Moderated Poster Session 7: Oncology: Prostate
June 29, 2010, 1400-1520

MP-07.01
Brachytherapy as Monotherapy for Clinically Localized Intermediate-Risk Prostate Cancer: Biochemical Outcomes and Toxicity Profile

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Introduction and Objective: Brachytherapy has been shown to have equivalent biochemical free and cancer specific survival to other treatment modalities including external beam radiotherapy (EBRT) and surgery for low risk patients. However, intermediate risk patients have historically not been offered brachytherapy as primary treatment. Given the ability to achieve extremely high dose rates that are not locally possible with EBRT, we hypothesize that brachytherapy may be equivalent to EBRT for treatment of intermediate risk prostate cancer. We have adopted its use as monotherapy for this risk group, and evaluated the biochemical control, along with the acute and delayed morbidity post treatment.

Methods: A retrospective review of patients treated with brachytherapy between June 2003 and Dec 2008 at the Manitoba Prostate Centre was conducted. Ninety-five patients were treated with brachytherapy alone for intermediate risk disease (T2b or T2c, Gleason score 3+4 = 7 or 4+3 = 7, PSA ≥10 but <20). Only patients with at least 3 post-treatment PSA measurements (n = 57) were assessed for biochemical failure (mean follow-up period 13.75 months, range 8 to 53 months). Biochemical (PSA) failure was defined using the Phoenix, or Nadir+2 definition and secondarily, the traditional American Society for Therapeutic Radiology and Oncology (ASTRO) definition of 3 consecutive rises over nadir. We also evaluated acute and late morbidities including urinary and bowel symptoms, and erectile dysfunction in all 95 patients.

Results: Of the 95 patients evaluated, no adjuvant treatment was given for biochemical control. In the 57 patients assessed for biochemical failure, PSA nadir ranged between 0.01 to 2.86; mean time to nadir = 22 months (range 2-57 months). Biochemical failure occurred in 1 patient (Phoenix) and in 2 patients (ASTRO). Within the entire study population (n = 95), 18 patients (19% ± 8%, 0.95 CI) had urinary retention > 2 weeks requiring catheterization; 4 patients (4.2% ± 4%, 0.95 CI) developed erectile dysfunction post treatment and 2 patients reported some degree of urinary incontinence.

Conclusions: Our results suggest that biochemical control can be achieved with brachytherapy alone for intermediate risk localized prostate cancer, with an acceptable rate of treatment related morbidity. Brachytherapy might be an alternative standard of care treatment for localized, intermediate risk prostate cancer.

MP-07.02
Consistency of Tumour Position on Repeat Prostate Biopsy in Men on Active Surveillance for Prostate Cancer: Implications for Focal Therapy

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Introduction and Objectives: Whether men on active surveillance (AS) for low volume, low-risk prostate cancer (CaP) can be effectively managed with focal therapy has yet to be determined. Transrectal ultrasound-guided biopsy (TRUS-BX) combined with other staging modalities are important parameters in deciding who may be a candidate for focal therapy (FT). Our aim was to investigate initial positive and repeat TRUS-BX findings in men on AS to determine how often and to what extent an altered disease profile occurred on second biopsy; the rationale being that this information may be important in managing candidates for FT.

Methods: Our institution prospectively maintains a TRUS-BX database, with 3 radiologists performing all biopsies (>2000 systematic biopsies/year). Our AS cohort typically have low grade, low volume disease (≤3 cores positive, less than 40% of any core positive, gleason ≤7) and are candidates for definitive therapy. Of those with CaP in a focal area of the prostate (1 side) on first biopsy, we determined whether CaP was evident in a second biopsy and whether it was identified in a new location such as the opposite side of the prostate. The difference in grade and percentage of cores positive for cancer between the first and second biopsy was also determined.

