Podium Session 1: Oncology: Prostate
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POD-01.01

Therapeutic Value of Lymph Node Dissection at Radical Prostatectomy: A Population-Based Retrospective Study

Siemens D, Withrow D, Groome P
Queen's University, Kingston, ON

Introduction and Objectives: The therapeutic benefit of pelvic lymph node dissection (PLND) at radical prostatectomy is still under debate. The overall effect of standard or extended node dissection on prostate cancer survival outcomes are complicated by variation in patient populations and study outcomes in most retrospective reviews. We report our findings of therapeutic effect of PLND for Ontario patients after radical prostatectomy.

Methods: The information sources for the study included electronic clinical data such as the Ontario Cancer Registry (OCR) and supplemented through an extensive chart review conducted by trained abstractors according to a standardized protocol. We used a retrospective case-cohort approach to assess the effect of lymph node removal on prostate cancer-specific mortality. A parent study population included a random sample of 1703 patients treated for cure in Ontario between 1990 and 1998, as well as 591 cases selected based on death from their prostate cancer within 10 years of diagnosis. From this group 313 patients meeting inclusion criteria for this study were identified. A Cox-proportional hazards model was used to determine the association between number of lymph nodes removed and risk of prostate cancer death, considering baseline disease characteristics, treatment and age as potential confounders. In a secondary analysis, the results were stratified based on nodal status.

Results: The crude hazard ratio (HR) showed a marginally statistically significant reduced risk of prostate cancer mortality as the number of LN removed via PLND increased (HR: 0.92, 95% CI: 0.84 – 1.01). None of the variables considered as confounders caused a change in the LN hazard ratio of greater than 10% and therefore were not included in the adjusted model. Stratification based on pathological nodal status did not significantly (>10%) change the HR.

Conclusion: These results seem to confirm a trend to therapeutic benefit of greater node removal with reduced prostate cancer mortality although the study was slightly underpowered. In this case-control study design of mostly low-to-intermediate risk patients in Ontario, the possible therapeutic benefit of PLND was found to be independent of pathological nodal status.

POD-01.02

Rising Hospital Admission Rates for Urologic Complications after Transrectal Ultrasound-Guided Prostate Biopsy

Nam R[1], Saskin R[2], Liu Y[2], Klotz L[1], Trachtenberg J[1], Stanimirovic A[1], Simor A[1], Narod S[1]
[1]University of Toronto, Toronto, ON; [2]Institute of Clinical Evaluative Sciences, Toronto, ON

Introduction and Objective: Transrectal ultrasound (TRUS)-guided prostate biopsy is widely used to confirm the diagnosis of prostate cancer. The technique has been associated with significant morbidity in a small proportion of patients.

Methods: We conducted a population-based study of 75,190 men who underwent a TRUS-guided biopsy in Ontario, Canada, between 1996 and 2005. We used hospital and cancer registry administrative databases to estimate the rates of hospital admission and mortality due to urologic complications associated with the procedure.

Results: Of the 75,190 men who underwent a TRUS biopsy, 33,508 (44.6%) were diagnosed with prostate cancer and 41,682 (55.4%) did not have prostate cancer. The hospital admission rate for urologic complications within 30 days of the procedure for men without cancer was 1.9% (781/41,482). The 30-day hospital admission rate rose from 1.0% in 1996 to 4.1% in 2005 (p-value for trend <0.0001). The majority of hospital admissions (72%) were for infection-related reasons. The probability of being admitted to hospital within 30 days of having the procedure rose four-fold between 1996 and 2005 (odds ratio = 3.7; 95% C.I.: 2.0 – 7.0, $p < 0.0001$). The overall 30-day mortality rate was 0.09%, but did not change over the study period.

Conclusions: The hospital admission rates for complications following a TRUS-guided prostate biopsy have risen dramatically over the last 10 years, primarily due to an increasing rate of infection-related complications.

POD-01.03

Human Kallikrein-2 Gene and Protein Expression Predicts Prostate Cancer at Repeat Biopsy

Satkunasivam R, Zhang W, Stanimirovic A, Klotz L, Trachtenberg J, Nam R
University of Toronto, Toronto, ON

Introduction and Objective: We have extensively examined and shown the predictive value of the human kallikrein-2 (hK2) protein and its gene, KLK2, to be an important predictor for prostate cancer at the time of screening biopsy. Extensive sequencing analysis has identified two single nucleotide polymorphism (SNPs) (rs2664155-G/A and rs198977-C/T) to be highly associated with prostate cancer (Nam et al, Clin Can Res, 2006). We examined whether these SNPs and hk2 serum levels could predict cancer at the time of repeat biopsy among patients with an initial negative biopsy.

