Moderated Posters 8: Prostate (Cancer/BPH)
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MP-08.01
Development of a Molecular Imaging System Based on the Transcriptional Activity of the DD3/PCA3 Non-coding RNA for Imaging Specifically the Prostate Cancer Cells

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Objectives: Molecular imaging plays an important role in oncology for staging of tumours. Unfortunately, the specificity and sensitivity of current techniques remain low. This study aims to improve the existing imaging system based on transcriptional activation, named as "Two -Step- Transcriptional Amplification (TSTA) system," with the goal to precisely image in vivo prostate cancer cells (PCa) by Positron Emission Tomography (PET). We have studied the potential of DD3/PCA3 promoter, a gene specifically expressed in PCa, to achieve this goal.

Methods: Various adenovirus constructs incorporating the DD3 promoter, the TSTA system and the Firefly luciferase reporter gene were generated and their specificity for PCa cells was tested in transient infection. By molecular engineering, we have improved the TSTA system and generated the 3STA. The luciferase activities of DD3-TSTA, DD3-3STA and PSA-TSTA (Prostate specific antigen) were compared in vivo by bioluminescence in xenograft mouse models.

Results: The DD3 promoter, is both specific to prostate and cancer cells. When DD3 promoter is incorporated in the amplification system TSTA and 3STA, it is specific to PCa cells and its activity is amplified more than 300 and 600 times, respectively, when compared to the activity of the DD3 promoter alone. Moreover, activity of DD3-TSTA and DD3-3STA is androgen-independent. In vivo, DD3-3STA activity is comparable to that obtained with the PSA-TSTA whose activity can be imaged by PET system.

Conclusions: The new system DD3-3STA allows specific and sensitive imaging of PCa cells. The new amplification system 3STA allows the DD3 promoter to produce reporter signal high enough to be detected by PET, a technology available in the clinic.

MP-08.02
The Effect of Age at Diagnosis on Prostate Cancer Mortality: A Grade-for-Grade and Stage-for-Stage Analysis

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Introduction and Objectives: The effect of age at diagnosis on cancer control in men with prostate cancer (PCa) has not been fully elucidated. To address this issue, we set out to assess the impact of age on long-term cancer-specific mortality (CSM) rates in a large cohort of patients with clinically localized PCa treated with radical prostatectomy (RP).

Methods: Overall, 205,551 patients with clinically localized PCa undergoing RP between 1988 and 2009 within the Surveillance Epidemiology and End Results database were included. Patients were stratified according to age: ≤50, 51-60, 61-70, and ≥71 years. The 15-year cumulative incidence CSM rates were computed. Competing-risks regression models were performed to test the effect of age on CSM in the entire cohort, and for each grade (Gleason score 2-4, 5-7, and 8-10) and stage (pT2, pT3a, and pT3b) sub-cohorts.

Results: The median age at diagnosis decreased from 66 years in 1988 to 61 years in 2009 ($p \leq 0.001$). Overall, 14,871 (7.2%), 73,734 (35.9%), 97,637 (47.5%), and 19,579 (9.5%) patients were aged ≤50, 51-60, 61-70, ≥71 years, respectively. Advancing age was associated with higher 15-year CSM rates (2.3 vs. 3.4 vs. 4.6 vs. 6.3% for patients aged ≤50 vs. 51-60 vs. 61-70 vs. ≥71 years, respectively; $p<0.001$). In multivariable analyses, age at diagnosis was a significant predictor of CSM, after accounting for confounders. This relationship was also observed in sub-analyses focusing on patients with Gleason score 5-7, and/or pT2 disease (all $p \leq 0.05$). Conversely, the effect of age failed to reach independent predictor status in men with Gleason score 2-4, 8-10, pT3a, and/or pT3b disease.

Conclusions: Our findings show that older patients are at higher risk of CSM compared to their younger counterparts, after accounting for the risk of dying from other causes. When considering patients affected by more aggressive disease, age at diagnosis does not represent an independent predictor of CSM.