Results: A sample of our AS cohort with CaP included 152 men who had 2 biopsies read by the same uropathologists. The mean age was 65 and the mean time between biopsies was 18 months with an average PSA increase from 5.71 to 6.6 (p = 0.0003). For positive cores, the mean % of cancer in individual cores was 8 on first biopsy and 9 on second biopsy (p = NS). The number of cores positive on first biopsy was 18% of all cores taken and on second biopsy was 13% (p < 0.0001). The Gleason score increased in 25 men (16%), stayed the same in 77 men (50%) and decreased or was undetectable in 53 men (34%) (p < 0.0001). On second biopsy, 51 men (33%) had no detectable cancer. When CaP was positive unilaterally on the first biopsy (n = 134), 13 patients (8.5%) had cancer detectable on the contralateral side only on second biopsy. Of those with unilateral cancer on initial biopsy 22 (14.5%) had cancer evident on both sides on second biopsy.

Conclusions: CaP was present on the contralateral side in 23% of repeat biopsies suggesting this should be performed prior to considering FT in men on AS.

MP-07.03
The Use of MRI-Guided Transurethral Ultrasound Therapy for the Treatment of Localized Prostate Cancer: A Phase I Study

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Introduction and Objective: Minimally-invasive treatments for localized prostate cancer, that offer good local control over disease with a low side-effect profile, would have a major impact in improving the management of this disease. MRI-guided transurethral ultrasound therapy is a candidate technology in which planar high-intensity ultrasound energy is delivered to the prostate gland, via a transurethrally inserted device to generate a precise region of thermal coagulation. Previous studies in gels and canines have demonstrated the feasibility of using active MR temperature feedback to control spatial heating to a specified target region. This phase I study was designed to evaluate the safety and feasibility of this technique in humans.

Methods: MRI-guided transurethral ultrasound therapy was administered to a pre-determined region of the prostate of men diagnosed with localized prostate cancer (pT1c-pT2a). Subjects immediately underwent radical prostatectomy post-procedure, and the pattern of thermal damage

measured on histology was compared with imaging predictions. The procedure utilized a 1.5T closed bore MRI and each subject received a combination of sedation and spinal anaesthesia to eliminate pelvic sensation and reduce motion. High-intensity ultrasound energy was delivered to a 180° sector in the prostate and spatial temperature maps were obtained every five seconds using the PRF shift technique. The temperature measured at the boundary of the target region during treatment was used by the treatment system to adjust the power and rotation rate.
Results: Five patients, median age 59 (range 49-69), have been successfully treated to date. Baseline biopsy gleason scores were 3+3 (n = 1) and 3+4 (n = 4) and the median pre-biopsy PSA, 4.5 (range 2.7-5.3). The transurethral device was inserted without difficulty into patients in the supine imaging position. Spinal anaesthesia and sedation effectively eliminated patient discomfort and motion during the 2 hour procedure. Precise positioning of the transducer within the prostate was achieved under image guidance, and successful device rotation was achieved within the prostate. MR temperature measurements within the prostate were achieved with a spatial resolution of 2 mm (in-plane) and a temperature uncertainty of 1°C every 5 seconds, using a conventional pelvic surface coil array. Temperature measurements were stable, and not affected by motion or breathing. A continuous pattern of heating was delivered over the target region, and the targeting accuracy was 1.0+/-1.5mm. There were no reported complications.
Conclusions: MRI-guided transurethral ultrasound therapy is safe and capable of generating a precise region of thermal damage within the prostate gland under active MR temperature feedback.

MP-07.04

The Effect of Obesity in Interpreting PSA Results Among a Prostate Biopsy Screening Cohort