Methods: We genotyped 941 men who underwent a repeat prostate biopsy using an extended biopsy pattern after an initial negative biopsy for the two KLK2 SNPs. We also measured hk2 serum levels prior to initial prostate biopsy. All other baseline risk factors and tumour markers were measured, including age, ethnicity, family history of prostate cancer, PSA, prostate volume and DRE. Logistic regression analyses were conducted to determine the significance of KLK2 SNPs and hK2 levels for predicting cancer at repeat biopsy.

Results: Of the 941 patients, 180 (19.1%) were found to have cancer. The baseline model of age, ethnicity, PSA, prostate volume and past histology were all important predictors for cancer. Mean serum hK2 levels were also significantly higher among cases (246.0 ng/mL) compared to controls (227.9 ng/mL, $p < 0.02$). Among the two SNP variants, rs198977 was positively associated with cancer at repeat biopsy (OR variant T allele = 1.5, 95% CI: 1.1-2.1, $p = 0.01$). The KLK2 rs198977 genotypes were positively associated with hK2 levels ($p = 0.02$). The addition of hK2 levels and KLK2 SNP to the baseline predictive model increased the area under the curve from a baseline model of 0.69 to 0.71 ($p = 0.01$). Hk2 and KLK2 genotype was more important for prostate cancer detection than PSA. When combined, the odds ratio for prostate cancer for patients with high hK2 levels and the variant T-allele of rs198977 was 3.77 (95% CI: 1.94 – 7.32, $p <$ 0.0001), compared to patients with low hK2 levels and the C-allele.

Conclusions: The KLK2 variant SNP, rs198977, was positively associated with hK2 levels and predicts prostate cancer at the time of repeat prostate biopsy. These findings may provide important information for the clinical management of patients being considered for repeat prostate biopsy after an initial negative biopsy.

POD-01.04

Postoperative PSA Kinetics Vary According to Values of PSA (Early vs. Late)

Fradet V[1], Paciorek A[2], Davis C[2], Carroll P[2]
[1]Centre De Recherche En Cancérologie De L'Université Laval/HDQ/CRCHUQ, Québec, QC; [2]Department of Urology, University of California, San Francisco, San Francisco, CA, USA

Introduction and Objective: Postoperative prostate-specific antigen (PSA) doubling time (PSADT) is an important predictor of prostate cancer-specific mortality in patients treated with radical prostatectomy. Whether PSA kinetics at very low PSA values reflects that of higher PSA values is unknown. In this retrospective cohort study, we test the hypothesis that, within the same patient, PSA kinetics differs across different PSA levels.

Methods: From the CaPSURE prostate cancer registry, we included all patients treated with radical prostatectomy from 1995 to 2008, that had at least 4 non-zero postoperative PSA measurements. Patients who had any neoadjuvant or adjuvant therapy were excluded. We compared the PSADT across range of PSA, in subject having at least 2 PSA measurements both below (early PSADT) and above (late PSADT) 0.2 ng/mL. A paired analysis was conducted using exact McNemar and kappa tests. The risk of short (aggressive) late PSADT was also assessed using conditional logistic regression models and c-statistics were used to assess the additional predictive value of early PSADT. The base model included age and cancer risk as covariables.

Results: The study population included 3098 patients, with a mean age of 63 (SD 6) years. The vast majority of cancer risk at diagnosis was intermediate or lower: 12 (4.8%) patients had a Gleason score of 8 or more, 7 (2.8%) patients had a clinical stage T3 or more and 19 (7.6%) patients had a PSA greater than 20. Overall, the mean PSADT was of 17.7 months (SD 1010.1). Late PSADT significantly differed from early PSADT (McNemar statistic $p < 0.01$). Early PSADT overestimates the aggressiveness of late PSADT (i.e., late PSADT is longer) in 77 (25%) patients. Early PSADT underestimates the aggressiveness of late PSADT (i.e. late PSADT is shorter) in 32 (10%) patients. The findings of the comparison analyses were robust to sensitivity analyses where the PSADT comparison cut-point varied from 3 months to 24 months, and where the threshold value for defining early versus late PSA varied from 0.1 to 0.4 ng/mL. At multivariate analysis, a short early PSADT doubled the risk of a short late PSADT (OR 1.87, 95% CI: 1.01-3.45, $p = 0.046$) but adds very little accuracy to the model (no change the c-statistic of 0.62).