MP-08.04
Utility of Preoperative 3 Tesla Pelvic Phased-array Magnetic Resonance Imaging in Prediction of Extracapsular Extension of Prostate Cancer and Its Impact on Surgical Margin Status

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Introduction and Objectives: Magnetic resonance imaging (MRI) of the prostate is gaining ground in the preoperative assessment of patients undergoing radical prostatectomy (RP). Yet, published reports of its predictive ability to detect extracapsular extension (ECE) have varied significantly. We evaluated the ability of 3 Tesla (3T) pelvic phased-array (PPA) MRI to predict ECE prior to RP and its subsequent effect on surgical margin status in a cohort of patients treated by a single surgeon.

Methods: We retrospectively evaluated 48 preoperative RP patients who underwent 3T PPA MRI at the discretion of the surgeon, based on the clinical probability of adverse pathological features. All MRIs were read by a single expert genitourinary radiologist. Tumour stage based on MRI was compared to pathological stage. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI in predicting ECE were calculated. Positive surgical margin rates of patients with ECE on MRI were compared to those without ECE on MRI.

Results: The MRI reports predicted 19 (40%) patients to be positive for ECE. Of these patients, final pathology revealed that 9 were positive for ECE and 2 had positive surgical margins. Of the 29 (60%) patients not predicted to have ECE based on MRI, 14 had positive ECE on pathology, while 12 had positive surgical margins. Preoperative 3T PPA achieved a sensitivity, specificity, PPV, and NPV of 44%, 61%, 55%, and 50%, respectively. Of the patients with ECE reported on MRI, 11% went on to have positive surgical margins compared to 41% of those without ECE on MRI ($p=0.404$).

Conclusions: At our centre, the use of preoperative 3T PPA MRI for predicting pathological ECE and surgical margin status is of questionable benefit. These findings suggest that preoperative MRI reports of organ-confined disease may lead to closer surgical dissection and subsequent positive surgical margins, regardless of true pathological staging.

MP-08.05

Development and Validation of a Markov Monte Carlo Model for Prostate Cancer Management

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Introduction and Objectives: Prostate cancer (PCa) is the most common non-skin cancer among men in developed countries. Several novel treatments have been adopted by healthcare systems to manage PCa. Observational and trial based studies on effectiveness often evaluated fewer treatments over limited follow-up. A contemporary decision analytic model was necessary to address these limitations by synthesizing the evidence on several treatments thereby forecasting short and long-term clinical outcomes. The objectives of this study were to develop and validate a Markov Monte Carlo model for the clinical management of PCa from diagnosis to end-of-life.

Methods: A decision model was developed to simulate the management of PCa from diagnosis to end-of-life. Health states modeled by risk at diagnosis were - active surveillance (AS), initial treatments (radical prostatectomy or radiation therapy), PCa recurrence, PCa recurrence free, metastatic castrate resistant prostate cancer (mCRPC) and death (cause specific/other causes). Treatment trajectories were based on state transition probabilities derived from the literature. Validation and sensitivity analyses assessed the accuracy and robustness of model predicted outcomes.

Results: Model predicted rates at 10-years were: AS (1.4%), delayed treatments for AS (2.5%), recurrence (28.6%), recurrence free (18.1%), mCRPC (7.5%), PCa death (9.1%), and death from other causes (33.6%). These rates at 15-years were 0.5%, 2.9%, 17.1%, 12.3%, 9.2%, 12.7%, and 45.9%, respectively. Over lifetime, 21% died from PCa and 79% died from other causes. Validation demonstrated good agreement between model predicted outcomes and observed outcomes. Sensitivity analyses indicated robustness of base case findings.

Conclusions: This validated model could forecast longitudinal changes in clinical outcomes pertaining to several treatments among individuals with PCa. This model could be used to assess healthcare resource use and costs associated with PCa treatments.

MP-08.06

Cost Comparison of Different Forms of Androgen Ablative Therapies in Metastatic Castration-resistant Prostate Cancer in Canada

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Introduction and Objectives: Androgen ablation (ADT) maintenance is recommended during castration-resistant prostate cancer; however the overall cost of medications during this phase is dramatically increasing with ADT accounting for almost 21% of the total cost. The objective of this study was to perform a cost comparison of different forms of ADT, including luteinizing hormone releasing hormone agonists (LHRHa) medications and surgical castration, over the phase of metastatic castration-resistant prostate cancer (mCRPC).