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Introduction and Objective: The effect of obesity has been established to dilute PSA concentrations and affect how PSA is interpreted. The clinical application of this effect remains unclear. We determined how obesity measured by Body Mass Index (BMI) could affect the significance of PSA levels among men undergoing prostate biopsy in a PSA screening program.
Methods: We conducted a case-control analysis among 786 men with a PSA level of <20 ng/mL who underwent a prostate biopsy using the probability of prostate cancer of greater than 25% using a Prostate Cancer Risk Calculator (www.prostaterisk.ca). We compared BMI measurements between prostate cancer cases and controls. We examined for confounding and effect modification to determine the effects of BMI on PSA in evaluating prostate cancer risk using multivariate logistic regression analysis.
Results: Among the 786 men, 203 (25.8%) were diagnosed with prostate cancer, consistent with the Prostate Cancer Risk Calculator prediction. PSA level did not predict the presence of prostate cancer. The median PSA level among cases (6.1 ng/mL) were not significantly higher than controls (5.8 ng/mL, $p = 0.11$). Similarly, the distribution of BMI among cases (median=26.4) and controls (median=26.7) were not significantly different ($p = 0.85$). However, when we stratified by obesity (BMI index ≤30 vs. >30), PSA levels were significantly higher among cases (median=6.1 ng/mL) than controls (median=5.7 ng/mL, $p = 0.05$). PSA was not significantly different between cases and controls among men with BMI >30. When we examined for confounding within a multivariate logistic model (including age, ethnicity, family history of prostate cancer, and DRE), both BMI and PSA were not significant predictors for prostate cancer. When the analysis was stratified by BMI index, the adjusted odds ratio for prostate cancer by PSA category was 1.7 (95% CI: 1.2-2.3, $p = 0.001$) for men with a BMI of ≤30. The adjusted odds ratio for prostate cancer by PSA category for men with a BMI >30 was 1.2 (95% CI: 0.7-2.2, $p = 0.44$).
Conclusions: Obesity measured by BMI appears to affect PSA as a risk modifier towards prostate cancer risk. The significance of PSA levels should be factored accordingly using BMI Index.

MP-07.05

New Variants at 10q26 and 15q21 are Associated with Aggressive Prostate Cancer in a Genome- Wide Association Study from a Prostate Biopsy Screening Cohort

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Introduction and Objective: Genome-wide association studies (GWAS) for prostate cancer have found extensive single nucleotide polymorphisms (SNPs) assoicated with prostate cancer. However, none have been found to be associated with aggressive forms of prostate cancer.
Methods: We conducted a GWAS among men who had a prostate biopsy, using a two-stage approach. In the first stage, 316 cases and 229 controls were genotyped using the Affymetrix 500K SNP array (443,816 SNPs). Cases were patients with aggressive forms of prostate cancer using the established D'Amico classification criteria, and controls were biopsy proven normal patients. In the second stage, we genotyped positive SNPs found from stage 1 among 3439 patients who underwent prostate biopsy for prostate cancer screening. We investigated their clinical significance by examining their association with D'Amico criteria outcomes and by nomogram analysis in predicting prostate risk.
Results: We found significant associations between aggressive prostate cancer and five single nucleotide polymorphisms (SNPs) in the 10q26 (rs10788165, rs10749408, and rs10788165, p-values for association $1.3x10^{-10}$-$3.2x10^{-11}$) and 15q21 (rs4775302 and rs1994198, p-values for association $3.1x10^{-8}$-$8.2x10^{-9}$) regions. Results of a replication study done in 3439 patients undergoing a prostate biopsy, revealed certain combinations of these SNPs to be significantly associated not only with prostate cancer but with aggressive forms of prostate cancer using an established classification criterion for prostate cancer progression (odds ratios for intermediate to high-risk disease 1.8 to 3.0, p-value 0.003 to 0.001). These SNP combinations were also important clinical predictors for prostate cancer detection based on nomogram analysis that assesses prostate cancer risk.
Conclusions: We identified significant associations at 10q26 and 15q21 with aggressive forms of prostate cancer. Nomogram analysis shows potential clinical applications of these SNPs in prostate cancer individual risk assessment.

MP-07.06

Dose Finding and Safety Analysis of Inecalcitol in Combination with Docetaxel-Prednisone Regimen in Hormone-Refractory Prostate Cancer (HRPC) Patients

