease.

MP-01.09

Autologous Blood Transfusion Does Not Protect from Homologous Blood Use During or After Open Radical Prostatectomy

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Introduction: The rationale for autologous blood transfusion (ABT) is to protect from homologous blood transfusion (HBT) and possible transmission of blood-borne infections and to conserve donor blood stocks. We examined ABT rates and trends as well as the rates of simoultaneous HBT to quantify the potential protective effect of ABT on HBT rates in open radical prostatectomy (ORP).

Methods: Between 1999 and 2008 in the state of Florida, 105 institutions provided access to ABT at ORP. At these centers, 20246 ORPs were performed. Rates and trends of ABT with or without HBT were assessed. Univariable and multivariable logistic regression analyses focused on prediction of HBT in patients who received ABT. Variables included age, race, surgical volume, and baseline Charlson Comorbidity Index (CCI).

Results: The overall rate of ABT was 9.2%. The proportion of patients receiving ABT remained stable over time (8.8-9.1%; $p=0.2$). Most ABTs occurred at ORP patients operated by low SV surgeons (50.1%). The rate of ABT use increased the most at ORPS performed by low SV surgeons (40.6-67.9%). The rate of HBT during the same period of time increased from 5.8 to 11.1% ($p<0.001$). The rate of HBT in patients receiving ABT was 9.1%. Conversely, the rate of HBT was 6.4% in patients not receiving ABT ($p<0.001$). Moreover, the use of ABT did not protect from HBT in any individual study year. ABT rate was 11.0% at ORP performed within the low SV tertile vs 9.8 and 6.5% in respectively the intermediate and high SV tertile ($p<0.001$). After adjusting for all covariates, patients operated by low and intermediate SV surgeons were respectively at 1.8 and 1.6-fold higher risk of ABT than patients operated by high SV surgeons ($p<0.001$). In multivariate analysis, HBT use was more frequent in patients receiving ABT (OR: 1.5, $p<0.001$).

Conclusions: Our data indicate that ABT use does not protect from HBT. Instead, ABT patients are 1.5 times more likely to require HBT. Additionally, low SV represents an important determinant of ABT use and indicates that less experienced surgeons use this modality more frequently than their high volume counterparts.

MP-01.10

Long-Term Cancer Outcomes after Radical Prostatectomy and Selective Salvage Radiotherapy in 1670 Pt2-3N0M0 Patients by Margins Status: Quantification of Overtreatment with Adjuvant Radiotherapy for All Positive Margins

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Introduction and Objective: The impact of positive surgical margins after radical prostatectomy on tumour recurrence and the necessity of adjuvant radiotherapy (RT) remains unclear. We analyse the outcomes of patients with pT2-3 N0 M0 prostate cancer without adjuvant radiotherapy after radical prostatectomy (RP) in relation to the use of salvage RT, stratified by margins status.

Methods: From the 2292 patients in our institutional database with pT2 or pT3 N0M0 prostate cancer without evidence of metastasis at time of RP, we excluded 622 patients. Exclusion criteria were neoadjuvant or adjuvant androgen deprivation therapy (ADT), adjuvant RT within 6 months of surgery or a detectable PSA at 3 months after RP. Incidence of biochemical recurrence, bone metastasis and start of salvage radiotherapy or hormonal treatment was assessed comparing margin-positive and margin-negative patients.

Results: 668 patients were margin-positive, of which 143 received salvage radiotherapy after a mean time of 36.4 ± 26.8 months, whereas 525 patients (78.6%) did not receive salvage treatment. Median follow-up was 92.7 and 75.6 months for margin- positive and -negative patients, respectively. At the end of follow-up, cancer-specific mortality in the radiation group was <1% (1 patient) compared to <1% (4 patients) in the radiation-free margin-positive group. 10 yr Kaplan-Meier estimates for bone metastasis-free survival was 99% for margin-negative patients and 97% for margin-positive patients (log-rank $p=0.0505$). In multivariate Cox regression analysis corrected for standard pathologic features, positive surgical margins after RP failed to prove a significant impact on time to bone metastasis (HR 1.284(95%CI 0.525-3.143; $p=0.5835$) whereas pathological stage and especially Gleason score were strong predictors. Of the margins positive patients only 5% of those 525 patients who did not receive salvage RT received definitive ADT contrasting with 68% of those 143 patients who received salvage RT.

Conclusions: Only 20% of patients with positive surgical margins in this series received salvage RT. Only 5% of those who did not receive salvage RT progressed to definitive ADT, suggesting that adjuvant RT would have been an overtreatment for the great majority. Biomarkers and risk factors of late progression may improve the selection of patients for adjuvant RT.

MP-01.11

Prospective, Randomized Use of the Barbed Vloc Self-Retaining Suture to Facilitate Vesicourethral Anastamosis During Robot Assisted Radical Prostatectomy: Time Reduction and Cost Benefit

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Introduction: The Van Velthoven vesicourethral anastamosis (VUA) is commonly used for urinary reconstruction during robot-assisted radical prostatectomy (RARP). Compared to standard monofilament posterior reconstruction (PR) and VUA technique, we sought to evaluate the effectiveness of an interlocked, barbed VLOC 180 suture (Covidien, Mansfield, MA) for urinary reconstruction.