Methods: Two Markov models were developed in order to simulate survival in mCRPC, and the cost of ADT as per Quebec's public healthcare system. The models include recently approved additional lines of treatment after and/or before docetaxel (i.e. abiraterone and cabazitaxel). Survival was based on clinical trial results and clinical practice guidelines found in a literature review. Costs are in Canadian dollars ($).

Results: The mean cost of ADT per patient in mCRPC over an average period of 28.1 months was estimated at: $1,413 for surgical castration, $8,346 for Eligard, $8,514 for Trelstar, $9,891 for Suprefact Depot, $10,032 Lupron Depot, and $10,172 for Zoladex. The corresponding values obtained with the alternate model (which includes abiraterone initiation prior to docetaxel therapy) over a 37.2 months were: $1,413, $11,078, $11,302, $13,130, $13,316 and $13,503, respectively. For each annual Canadian cohort of 4,000 mCRPC patients, for a 28.1 months period, the total cost of ADT was estimated at $ 5.6 million for surgical castration, and between $33.4 and $40.7 million for LHRHa therapy. For a 37.2 months period, the total cost for surgical castration remained the same and was between $44.3 and $54.0 million for LHRHa therapy.

Conclusions: Our study estimates the costs associated with the use of different ADT in mCRPC. Increasing the use of least costly forms of ADT will result in potential cost savings during the mCRPC phase.

MP-08.07

Extremely High Levels of PCA-3 is Associated with Prostatic Inflammation

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Introduction: It has been suggested that PCA3 testing in the general male population might lead to earlier diagnosis and management changes that improve outcomes for men with or at risk of prostate cancer. In the setting of high level PCA3 (>100) clinical evaluation, cancer specificity of the urinary PCA3 test appears to be maintained in the face of prostatitis. We aimed to analyze the impact of PCA3 ratio >100 in post-prostatic massage urine in the clinical management of patients with abnormal PSA and in those with already known disease (active surveillance), evaluating its diagnostic ability and predictive value of tumour aggressiveness.

Methods: Observational, prospective, single centre study of patients with suspected prostate cancer who are candidates for biopsy and in patients on active surveillance. We present a series of 260 consecutive samples of urine collected post-prostatic massage from January 2012 to August 2013. We analyzed the fate of 16 patients with PCA3 ratio >100 and corresponding biopsy.

Results: Mean age and PSA of the sixteen patients, 62% had prostate cancer of which 65% were high grade. Among patients without cancer at biopsy, 83% had demonstrated acute inflammation at biopsy. The sensitivity and specificity of high PCA3 in our cohort is 62% and 39 % respectively. The mean age, PSA, PCA-3 in our cohort were 68, 112, 7.01 respectively.

Conclusions: Despite prior evidence suggesting that inflammation does not cause elevated PCA-3, our data indicate that some men with extremely high levels do have significant inflammation. Clinicians should be aware of these findings. More data are required to validate these results.

MP-08.08

Comparison of the Cancer of the Prostate Risk Assessment (CAPRA) and D'Amico Classification after External Beam Radiotherapy or Permanent Seed Prostate Brachytherapy

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Introduction and Objectives: The CAPRA score has been validated in several surgical cohorts and is easy to use. We studied its value compared to the D'Amico classification to predict biochemical failure (bF) in patients treated with different radiation techniques for D'Amico low- or intermediate-risk prostate cancer.

Methods: We analyzed 744 patients treated without any androgen deprivation and with either external beam radiotherapy (EBRT) (52.7%) or brachytherapy (BT) with I125 (47.3%) for D'Amico low-risk or lower tier intermediate risk cancer. 14% had a PSA >10 ng/mL, 39% a Gleason 7 and 5% both factors. EBRT dose levels were extreme hypofractionation (45 Gy in 9 fractions) in 10%, 76-79.2 Gy in 32.7% and 70.2-74 Gy in 20%. All patients without bF had a minimum of 36 months follow-up. Cox regression analysis was used to predict for biochemical failure (bF), as per the Phoenix definition (nadir PSA +2ng/ml).