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Introduction and Objective: Inecalcitol is a novel synthetic vitamin D3 analogue with potent antiproliferative effects in human cancer cell lines and a 100-fold lower hypercalcemic activity than calcitriol in animal models.
Methods: In this study, escalating dosages of inecalcitol was combined to chemotherapy in naive HRPC pts. Safety and efficacy were evaluated in groups of 3-6 patients receiving inecalcitol daily or every other day on a 21-day cycle in combination with docetaxel (75 mg/m2 q3w) and oral prednisone (5 mg bid). Biphosphonates were prohibited during the first cycle. Patients received up to six cycles unless unacceptable toxicity or disease progression. Primary endpoint was dose limiting toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Calcemia, creatininemia and CBC were assessed weekly; biochemistry, ECG and PSA every 3 weeks. Efficacy endpoint was PSA response defined as ≥30% decline within 3 months.
Results: Seven dose levels, from 40 to 2000 µg have been evaluated in 47 pts; 42 have completed the study (14 bone metastases; 5 extrasqueletic

metastasis, 21 bone and extrasqueletic metastases; 2 PSA-only disease) of which 33 pts have completed 6 cycles and 5 pts are still being treated at 2000 µg. Median age was 71 years [range, 53-87], median Gleason score (Gs) 7 [42% Gs 10-8, 58% Gs 7-6] and median PSA 41.5 ng/mL [range, 0.9-962.4]. No significant changes in calcemia were observed. Eleven pts showed a hypercalcemia G1 of short duration and just above the upper limit of normal value. No hypercalcemia G2 was observed. Most adverse events (AE) were G1-2, asthenia (19 pts), constipation (14 pts), diarrhea (13 pts). G3-4 AEs were neutropenia (11 pts) lymphopenia (9 pts), asthenia (3 pts), general health deterioration (2 pts) and diarrhea (1 pt). None of these AEs was considered related to inecalcitol. Of the 38/42 evaluable pts for PSA response, 33 (87%) had ≥30% PSA decline.
Conclusions: Results from this ongoing study show the safe toxicity profile of inecalcitol when given daily in HRPC pts even at mg level. PSA responses with this combination are encouraging. As DLT was not reached, higher dose of inecalcitol (4000 µg/day) are being tested.

MP-07.07
Implication of the Alternative NF-kappaB Pathway in Prostate Cancer Progression
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Introduction and Objective: Our previous study on prostate cancer (PCa) tissues shows that the alternative NF-kB proteins RelB and p52 localize to the nucleus more frequently than classical NF-kB proteins RelA and p50. We also reported on a small cohort that the nuclear localization of RelB correlates with increasing Gleason scores. The present study attempts to confirm this observation in a larger cohort and determine if this pathway may be implicated in the stage progression of prostate cancer.
Methods: To evaluate RelB expression and cellular localization, archival formalin-fixed, paraffin-embedded prostate specimens were used to construct a first tissue microarray (TMA) containing non-malignant tissue adjacent to the tumour (n = 55), prostatic intraepithelial neoplasia (PIN) (n = 31) and hormonosensitive (HS) PCa samples (n = 63). A second TMA was also built including hormonorefractory (HR) tumour specimens (n=36). Statistical analyses were used to evaluate the correlations between RelB and clinical and pathologic disease progression.
Results: Our immunohistochemical analysis showed a differential expression between non-malignant and tumour tissues. Indeed, RelB was largely expressed in the cell cytoplasm of tumours, including HS (87,3%) and HR (91,7%) samples compared to non-malignant tissue adjacent to the tumour (49,1%; $p < 0,001$) and PIN (48,4%; $p < 0,001$). Moreover, RelB was more frequently localized in the nucleus of HR PCa (97,2%) than in HS (63,5%; $p < 0,001$), non-malignant tissue adjacent to the tumour (51%; $p < 0,001$) and PIN (48,4%; $p < 0,001$).
Conclusion: RelB is over-expressed in PCa tissues with a frequent nuclear localization that increases with PCa stage progression. This extremely high nuclear expression in HR PCa tissues suggests that activation of the alternative NF-kB pathway may be implicated in the PCa progression from HS to HR status. Ongoing studies including the other alternative NF-kB p52 will hopefully shed light on the role of both NF-kB pathways in prostate cancer progression, its use as a potential prognostic marker as well as a possible therapeutic target for the future.