Methods: A prospective, randomized study was conducted in 50 consecutive RARP cases by a single surgeon (KCZ) in which either standard or VLOC VUA was performed. Standard VUA was performed using three, 4-0 Monocryl sutures all secured with LapraTy clips (1 single 6 inch for PR and 2 attached 6 inch for VUA). The study group involved two, 3-0 6-inch VLOC 180 sutures, loop-interlocked and for knotless PR and VUA. Assurance of watertight closure with a 300 mL saline visual cystogram intraoperatively was performed in all cases (Figure 1). Time to complete the suture setup by the nursing personnel, anastamosis time and need to adjust suture tension were recorded. Suture related complications, continence and a cost analysis were also analyzed.

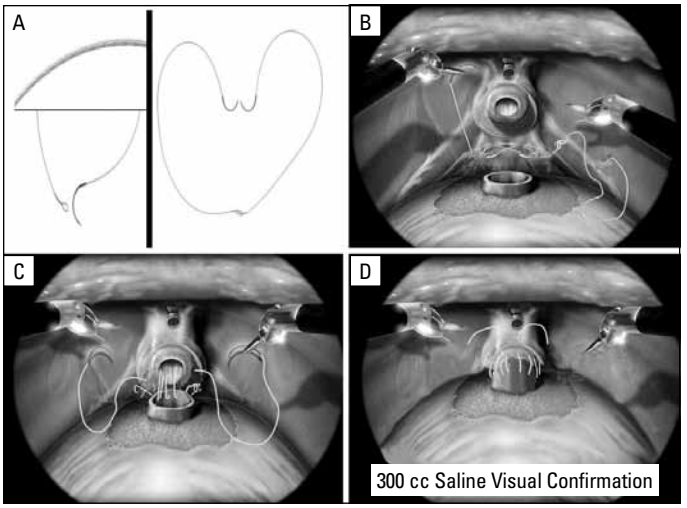

Fig. 1. MP-01.11

Results: Compared to our conventionalreconstruction technique, there was a significant reduction in mean nurse setup time of suture material (31 vs 294 sec; $p<0.01$) and reconstruction time (13.1 vs 20.8 min; $p<0.01$). Need to readjust suture tension or place additional LapraTy clips to establish a watertight closure was observed in 8 (32%) vs 2 (8%) of cases ($p=0.03$). A cost reduction was also seen at our institution (48.05$ vs 70.25$CAN) with the use of the interlocked VLOC technique. Time to foley removal was comparable between groups (4.1 vs 4.2 days, $p=0.87$). With a mean followup of 6.2 months, no delayed clinical anastamotic leaks or bladder neck contractures were observed in either group. Pad-free continence outcomes at 1 (76%vs80%,$p=0.73$), 3 (84% vs 88%,$p=0.68$) and 6 months (89% vs 90%,$p=0.95$) were also comparable.
Conclusions: The unidirectional barbed VLOC suture appears to provide a safe, more efficient and cost effective PRand VUA during RARP. Use of the interlocked VLOC suture technique prevents slippage, precluding the need for assistance, knot tying, and constant reassessing of anastomosis integrity.

MP-01.12

Intermittent Androgen Deprivation Therapy in the Management of Castrate Resistant Prostate Cancer (CRPCa): Results of a Multi-institutional Randomized Prospective Clinical Trial

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Background: Patients who develop CRPCa typically continue on androgen deprivation therapy (ADT). Whether these patients need to remain on ADT has not been well studied. We conducted a multi-center randomized trial to compare intermittent versus continuous approach to ADT in CRPCa patients. Overall survival, health related quality of life (QOL) and cost were the main endpoints. We hypothesized that the intermittent approach would be cost-saving while maintaining similar oncologic and QOL outcomes.
Methods: CRPCa patients were randomized 1:2 to continuous or intermittent luteinizing hormone releasing hormone agonists (LHRHa). Patients were followed with clinical assessments, laboratory investigations, and QOL questionnaires (EORTC QLQ-C30 or PROSQOLI) every 2 months. If the serum testosterone rose above castrate levels (1.75 nmol/L), LHRHa were re-initiated. The study was designed to close if >50% of patients needed to restart ADT in the intermittent arm.
Results: 31 patients were followed with a median follow-up of 26.8 months; 18 in the intermittent arm and 13 in the continuous. 12/18 patients on the intermittent arm were re-initiated on LHRHa at a median time of 17.9 months. There was no difference in overall or cancer-specific survival between the two arms. There was no statistically-significant difference in QOL between the two arms at 0 and 12 months. The total mean costs at 24 months were significantly lower in the intermittent arm (3135 $CAD vs 8253 $CAD, $p=0.0167$) compared to the continuous arm largely due to the reduced costs of the LHRHa.
Conclusions: We have observed that intermittent ADT in patients with CRPCa, using a testosterone of >1.75 ngmol/L as a trigger to re-initiate LHRHa, results in a substantial cost savings with no negative impact on oncologic and QOL outcomes. These findings need to be corroborated in a study with a larger sample size.