Results: Median follow-up for patients without bF was 56 (range 36-114) months. Forty-seven patients (6.3%) presented with a biochemical recurrence. The 5-year bF-free survival was 95%, 90% and 80% for a CAPRA 0-2, 3-5 and 6-7 respectively (log rank $p<0.001$) where it was 94% and 90% for D'Amico low and intermediate risk cancers ($p=0.026$). In multivariate analysis adjusted for treatment type, the CAPRA score as a con-

tinuous variable (HR 1.39, 95% CI 1.14-1.71, p=0.002) was predictive of BF, while D'Amico classification was not (p=0.21). The area under the curve (AUC) of the CAPRA as a continuous variable at 5 years was 0.62 (p=0.005). For the D'Amico classification, the sensitivity/specificity at 5 years was 61.6%/50.0%.
Conclusions: The CAPRA score was superior in predicting bF than the D'Amico classification. Each 1-point increase increased the risk of bF by 39%.

MP-08.09

IKKe Impacts Growth of Castrate-resistant Prostate Cancer Tumours Through the Control of IL-6 Gene Expression

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Introduction and Objectives: Elevated IL-6 serum levels have been associated with metastasis-related morbidity in prostate cancer (PCa) patients. We have extensively studied IKKe in PCa and established that over-expression of IKKe in hormone-sensitive (HS) PCa cell lines, which resulted in its nuclear translocation, induced IL-6 secretion. We also reported that PCa cell lines lacking androgen-receptor expression exhibit high constitutive IKKe expression and IL-6 secretion whereas only very low IKKe expression were observed in HS PCa cell lines. We hypothesized that the deregulation of IKKe expression leads to the activation of several transcription factors that control cytokine gene expression, particularly IL-6 that acts as a positive growth factor for PCa cells.
Methods: Using pIL6-CAT constructs, in which a reporter gene was cloned under the control of mutated IL-6 promoters, we studied the IKKe-dependent activation of IL-6-transcription factors. To characterize the impact of IKKe depletion on tumour growth and IL-6 tumour secretion, we also developed in the SCID mouse a doxycycline-inducible PCa xenograft model able to control IKKe expression.
Results: We demonstrated that IKKe nuclear translocation induces the activation of the NF-IL6 transcription factor resulting in a NF-kB-independent transcription of the IL-6 gene. We also performed an extensive in vivo mouse xenograft-based experiment (73 mice) to study the effect of IKKe depletion on CR PCa cell proliferation and IL-6 tumour secretion. We observed a significant growth delay for PC3-6TR-shIKKe cells injected in SCID mice fed with a dox-supplemented diet in comparison with mice fed a normal diet. Finally, we found a decrease in IL-6 and IL-8 levels that strongly correlated with tumour growth inhibition.
Conclusions: These results provide solid evidence for a role of IKKe in PCa cell proliferation and survival, perhaps in part by the activation of the IL-6 gene promoter.

MP-08.10

Greenlight XPS-180W Laser Vaporization of the Prostate for Benign Prostatic Hyperplasia: A Global, Multi-centre Study Including 1053 Patients, Analysis of Complication Rates and Outcomes at 2 Years

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Introduction and Objectives: The aim of this study was to evaluate the safety and outcomes at 2 years of the new Greenlight XPS-180W laser system (AMS, Minnetonka, MI, USA) for the treatment of BPH in a large multicentre cohort.
Methods: A total of 1053 patients underwent Greenlight laser photoselective vaporization for the treatment of BPH at 6 international centres between 2010 and 2012. Perioperative variables (International Prostate Symptom Score (IPSS), QoL, maximum flow rate (Qmax), post-void residual (PVR) and PSA levels were recorded at baseline, 3 and 6, 12 and 24 months postoperatively when available. Complications and outcomes were analyzed according to prostate volume >80 and < 80 cc as defined by preoperative transrectal ultrasound.
Results: In terms of complication aside from conversion to TURP that was more prevalent in patients with larger glands (11.2% vs. 1.1%; p<0.001), all other rates of complications including perforation (0.6% vs. 0.6%), bleeding obscuring vision (3.8% vs. 6.7%), bleeding hematuria (0.5 vs. 0%) and blood transfusion (0.3% vs. 0.5%) were relatively low and equivalent between the two groups. Statistically, significant improvements compared to baseline were noted in all key clinical outcome parameters postoperatively at 3, 6, 12 and 24 months without detected difference between the two groups (Fig. 1). Overall, at 24 months compared to baseline median, IPSS decreased from 21.0 to 4.2 while Qmax increased from 6.9 to 19 and QoL improved from median score of 5 to 1. PSA decreased from a mean of 4.4 to 2.7 (p<0.05).
Conclusions: XPS systems provide safe and effective tissue vaporization with significant clinical relief of BPH obstruction associated with objective outcomes and PSA reduction at 24 months confirming the mid-term durability of this procedure regardless of prostate size.