MP-07.08
Correlation between IKKe Expression and Prostate Cancer Progression *in vivo*
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Introduction: Overexpression of pro-inflammatory cytokines has been associated with prostate cancer (PCa) progression and hormone-refractory (HR) status. Previous work has shown that IKK plays a part in chronic inflammatory states, such as the rheumatoid arthritis. We have previously reported differences in IKK expression between hormone-sensitive (HS) and HR cell lines. HR cells express significantly higher levels of IKK than HS cells. In addition, IKK modulation (knockdown or overexpression) correlates with IL-6 secretion in HS and HR cell lines. Since IL-6 and IL-8 are associated with PCa progression, we formulated the hypothesis that IKK may be implicated in the progression of HS to HR status.
Methods: To validate this hypothesis, we performed IKK staining on paraffin-embedded prostate tissue microarrays containing cores from normal tissues (n = 47), non-malignant tissues adjacent to the tumour (n = 53), prostatic intraepithelial neoplasia (PIN) (n = 28), HS tumours (n = 62) and TURP samples from HR patients (n = 31). We also evaluated if the IKK expression was predictive of eventual clinical outcome.
Results: We found a clear correlation between the cytoplasmic levels of IKK expression in PCa and cancer progression. We observed a low cytoplasmic IKK expression in normal, PIN, and non-malignant tissues adjacent to the tumour, for which no difference in IKK levels was found. HS tumours presented a significant increase of cytoplasmic IKK expression compared to normal tissue, PIN and non-malignant tissues adjacent to the tumour ($p \leq 0,005$). Moreover, we observed the highest cytoplasmic IKK expression in HR tissue ($p = 0,005$). Finally, we studied the link between cytoplasmic IKK expression levels and clinical outcome. In a subset of patients where tissue from the same patient at diagnosis and at the time of HR status was available IKK expression was predictive of progression to metastases and HR status (Pearson correlation = 0,340; $p = 0,007$). We however found no correlation between nuclear IKK level and pathologic status or cancer progression.
Conclusions: Our results suggest that IKK is involved in PCa stage progression and may be implicated in the progression from HS to HR status. These findings justify further studies to elucidate the exact mechanisms surrounding IKKe in PCa progression.

MP-07.09
Disease Outcome of 261 Patients with a Prostatic Specific Antigen (greater than or equal to) 20 ng/mL Treated with Radical Prostatectomy at a Single Institution
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Introduction and Objective: Patients with high prostatic specific antigen (PSA) levels have often been recommended treatment with either radiation therapy or androgen deprivation because of the high risk of metastasis. We reviewed our experience in patients with a preoperative serum PSA ≥20 ng/mL treated with radical prostatectomy (RP). Our objective was to describe disease recurrence and mortality patterns.
Methods: Between 1988 and 2007, 261 patients with a median (range) age of 63,2 (45 to 81) years with a preoperative PSA ≥20 ng/mL, underwent RP in our institution. All patients had a negative preoperative bone scan and negative additional radiological testing as needed. Charts were comprehensively reviewed. The Kaplan-Meier method was used to analyze the disease-free survival for PSA and clinical recurrence.
Results: Median (range) PSA was 29.4 (20-1000 ng/mL): 137 (52,5%) had a PSA level between 20 and 30 ng/mL while 81 (31%) of patients had a PSA level ≥40 ng/mL. At final pathology, the disease was organ confined in 89 (34%), extra capsular extension was found in 158 (60%), seminal vesicle invasion in 100 (38%), lymph node involvement in 84 (32%) and positive surgical margins in 163 (62%). Eighty-nine patients received neoadjuvant androgen deprivation therapy (ADT), 152 had ADT with or without radiation therapy after RP, 29 had adjuvant radiation therapy and 76 had salvage radiation therapy. With a median follow-up of 7.75 years, 20/59 patients died from prostate cancer while 33 died from other causes (6 patients with cause of death unknown) and 159 patients had biochemical recurrence, of which 28 developed bone metastasis. One hundred and two patients remained biochemical free at a mean follow-up of 8.9 years. The actuarial recurrence-free survival at 5 and 10 years was of 45.7% and 34.8% respectively.

Conclusions: Even alone, radical prostatectomy performed in a high-volume institution may provide cure in up to a third of patients with very elevated PSA (>20 ng/mL). Despite a high rate of recurrence in this aggressive form of disease, about only a third of deaths are caused by prostate cancer which highlights the importance of postoperative adjuvant therapies.