MP-01.13

Population Based Study of the Treatment of Patients with Prostate Cancer in British Columbia

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Introduction and Objectives: Cancer Care Ontario has described goals for quality care for radical prostatectomy (RP) including a positive margin rate of less than 25% for those with pT2 disease. Three randomized trials have demonstrated that post radical prostatectomy (RP) adjuvant radiation therapy (RT) decreases biochemical relapse for men with adverse pathology and, in the most mature trial, improves overall survival. Our objectives were: 1) To describe the use of RT, Androgen Deprivation Therapy (ADT) and RP in a contemporary series of prostate cancer patients at a population level in British Columbia (BC) and 2)To describe the pathologic stage, and margin status and use of post RP adjuvant RT for those treated with RP.
Methods: All incident patients with prostate cancer diagnosed between January 2005 and December 2007 were identified from the BC tumour registry. Cases were then linked to radiotherapy records which included dose and modality (high dose external beam (EBRT), and Brachytherapy (BT)), and to pharmacy records that included all androgen deprivation therapy (ADT) prescriptions. The pathology reports in the tumour registry were reviewed to determine cases treated with RP and to determine risk factors for relapse (nodal status, seminal vesicle (SV) invasion, extracapsular extensions (ECE) and positive margins). Post operative assessment by an oncologist and the use of post operative adjuvant RT within 6 months of RP for those with risk factors for relapse were identified.
Results: Overall, 9223 patients with prostate cancer were identified. Primary therapy within 12 months of diagnosis was RP in 2081 (23%), EBRT in 2008 (22%), BT in 688 (8%), ADT in 1338 (14%), and no initial therapy (i.e., active surveillance or watchful waiting) in 3109 (33%). Positive margins were found in 37% of all patients treated with RP, and 30% and 57% of those with pT2 and pT3 disease respectively. Of the 1015 post RP patients (47% of all RP cases) with adverse RP pathology (positive margins, ECE or SV invasion), 230 (23% of those with these risk factors) were seen within 6 months of RP by an oncologist and 2% had adjuvant RT.
Conclusions: The majority of patients with prostate cancer in BC in 2005 to 2007 were treated with curative intent. One quarter were treated with RP, and one third were treated with RT. Positive margin rates for pT2 cancers exceeded the Ontario goal rate of 25%. The majority (75%) of those with risk factors for relapse after RP were not seen within 6 months of RP by an oncologist, and very few received adjuvant RT.

MP-01.14

The Effect of ADT on Objective Cognitive Performance and Self-Reported Cognitive Function in Men with Prostate Cancer

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Background: ADT is used to treat almost 50% of prostate cancer (PC) patients. Despite slowing disease progression and prolonging survival, ADT is associated with numerous side effects. However, the impact of ADT on self-reported and objective cognitive function remains unclear.

Methods: Three groups of males age 50+ were included; PC patients starting continuous ADT (n=77), PC controls not receiving ADT (n=85), and healthy controls (n=83). A self-reported cognitive function questionnaire (FACT-Cog) and a battery of neuropsychological tests examining 8 cognitive domains were administered at baseline, 6 months and 12 months later. The FACT-Cog scores and the battery test scores were compared between groups at baseline, and change scores over the 12 month period were analyzed using ANOVA and multi-variable linear regression. To examine whether changes in objective cognitive scores correlated with changes in FACT-Cog scores, Pearson correlations were calculated.

Results: FACT-Cog scores obtained at baseline did not significantly differ between the 3 groups ($p>0.05$). ADT users did not report a greater decline in self-cognitive function overtime compared to PC controls or healthy controls ($p=0.21$). Attention and Processing Speed, Visual Memory, Language and Executive Function scores did not significantly differ between groups ($p>0.05$). At 12 months, ADT users had significantly declined on the Longest Digit Span Forwards (Immediate Memory), Spatial Span Backwards (Working Memory), and Card Rotations tasks (Visuospatial Ability) ($p<0.05$). Correlations between FACT-Cog and objective cognitive test scores were weak at baseline and overtime (all $r<0.20$).

Conclusions: Preliminary analyses suggest little or no deleterious effect of ADT on self-reported cognitive function over 12 months. Objective cognitive performance of ADT users declined over 12 months on 3 cognitive tests, indicating a possibility of ADT's long-term impact on selected cognitive domains. Correlations between FACT-Cog scores and objective cognitive performance were poor.

MP-01.15

Treatment for Recurrent Localized Prostate Cancer Following Radiation Failure with High Intensity Focused Ultrasound: Initials Results

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Introduction and Objective: Local relapse after External Beam Radiation (EBRT)or Brachytherapy (BT) for localized PCa has been reported in 30-40%. Current salvage therapy alternatives include radical prostatectomy, BT, cryotherapy and high-intensity focused ultrasound (HIFU). HIFU is a minimally invasive ablation technique using ultrasound waves ostatectomy.

Methods: From April 2006 to Sept 2009, 62 patients (pts) with histological confirmed diagnosis of recurrent localized PCa after EB RT or BT, with clinical stage T1-T2, PSA level ≤10ng/mL, pre Gleason score ≤8 in absence of distant metastasis were submitted to treatment using Sonablate®500. PSA levels, IPSS and IIEF-5 questionnaires were assessed at 45, 90, 180 days and 12 months respectively. Biopsy was done at 180 days post-HIFU. Biochemical failure was defined according to the Phoenix criteria. Mann- Whitney U test was used $p<0.05$ for statistical significance.