MP-08.11

Evaluating the Correlation of Serum Gonadotropins with the Development of Castrate Resistant Prostate Cancer

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Introduction and Objectives: It has been postulated that follicle-stimulating hormone (FSH), released by the pituitary or endogenously produced by cancer cells, may lead to a proliferative response of prostatic cells and angiogenesis in the tumour microenvironment. Herein we investigate the association of serum FSH and time to castrate resistant prostate cancer (CRPC).
Methods: This was a single centre retrospective study of men with advanced prostate cancer followed in a clinical research centre at Queen's University. Patients were included if they had received androgen deprivation therapy (ADT) and had at least one serum FSH measurement while on therapy. The primary outcome was time of ADT initiation to the development of CRPC. Castrate resistance was defined as three consecutive rises in PSA, separated by at least 2 weeks. Inclusion required ADT to be continuous for 6 months and testosterone to be maintained below 1.7 nmol/L. FSH was analyzed as both a continuous and categorical variable. Spearman correlation coefficients and the Mann-Whitney test were used to analyze associations.
Results: Of the 323 men in the database, 85 patients met the inclusion criteria. The median follow-up from initiation of ADT was 2.98 years (range 0.5-14.5). Of these patients, 45 progressed to CRPC with a median time to progression of 2.3 years (0.4-9.7). The median max-FSH level was 6.2 mIU/mL (1.5-28.1). As a continuous variable, there was an inverse, but non-significant correlation between FSH and time to CRPC (r=-0.247, p=0.10). When analysed at a threshold of 4.8 mIU/ml (lowest tertile), there was a significant association of higher FSH levels and shorter time to CRPC (median 2.02 years vs. 3.29 years, two-tailed p=0.019).
Conclusions: Given the upregulation of FSH receptors on androgen-independent cells and the potential proliferative properties of the receptor-ligand interface in vitro, our data further support a clinically relevant role of FSH in prostate cancer progression.