MP-07.10

Bone Health Practices in Men on Androgen Deprivation Therapy (ADT): A Population-Based Analysis of 25,802 Patients

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Introduction and Objective: ADT is used in up to 1 in 2 men with prostate cancer. Osteoporosis and fragility fractures are important side effects of ADT. Guidelines recommend 2 important bone health practices for men on ADT – measurement of bone mineral density with dual x-ray absorptiometry (DEXA) and use of bisphosphonates in men at risk of osteoporosis. The implementation of these guidelines in routine practice is not well known.

Methods: Using linked administrative databases, we identified 25,802 men (mean age 75.9 y, range 66-100 y) with prostate cancer who were treated with at least 6 months of ADT (82.7%) or who underwent bilateral orchiectomy (17.3%) in Ontario, Canada between 1995 and 2005. Performance of DEXA and prescription of bisphosphonates were captured using specific procedure codes and drug identification numbers, respectively. Prior use of DEXA and bisphosphonates, as well as prior diagnoses of osteoporosis and fragility fracture, were captured with specific diagnostic codes and a 3-year look-back period. Annual rates per 100 person-years were determined for both outcomes.

Results: Among 25,802 men, 3.09% had a DEXA more than one year prior to starting ADT, 3.14% had a prior diagnosis of osteoporosis, and 1.89% were using a bisphosphonate prior to ADT initiation. The rate of undergoing DEXA within 2 years of starting ADT rose from 0.50 per 100 person-years in 1995 to 19.47 in 2005. Rates of DEXA testing were somewhat higher among those with a prior diagnosis of osteoporosis, prior DEXA test, or prior fragility fracture but did not reach rates above 50 per 100 person-years in any of these groups. Bisphosphonate use increased from 0.27 per 100 person-years in 1995 to 3.18 in 2005 among prior non-users. More men on ADT were started on a bisphosphonate in the third year after starting ADT as compared to the second year, and rates were higher in year 2 than year 1. Less than one-third of men starting a bisphosphonate underwent any DEXA testing within 12 months of bisphosphonate initiation.

Conclusions: Rates of DEXA testing and bisphosphonate use have increased over time among older men starting ADT, but significant gaps and delays remain in the quality of bone health care in this population.

5-STAR

MP-07.11

The Rate of Side Specific ECE is Closely Related to the Rate of Ipsilateral Lymph Node Invasion in Patients Undergoing Radical Prostatectomy

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Introduction and Objective: Several risk stratification schemes are available for the prediction of the need for extended pelvic lymph adenectomy (ePLAD) in patients with prostate cancer undergoing radical prostatectomy (RP). None of those tools rely on pathological diagnosis. We examined the relationship between ECE and side specific and overall rate of LNI and ePLND.

Methods: Between 1996 and 2008, 4806 patients underwent a RP with an ePLAD at a single European institution. Clinical and pathological information was available for 4790 men. Analyses were performed using the entire dataset as well as in a side specific fashion, where each lobe of the prostate and ipsilateral lymph node invasion was considered without accounting for contra lateral finding.

Results: Overall, 7.9% of all patients undergoing LND had lymph node invasion (LNI). The rate of LNI was 0.8% in absence of ECE vs. 5.7% and 15.1% when respectively side specific ECE or bilateral ECE was recorded. The rate of concordance (75.5%) between side specific ECE and side of LNI was statistically significant ($p < 0.001$) and independent predictor status of ECE, (none vs. side specific (OR: 5.66; $p < 0.001$) and none vs. bilateral (OR: 10.97; $p < 0.001$) was confirmed in multivariable models including PSA, biopsy Gleason sum and clinical stage.

Conclusions: Single sided ECE might indicate the predominant localization of the main tumour within the prostate. Our data demonstrated a relationship between ECE and the risk of ipsilateral LNI. These findings should be considered in future studies, including assessment of preoperative side specific tumour characteristics and side specific index tumour volume for testing the ability of developing side specific LNI prediction tools. These prediction tools could enable the surgeon to better decide if in such patients, a side specific extended or pelvic LND is required.