Results: Age 68.01±5.27 yrs, PSA 4.08±2.96 ng/mL, prostate volume 25.59±9.59 cc. IPSS 7.52±4.81, IIEF-5 9.10±8.42 scores. 25(40%) cases, Gleason ≤6, 24(39%) Gleason 7 and 13(21%) Gleason 8. 55 pts (89%) had EBRT and 7(11%) had BT. 16 (26%) pts had androgen deprivation pre HIFU. Mean follow-up was 16 months. At follow-up, 13 (21%) pts presented local relapse by Day 180. Progression Free Survival at 3 years was 60%. At univariable analysis, prostate volume ($p=0.010$), IPSS ($p=0.002$), and IIEF-5 ($p=0.010$) showed statistically difference at 12 months compared with the basal values. The median PSA value 0.77ng/mL, 0.62ng/mL, 0.80 ng/mL and 0.64ng/mL at 45, 90, 180 and 12 months respectively. Complications incontinence 2(3%), rectourethral fistula 2(3%), and urinary retention 3(5%).

Conclusion: Our initials results using HIFU (Sonablate®500 system) showed a low rate of complications with acceptable oncologic results at short-term. HIFU as salvage treatment is promising treatment option, especially for suboptimal candidates for salvage prostatectomy. Furthermore prospective multicenter controlled trials are underway.

MP-01.16

Long Term Complications in Men after Radical Prostatectomy Who Have Early or Late Radiation

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Introduction and Objective: Men with prostate cancer who are treated with early radiation after radical prostatectomy (RP) may have increased risk of urinary incontinence, bladder neck contracture (BNC) or urethral stricture (US) as compared to those treated with late radiation. This is thought to be due to radiation damage on healing tissues postoperatively. We undertook to evaluate the complication rates of men treated with surgery followed by early or late external beam radiation (RT).

Methods: Retrospective outcomes were determined up to 3 years post treatment for 652 patients who underwent a RP followed by early RT (<6months after surgery) or late RT (≥6 months after surgery) between Jan 2000 – Oct 2007. Urinary incontinence was defined as the presence of any leakage. BNC and US were diagnosed on cystoscopic findings. Fisher's T test was used to analyze the data.

Results: 162 (24.8%) patients had early radiation and 490 (75.2%) had late radiation. Mean age at RP was 60.4 years (range 41-76 years). Mean time to early and late RT was 3.6 months (range 1-5 months) and 30.1 months (range 6-171 months) respectively. The median radiation dose was 66Gy (range 50 – 70Gy). Of the early RT patients, 88/162 (54.3%) were incontinent postoperatively. Of these, 42 (25.9%); 30 (18.5%) and 27 (16.7%) were incontinent at 1, 2 and 3 years post RT respectively. Of the late RT patients, 170/490 (34.7%) were incontinent postoperatively. Of these, 95 (19.4%); 82 (16.7%) and 72 (14.7%) were incontinent at 1, 2 and 3 years post RT respectively. BNC developed postoperatively in 27/652 (4%) patients, US in 10/652 (1.5%) and 1 patient developed both. At 3 years post RT, 23/27 BNC resolved, 1 persisted and 3 were status unknown. At 3 years post RT, 6/10 US had resolved and 4/10 were status unknown. Throughout the 3 years post RT, 16 new BNC occurred (12 resolved) and 5 new US occurred (3 resolved). There was no significant difference in rates of incontinence, BNC and US between early and late radiation at 3 years post RT.

Conclusions: Incontinence was frequently reported post-RP and this improved over time despite the use of post-operative RT. There was no significant difference between early and late RT at 3 years post radiation in terms of incontinence, bladder neck contractures and urethral strictures. This suggests that the timing of radiation does not alter the incidences of these complications after RP.

MP-01.17

Prognostic Merit of High-Grade Prostatic Intraepithelial Neoplasia in Determining the Future Probability of Developing Adenocarcinoma of the Prostate

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Introduction and Objective: There have been conflicting reports regarding the need for repeat Trans Rectal Ultrasound (TRUS) guided prostate biopsies following the diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN). We have evaluated this issue in our community where 10-12 core biopsies (Bx) are the standard.

Method: 1368 biopsies (1129 patients) from 2005 to 2010 were retrospectively analyzed. Age, PSA value at time of biopsy, number and location of cores sampled were all documented. The pathological states of each core functioned as the primary evaluative measure. Patients were included only if their PSA was between 4-10.

With a 5% level of significance, an absolute z value of 1.960 would have to be observed between HGPIN and negative CaP progression rates for HGPIN to be considered of significant effect.

Results: 755 patients met the inclusion criteria outlined in the Methods. Among this subset of patients, 6.2% of initial Bx patients exhibited HGPIN. 48.9% of these patients underwent re-Bx**. 30.4% of this cohort progressed to CaP upon re-Bx** (median re-Bx rate = 4.1 months).