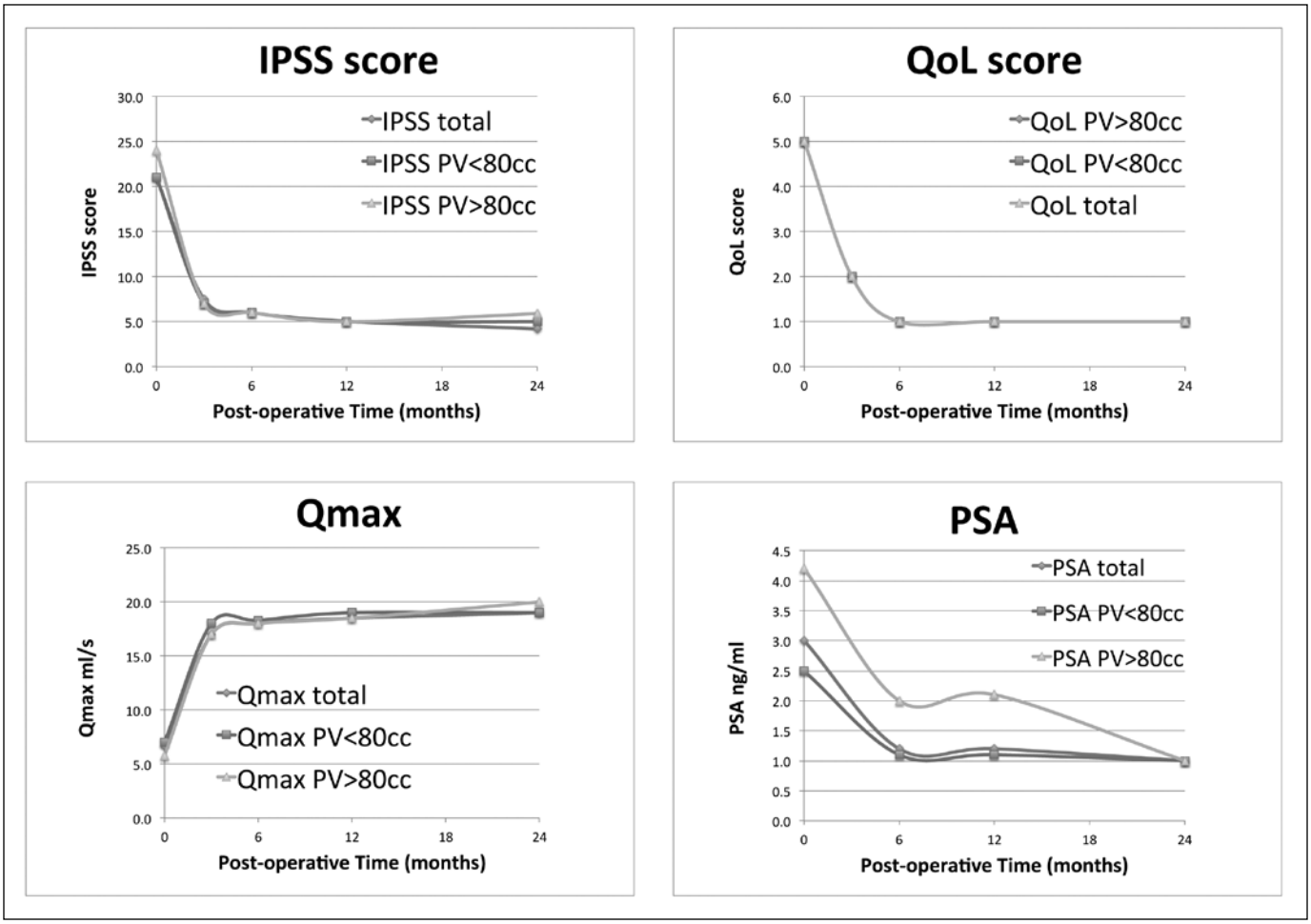

Fig. 1. MP-08.10.

MP-08.12

The Importance of Other Cause Mortality and Cardiovascular Morbidity in Patients with Metastatic Prostate Cancer Exposed to Conventional Androgen Deprivation Therapy

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Introduction and Objectives: Recent reports indicated important cardiovascular (CV) morbidity and mortality in patients exposed to androgen deprivation therapy (ADT), especially in those with baseline CV comorbidities.

Methods: Patients aged 65 years and older with metastatic PCa who received ADT were abstracted from the Surveillance and Epidemiology and End Results (SEER) Medicare database, between 2000-2009. We examined the rates of cancer specific (CSM) and other cause mortality (OCM) in individuals with metastatic prostate cancer (PCa) exposed to ADT. Among OCM cases, we focused on deaths attributed to CV complications. Additionally, we repeated the analysis in patients with baseline CV comorbidities, since these individuals may be at highest risk of CV mortality when exposed to ADT.

Results: Of 4230 patients with metastatic PCa exposed to ADT the rates of OCM were 22.7% at five years compared to 55.6% for PCa mortality. Of individuals who died of OCM 496 (56.6%) deaths were attributed to CV causes. At baseline, 1414 (33.4%) patients had CV comorbidities. When focusing exclusively on this sub-cohort, the 5-year OCM and CSM rates were 29.1% vs. 53.7%, respectively. Of the 373 (26.4%) deaths from other causes, 181 (48.5%) were attributed to CV causes.

Conclusions: As many as 1 in 4 deaths that occur in patients with metastatic PCa treated with ADT were attributable to OCM rather than PCa itself. Moreover, CV deaths occurred in half of patients dying from OCM. These observations emphasize the importance of comorbidities in this patient group. More specifically, baseline comorbidities were particularly important in patients with CV disease. In this subgroup, the rate of OCM was approximately 30%. Possibly, the introduction of new ADT agents such as LHRH blockers may reduce the risk of death from CV causes.