Among the eligible Bx patients, 54.7 % exhibited negative pathological results upon their first biopsy. 28.8% of these patients underwent repeat biopsy. **40.3% of patients belonging to this initially negative cohort proceeded to demonstrate carcinoma upon re-Bx** (median re-Bx rate = 21.1 months). The rates of CaP progression for initial HGPIN (30.4%) and negative (40.3%) patient cohorts were not significantly different ($z=1.023$, $p=0.3063$). Single and multi focal HGPIN patients however, exhibited different rates of CaP progression. 16.7% of single focal cases progressed to cancer. 45.5% of multi focal cases showed CaP upon re-Bx ($z=1.499$, $p=0.1339$).

Conclusion: The overall prognostic value of HGPIN was not statistically significant when measured against the observed development of CaP in the negative biopsy patients. However, multifocal HGPIN had a higher incidence of progression to cancer on re-biopsy than unifocal HGPIN. These findings suggest that only patients with multifocal HGPIN warrant repeat TRUS biopsy of the prostate.

MP-01.18

Open Radical Prostatectomy in the Elderly: A Case for Concern?

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Introduction and Objective: Open radical prostatectomy (ORP) in individuals aged 75 years or older may be associated with a limited survival benefit. We tested the hypothesis that ORPs in elderly patients are predominantly performed at low volume and/or at non-academic institutions.

Materials and Methods: Within the Health Care Utilization Project Nationwide Inpatient Sample (NIS) we focused on patients in whom ORP was performed within the 10 most contemporary years (1998-2007). In those individuals, we examined the rate of ORP in elderly patients according to intraoperative and in-hospital complication rates. Subsequently, we stratified the rates according to annual hospital volume (AHV) tertiles and institutions type. Multivariable logistic regression analyses further adjusted for race and baseline Charlson Comorbidity Index (CCI).

Results: Overall, 115623 patients undergoing ORP were identified, among those 2110 individuals were aged 75 years or older (1.8%). The annual ORP rate ranged from 2.6 to 2.0% ($p=0.9$). The vast majority of elderly patients treated with ORP were operated at low (36.4%) and intermediate (35.9%) volume institutions. The intraoperative complications were higher at low (2.7%) and intermediate (2.5%) volume hospitals than at high volume centers (1.9%, $p=0.6$). Similarly, the rates of in-hospital complications were also higher at low (19.2%) and intermediate (17.0%) volume hospitals, than at high volume centers (13.3%, $p=0.02$). Intraoperative complications were 2.7 vs 2.1% ($p=0.3$) and in hospital complications were 19.1 vs 13.9% ($p=0.002$) at non-academic vs academic institutions, respectively.

Conclusion: It is worrisome that the vast majority and of elderly patients is treated at low or intermediate volume (72.3%) and/or non-academic (56.2%) hospitals. This finding is even more worrisome, since the complication rates at lower volume institutions are higher. More favourable in-hospital complication rates were also recorded for teaching institutions than for non-teaching centers.

MP-01.19

The Effects of Exercise on Prostate Cancer in the Active Surveillance Cohort

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Introduction and Objectives: It is well established that the risk of developing prostate cancer (PCa) is largely influenced by lifestyle behaviours. While a number of studies have shown an inverse correlation between increased exercise and PCa risk and progression, others have yielded mixed results. In addition, the mechanisms underlying the relationship between exercise and PCa are largely unknown. Presently, we aim to investigate the association between exercise and PCa progression in the Active Surveillance Prostate Cancer (AS) cohort and to gain insight into the molecular mechanisms involved. We hypothesize that exercise reduces PCa progression by improving immune function and body composition, altering the insulin axis, and reducing oxidative stress.

Materials and Methods: The AS cohort at the Sunnybrook Health Sciences Centre consists of patients with early-stage, locally confined PCa who have not undergone radical treatment for their cancers. 100 men on AS, as well as 100 men initially on AS but who have since been radically treated, will complete a lifestyle assessment questionnaire. Participants are asked about their exercise behaviours from the time of their PCa diagnosis, as assessed by the WHO STEPS Instrument. Total exercise is calculated in terms of metabolic equivalent task hours (MET-hours) per week. Additionally, serum samples will be obtained from participants for PCa biomarker analysis.

Results: Preliminary data has been obtained from 73 untreated and 37 treated patients, with a mean age of 68.10 ± 8.78 years and 73.35 ± 6.86 years, respectively. Mean BMI (kg/m2) in the untreated group is 26.65 ± 3.46 compared to 27.54 ± 3.90 in the treated group. For the 37 treated patients, the time between diagnosis and treatment varied greatly between patients, ranging from 0.38 to 11.20 years, with a mean of 4.24 ± 2.58 years. Initial results indicated that, from the time of diagnosis, untreated patients (mean: 87.78 ± 55.56 MET-hours per week) reported 34% more exercise than treated patients (mean: 65.71 ± 54.64 MET-hours per week). As patient accrual is ongoing, we will re-evaluate the results upon study completion. Mechanistic studies have not yet been completed.

Conclusions: Initial results (n=110) show that exercise may play a protective role against the progression of PCa, as observed by comparing the MET-hours per week reported by untreated and treated PCa patients. Upon completion, this study will help clarify the association between exercise and PCa progression, and will help elucidate some of the mechanisms involved. Thus, it may ultimately lead to the use of exercise as an adjunct to traditional treatments.

MP-01.20

Robot–Assisted Laparoscopic Prostatectomy (RALP): Initial Single Surgeon Series

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Introduction and Objectives: RALP is a relatively new procedure for the treatment of clinically localized prostate cancer. We report our experience.

Methods: Using an anterior approach, a bladder neck sparing RALP was performed. Clinical outcomes and adverse events are analyzed.

Results: 219 patients were identified having a mean PSA of 6.0 ± 4.5 ng/mL. Clinical stage included 206 (94.1%) T1c and 13 (5.9%) T2a, having a mean Gleason score of 6.5 ± 0.8. Average blood loss and hospital duration were 101.0 ± 147.5 mL and 1.2 ± 0.9 days, respectively. 185 (84.5%) patients had bilateral, 19 (8.7%) had unilateral and 15 (6.8%) did not undergo nerve sparing prostatectomy. The urethral catheter was removed at a median 5.0 ± 3.5 days. Of the 146 patients having a minimum 12 month follow-up, 136/146 (93.1%) achieved urinary continence without pads within 12 months, with a mean time to continence of 10.8 ± 8.7 weeks. 164/204 (80.3%) of those undergoing either unilateral or bilateral nerve-sparing had post–surgery penile rehabilitation [phosphodiesterase-5 inhibitor ± vacuum erection device (VED)]. 72/164 (43.9%) patients had baseline SHIM ≥ 21, of whom 32 / 72 (44.4%) reported sexual potency post-surgery. The mean Gleason score was 6.5 ± 1.0. 36/219 (16.4%) patients had positive surgical margins. 2 (1.0%) pTx, 31 (14.2%) pT2a, 13 (5.9%) pT2b, 144 (65.7%) pT2c and 29 (13.2%) pT3 cancers were reported, having a mean prostate volume of 44.8 ± 12.7 mL. Adverse events included 5 (2.2%) prolonged urine leak, 3 (1.4%) pelvic hematoma, 1 (0.5%) urinary tract infection, 2 (1.0%) deep vein thrombosis and 5 (2.2%) bladder neck contractures.

Conclusions: RALP is an effective treatment option for clinically localized prostate cancer with low patient morbidity.

MP-01.21

Head to Head Comparison Of two Currently Used Nomograms Predicting Side Specific Extra Capsular Extension to Indicate Nerve Sparing during Radical Prostatectomy

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Background: Two tools predicting the probability of side specific extra capsular extension (ECE) are available in the literature to help w ith patient selection for nerve sparing (NS) during radical prostatectomy. They allow decisions about unilateral, bilateral or no nerve sparing procedures. The aim of the study w as a head to head comparison of these tools via an external validation combined with a probability cut-off identification.

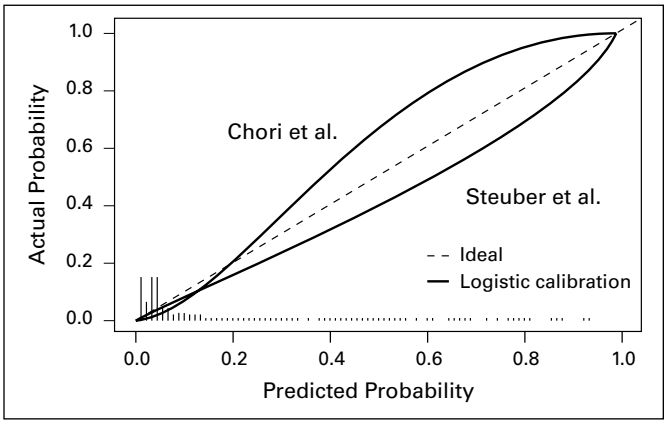

Fig. 1. MP-01-21

Methods: For external validation, 362 prostate half lobes of patients who underwent robotic assisted radical prostatectomy were used. All data were prospectively filed in a computer database. Prostatectomy specimens were processed according to the Stanford protocol. The full models of the nomograms of Ohori et al. and Steuber et al. were applied to the dataset using PSA and side specific clinical stage, biopsy Gleason score, %positive cores, and %cancer in cores as predictors. Nomogram derived predictions of ECE were used for external validation using discrimination for predictive accuracy (area under the ROC curve), calibration plots and cut-off identification.

Results: In the study cohort, median age was 61 years, and median PSA 6.6ng/mL. Clinical stage was T1c in 71.8%, T2a in 20.4%, T2b in 6.1% and T2c in 1.7%. Biopsy Gleason was <= 6 in 42%, 7 in 52% and >7 in 6%. Pathologically organ confined cancer was observed in 79.6% and pT3a in 14.4% and pT3b in 6.1%. The predictive accuracy of the Ohori nomogram was at 0.84 and of the Steuber Nomogram at 0.83 (comparison $p>0.05$). In the calibration plot (Figure 1), the Steuber nomogram showed less departures from ideal predictions then the Ohori nomogram. The best probability cut-off to allow NS for the Ohori nomogram seemed to be <9%, permitting NS in 59.8% of all cases and being associated with a false negative rate of 13.5%, a sensitivity 86.4% and a specificity of 65.8%. The best cut-off for the Steuber nomogram seemed to be 8%, permitting NS in 54.5% and associated with a false negative rate 10.8%, a sensitivity of 89.1% and a specificity of 60.0%.