MP-08.13

Intensity-modulated Radiation Therapy Leads to Survival Benefit Only in Patients with High-risk Prostate Cancer: A Population-based Study

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Introduction and Objectives: To evaluate the survival benefit associated with intensity-modulated radiation therapy (IMRT) as compared to initial observation in a large cohort of prostate cancer (PCa) patients representing the U.S. population.

Methods: Overall, 42,483 patients diagnosed with PCa treated with IMRT or initial observation between 2001 and 2007 within the Surveillance, Epidemiology, and End Results (SEER)-Medicare were evaluated. Patients in both treatment arms (IMRT vs. initial observation) were matched using propensity-score methodology. The 8-year cancer-specific mortality (CSM) rates were estimated, and the number needed to treat (NNT) was calculated. Competing-risks regression analyses tested the relationship between treatment type and CSM. All analyses were repeated after stratifying patients according to tumour risk group (low- and intermediate- vs. high-risk), age (<73 vs. ≥73 years), and Charlson comorbidity index (CCI, ≤1 vs. >1).

Results: After propensity-score matching, 14,857 (77.9%) and 4,207 (20.1%) patients had low/intermediate- vs. high-risk PCa, respectively. The 8-year CSM rates were 3.4 and 4.1% for patients treated with IMRT vs. initial observation, respectively (P<0.001). The corresponding 8-year NNT was 142. In patients with low/intermediate-risk disease, IMRT was not associated with lower CSM rates compared to observation (8-year CSM rates: 2.5 vs. 1.8%, respectively; P=0.7). In patients with high-risk disease, the 8-year CSM rates for IMRT vs. observation were 5.8 vs. 10.5%, respectively (p<0.001). The corresponding number needed to treat was 21. When high-risk patients were stratified according to age (<73 vs. ≥73), and CCI (≤1 vs. >1) the 8-year CSM rates for IMRT vs. observation were 4.3 vs. 9.4% and 6.9 vs. 11.9% and 5.3 vs. 11.4% and 6.1 vs. 10.1%, respectively (all p<0.001). The corresponding NNTs were 19, 21, 16, and 25, respectively. These results were confirmed in multivariate analyses, where the protective effect of IMRT on CSM was more evident in high-risk patients with younger age and lower comorbidities (all p≤0.001).

Conclusions: In patients with low/intermediate-risk PCa, the use of intensity-modulated radiotherapy was not associated with a PCa-specific survival improvement after 8 years of follow-up. Conversely, this approach leads to a significant survival advantage compared to initial observations in patients with high-risk disease. The highest survival benefit was observed among younger and healthier patients.

MP-08.14

Reducing the Over-diagnosis of Prostate Cancer with the Judicious Use of First-Time Biopsy: Validation of the Toronto Biopsy Avoidance Tool (T-BAT)

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Introduction and Objectives: Concerns have been raised about over-diagnosis of prostate cancer (PC), risk biopsy-associated sepsis, and anxiety provoked by active surveillance. To help identify situations in which biopsy can be deferred or avoided, we previously developed a tool predicting the probability of low risk or no PC (i.e., whereby the biopsy results would not trigger radical intervention). The current objective was to validate these models in a separate database.

Methods: A validation cohort of men referred for first biopsy was created using a separate biopsy dataset at our institution. The model predicts a composite outcome of negative biopsy or Low risk PC (no Gleason pattern ≥4, ≤3 positive cores, and no core with >50% cancer involvement). Predictors include age, ethnicity, family history of PC, DRE, and PSA. IPSS was added as an optional field. Model discrimination was assessed using area under the receiver operating characteristics curves (AUC). Calibration plots were used to assess accuracy the predicted probabilities. Decision curves were used to assess instances in which the prediction models offer a net benefit compared to "biopsy all" or "biopsy nobody" strategies.

Results: The validation cohort included 1410 men, of which 257 (18.2%) had low risk PC and 524 (37.2%) had non-low risk PC. The model predicting low risk/no pc had an AUC of 0.75 (95%CI=0.72-0.78). Calibrations curves demonstrated excellent calibration between predicted and observed probabilities. According to decision curve analyses, the model offers a net benefit if the threshold for deferring biopsy was a probability of having low risk PC or no PC of 30-95%.