Conclusions: The Ohori et al and the Steuber et al. nomograms allow highly accurate and comparable predictions of the risk of side specific ECE. This allows reliable treatment decision making for NS. The most appropriate probability cut-off to indicate NS seems to be 9% for the Ohori et al. nomogram and 8% for the Steuber et al. nomogram.

MP-01.22

TMPRSS2:ERG and PCA3 Transcript Markers for Urine-Based Prostate Cancer Detection with High Specificity and Sensitivity

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Introduction and Objectives: Both *TMPRSS2:ERG* fusion and *PCA3* ue to prostate cancer (PCa), and have great potential for noninvasive diagnosis and prognosis of prostate cancer in patients' bodily fluids. Our study objectives are to study the specificity, sensitivity and clinical utility of a panel of *TMPRSS2:ERG* fusion isoform markers in urine from diverse clinical contexts and to evaluate the correlation between *TMPRSS2:ERG* and *PCA3* markers in urine specimens.

Methods: A total of 101 subjects were enrolled in 2008 from urological oncology clinics to form three study groups: 44 PCa free, 46 confirmed PCa and 11 negative prostate biopsies. The PCa free group included females, healthy young men and post-radical prostatectomy patients. The confirmed PCa group composed of patients under active surveillance, scheduled for treatment or with metastatic disease. Urine was collected after attentive digital rectal exam and coded to blind group allocation for laboratory test. RNA from urine sediments was analyzed using a panel of 4 *TMPRSS2:ERG* fusion markers along with*PCA3*, *PSA*, *ERG* markers using quantitative PCR.

Results: Our fusion markers demonstrated a very high technical specificity and a sensitivity of detecting a single fusion-positive cancer cell (VCaP) in the presence of 3000-9000 cells in urine sediments. In clinical analysis, no fusion-positive samples in the PCa free group (0/44), while 16 of 46 (34.8%) fusion-positive samples in the confirmed PCa group. The fusion incidence varied significantly among three PCa subgroups. The clinical sensitivity increased to 45.4% in cancer patients prior to treatments. The fusion markers were detected in 2 of 11 (18.2%) biopsy-negative patients, suggesting potentially false negative biopsies. Interestingly, the fusion status was strongly associated with the over-expression of *PSA* and *PCA3* markers in urine. The two biopsy-negative cases detected with the *TMPRSS2:ERG* fusion also exhibited strong *PCA3* over-expression in urine.

Conclusions: Our new panel of isoform-specific fusion markers provided a very specific and sensitive tool for urine-based detection of PCa. Theses markers can potentially be used to diagnose patients with PCa who have negative biopsies. *PCA3* marker is highly associated with the *TMPRSS2:ERG* fusion status in urine and may be coupled with the fusion markers for molecular diagnosis of false biopsy-negative patients.

MP-01.23

Active Inflammatory State and Reactivity of Normal Prostate Epithelium and Aggressive Prostate Cancer

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Introduction and Objective: Chronic inflammation is emerging as a potential prostate cancer causal factor. However, very little is known about the interaction of normal prostate inflammation on carcinogenesis. Here, we sought to determine effect of the inflammatory status and reactivity of normal prostate epithelial cells on prostate carcinogenesis.

Methods: Patients signed an IRB-approved informed consent. Cell culture of human primary prostatic epithelial cells were derived from 24 radical prostatectomy or cystoprostatectomy specimens, of which 15 had aggressive prostate cancers (Gleason ≥8 or pathological stage T3). Prostate needle biopsies were taken in normal areas of the peripheral zone of the gland. Biopsies were incubated overnight in complete MEM (37°C-5% CO2) containing type III collagenase (800 U). Dispersed cells were centrifuged, suspended in 13 mL complete KSFM and transferred in a 75 CC cell culture flask. Confluence was reached within 2 to 3 weeks. Characterization of the cultured epithelial cells was made through immunofluorescence using AE1/AE3 (DAKO, dilution 1:25) antibody specific to cytokeratins. Green Alexa Fluor 488 was the secondary antibody and nuclei stained with blue DAPI.

Induction and measure of inflammation: 7200 cells/well were seeded in 96 well plates. In half of the wells, poly (I:C) 10 µg/mL was added to induce inflammation and plates were incubated for 20 hours. IL-8 content in the culture medium was evaluated using the human IL-8 Elisa Max deluxe set-Biolegend, after removal of the culture medium, washing and fixing of cells in formalin. IL-8 production was normalized to total DNA, measured using a DRAQ5 LI-COR protocol. The Fligner-Policello statistic was used to compare IL-8 expression across groups because of unequal dispersions.

Results: Cultured epithelial cells expressed a typical prostate epithelial cell cytokeratin pattern. Cell cultures derived from patients harbouring aggressive cancers produced significantly (p=0.049) more IL-8 (median: 15.4; IQR: 6.2-24.8) than cultures derived from patients harbouring less aggressive cancers (median: 6.9; IQR: 3.8-9.9). The production of IL-8 induced by poly(I:C) did not differ across cancer groups (p=0.182). Use of NSAID before surgery did not differ (Fisher's exact p=0.259) between patients with more or less aggressive cancers; and did not affect IL-8 production.

Conclusions: A high baseline pro-inflammatory status of normal prostate epithelium is associated with a more aggressive form of prostate cancer. More research to decipher the possibly causal relationship linking inflammation to prostate carcinogenesis is needed.

MP-01.24

Association of Adipokines with Prostate Cancer and High Grade Disease Depends on Body Mass Index

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Introduction and Objectives: Diet and obesity are associated with prostate cancer (PCa). We set out to determine if a group of serum adipokines were associated with PCa or high grade disease at biopsy.

Methods: Prospectively collected serum specimens from the GU Biobank at the Princess Margaret Hospital were utilized. From this biobank, 50 patients with Gleason 6 PCa, 50 patients with HG Gleason ≥7 PCa and 100 patients with negative biopsies were randomly chosen in a case-control fashion. For each group 50% of patients were chosen with a BMI ≤27 and 50% were chosen with a BMI >27. A panel of 11 adipokines (Adiponectin, leptin, PAI, Resistin, HGF, IL-1beta, IL-6, IL-8, MCP1, NGF, TNF alpha) were assayed from each patient. Association of adipokines with PCa or HG PCa was evaluated by receiver operating characteristic curve (ROC)/area under the curve (AUC) analysis and univariate logistic regression (LR).

Results: This patient cohort had a median PSA of 5.8 ng/mL, a median age of 62 years and a median BMI of 27.2 kg/m^2. None of the adipokines correlated with BMI except leptin (p<0.01). There were no significant correlations between individual adipokines. ROC analysis showed that Resistin (AUC 0.64; 95% CI 0.5-0.74) and MCP-1 (AUC 0.61; 95% CI 0.49-0.72) were the top ranked markers for discriminating cancer from no cancer among those with a BMI ≤27. In those with a BMI >27, IL-1 beta (AUC 0.61; 95% CI 0.49-0.72) and IL-6 (AUC 0.61; 95% CI 0.49-0.70); displayed the best discrimination. In the case of HG disease, NGF (AUC 0.69; 95% CI 0.57-0.81) and IL-1 beta (AUC 0.66; 95% CI 0.54-0.78) were most predictive among those with a BMI >27, while neither were predictive in the lower BMI group. Conversely, MCP-1 (AUC 0.61; 95% CI 0.47-0.73) and adiponectin (AUC 0.60; 95% CI 0.45-0.74) demonstrated the highest discrimination among those with a BMI ≤27. Using LR, only MCP-1 (OR 1.83, p=0.05) was associated with PCa among the low BMI group, while none of the markers were significant in the high BMI group. By contrast, NGF (OR 2.61; p=0.01) and IL-1 beta (OR 2.46; p=0.03) maintained an association with HG disease among the high BMI group, with none of the markers being significant in the lower BMI group.

Conclusions: Several adipokines demonstrate potential as predictive markers of PCa when BMI stratified. Of note, NGF was the only adiopkine with selective discrimination for HG PCa.

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Potential Utility of a Germ-Line Genetic Test for Prostate Cancer Diagnosis in a Canadian Cohort

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Introduction and Objectives: Genomewide association studies (GWAS) have resulted in the identification of over 30 single nucleotide polymorphisms (SNPs) consistently associated with prostate cancer (PCa) risk in Caucasian men. Their effect is moderate on an individual basis, but a test based on a collection of these SNPs has been shown to better predict for PCa risk. We sought to validate these findings in a Canadian cohort of men and to determine how this new test compares with and adds to existing predictors of PCa.

Methods: Using the prospective Princess Margaret Hospital GU serum biobank we evaluated the performance of a genetic test based on 33 SNPs for its ability to predict for overall and high-grade (HG, Gleason ≥7) PCa in 745 Caucasian men. The genetic test was compared with existing PCa risk factors including age, family history, digital rectal examination (DRE) and PSA using the area under the receiver operating characteristic curve (AUC) along with univariable and multivariable logistic regression analyses.
Results: 48% and 23% of these patients were diagnosed with overall PCa and HG disease, respectively. For overall PCa risk, the genetic score outperformed all other risk factors examined including PSA with AUCs of 0.64 vs 0.55 respectively. In a multivariable model incorporating PSA, DRE and age, the OR for the genetic test was 2.72 ($p<0.001$) with an AUC of 0.69 for the whole model compared to 0.63 without the genetic test. With regard to HG disease the AUC of the genetic test was 0.63 which compared favourably to PSA (AUC 0.62) and DRE (0.64). In a multivariable model the genetic score was an independent predictor for HG disease and added to a model containing age, PSA and DRE (AUC 0.72 vs 0.75 respectively).
Conclusions: A genetic test based on SNPs identified by GWAS has the potential to act as a new biomarker of overall and HG PCa risk. Further study is required prior to its widespread adoption.