Conclusions: In a validation cohort of men referred for biopsy, we have demonstrated that the T-BAT can guide clinicians in using biopsy more judiciously. Our model predicting low risk or no PC offers benefit over a wide, clinically relevant, range of probability thresholds.

MP-08.15

Creation of the Toronto Biopsy Avoidance Tool (T-BAT) with Clinical Parameter-only and Adipokine Biomarker-augmented Versions

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Introduction and Objectives: Given increasing concern regarding the over-diagnosis of prostate cancer (PC), our aim was to create a tool to predict the probability of low risk PC or negative biopsy (i.e., where intervention is not likely needed) among patients undergoing their first biopsy, with 2 versions: (1) a clinical parameter-only tool, and (2) a tool using clinical parameters and adipokine biomarkers.

Methods: Patients undergoing their first biopsy were identified. Clinical parameters considered for model inclusion were age, abnormal digital rectal exam (DRE), PSA, family history of PC, ethnicity, and body-mass index (BMI). Adipokines studied include resistin, tumour necrosis factor alpha, interleukin-6 (IL-6), nerve growth factor, hepatocyte growth factor and monocyte chemoattractant protein-1. The primary outcome was a composite of negative biopsy or Low risk PC (no Gleason pattern≥ 4, ≤3 positive cores, and no core with >50% cancer involvement). Multivariable logistic regression models that minimized mean squared error and maximized out-of-sample area under the receiver operating characteristics curve (AUC) were chosen.

Results: In our cohort of 1061 men, 365 had non-low risk PC. IL-6 was the only adipokine predictive of outcomes in univariate analyses. Age, PSA, DRE, family history and ethnicity were selected for inclusion in the clinical parameter-only model. The AUC for predicting odds of low risk/no PC was 0.749 (0.716-0.781). The same clinical parameters along with IL-6 were included in adipokine models. The AUC for predicting odds of low risk or no PC was 0.751 (95%CI=0.719-0.783).

Conclusions: A prediction model was successfully created for probability of either negative biopsy or low risk PC (i.e. no intervention needed) in patients undergoing first biopsy. While addition of IL-6 improved discrimination, the difference was not clinically meaningful. Validation of the clinical parameter-only version is underway.

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Prostate Biopsy Trends in Relation to U.S. Preventative Task Force Recommendations against Routine PSA-Based Screening: A Time-series Analysis

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Introduction and Objectives: In May 2012, the U.S. Preventative Task Force (USPTF) released recommendations against routine prostate-specific-antigen (PSA) screening for prostate cancer (PC). Our study objective was to examine how this event has impacted our institutional biopsy rate and cancer detection using a time-series analysis.

Methods: We examined our institutional prostate biopsy database from October 2008 to June 2013. Biopsies for active surveillance or solely targeting MRI-detected lesions were excluded. Low-risk PC (LRPC) was defined as no Gleason pattern ≥4, ≤3 cores involved or ≤1/3 of total number of cores involved, and no core with >50% cancer involvement. High grade PC (HGPC) was defined as Gleason 7-10. A time-series analysis using interventional auto-regressive integrated moving average (ARIMA) models with step intervention functions were conducted to examine the effect of the recommendations on number of biopsies performed and cancer detection per month.

Results: Within the study period, 3408 biopsies were performed and 1601 (47.0%) PCs were detected (LRPC = 563 (16.5%); HGPC = 914 (26.8%)). The median for biopsies per month decreased from 64 (IQR=58-78) before recommendations to 34 (IQR=27-39) afterward (p=0.003), while median number of patients undergoing their first-time biopsies decreased from 45 (IQR=41-57.5) to 24 (IQR=20-32, p=0.025). The median number of LRPCs detected per month decreased from 10 (IQR=8-14) to 5 (IQR=4-7, p=0.012), while the median number of HGPCs detected per month decreased from 17 (IQR=15.5-21) to 10 (IQR=9-11, p<0.001).

Conclusions: Since the USPTF recommendations, the number of biopsies performed (total and first-time biopsies), based on referrals from our catchment area, has decreased. This is likely due to decreased PSA screening and referral by general practitioners. Although encouraging that less low risk PCs are being diagnosed, the magnitude of sudden decrease in the detection rate of Gleason 7-10 PCs is concerning.