Conclusions: After radical prostatectomy, PSA kinetics at very low PSA values significantly differs from the kinetics at higher PSA values as commonly evaluated after PSA recurrence. Early PSA kinetics may be more likely to overestimate the aggressiveness of later PSA kinetics. PSA kinetics in the very low PSA range should be interpreted with caution, and may not be the ideal biomarker to help select patients for adjuvant therapy.

POD-01.05

Long-Term Results of Salvage Cryotherapy for Prostate Cancer

Williams A, Martinez C, Chalasani V, Lu C, Ng C, Chin J
Department of Urology, University of Western Ontario, London, ON

Introduction and Objective: Salvage treatment of prostate cancer recurrence following external bean radiation therapy (EBRT) is morbid, as such many minimally invasive approaches have been trialled. The primary problem with comparing salvage techniques following EBRT is the lack of long term data. We reviewed the long term salvage cryotherapy to the prostate gland in a single institution, single surgeon series.

Methods: A retrospective analysis was performed on all patients undergoing salvage cryotherapy for locally recurrent prostate cancer after EBRT by a single surgeon at our institution from 1995-2004. Preoperative, perioperative and postoperative data was reviewed and recorded. Follow-up mortality data, PSA results, bone scan results and any details of hormone therapy were recorded for this study.

Results: There were 187 patients included in the current study, from which 176 patients had records available for follow-up, giving a follow-up rate of 94%. Mean follow up was 7.46 years (1-14 years). Fifty-two patients were followed for greater than 10 years. Prostate cancer recurrence, when it occurred, was at an average of 2.3 years following cryotherapy. Average time to hormone therapy in these patients was 2.8 years. Results are summarized in Table 1.

Table 1. POD-01.05.

	5 years n = 126	8 years n = 88	10 years n = 52
Disease free survival*	38%	27%	15%
Disease free survival (pre-salvage PSA <4 ng/mL*)	79%	39%	43%
Disease free survival (pre-salvage PSA >4 ng/mL*)	27%	24%	11%
Overall survival	92%	94%	94%
Disease specific survival	94%	95%	96%

PSA = prostate-specific antigen; *ASTRO definition of recurrence and no metastases or biopsy proven disease.

Conclusion: This study represents the longest and largest single centre salvage cryotherapy series in the literature. Disease free survival rates of 43% were achieved at 10 years in patients with pre-salvage treatment PSA <4ng/mL whilst it was only 11% in those with a PSA >4ng/mL. 10 year overall and disease specific survival was high regardless of disease recurrence. We believe that with appropriate patient selection cure can be attained with salvage cryotherapy, however it is important to note that 10-year survival was high regardless of disease status. We believe that salvage cryotherapy not only for curing selected patients but also has a role in delaying the introduction of hormone therapy and reducing tumour burden.

POD-01.06

Types of Fractures and Risk Factors for Fractures in Men with Prostate Cancer on Androgen Deprivation Therapy

Alibhai S[1], Duong-Hua M[2], Cheung A[1], Sutradhar R[2], Warde P[1], Fleshner N[1], Paszat L[2]
[1]University Health Network, Toronto, ON; [2]Institute For Clinical Evaluative Sciences, Toronto, ON

Introduction and Objective: Accumulating evidence demonstrates that androgen deprivation therapy (ADT) is associated with osteoporosis and fragility fractures of the spine, hip, and wrist. One study has suggested ADT use may also be associated with non-fragility fractures in older men. Whether other clinical risk factors independently increase the risk of fractures is not certain. We sought to confirm whether ADT increases the risk of non-fragility fractures and fractures leading to hospitalization. We also explored other risk factors for fractures in men on ADT.

Methods: Using linked administrative databases in Ontario, Canada, men age 66 or older with prostate cancer on continuous ADT for at least six months or who underwent bilateral orchiectomy (n = 19,079) were matched with men with prostate cancer who had never received ADT. Matching variables included age, prior cancer treatment, year of diagnosis, comorbidities, medications, prior fractures, and socioeconomic variables. Primary outcomes were development of a typical fragility fracture, any fracture, and fractures requiring hospitalization. Independent predictors of fracture outcomes were assessed using Cox proportional hazards models.

Results: Over a mean 6.47 y of follow-up, ADT use was associated with an increased risk of both fragility fracture (hazard ratio (HR) 1.65, 95% confidence interval (CI) 1.53, 1.78) and any fracture (HR 1.46, 95% CI

1.39, 1.54). ADT users had a higher frequency of fractures requiring hospitalization as well as hip, other femur, wrist, upper arm, spine, lower leg, and pelvic fractures (all $p < 0.05$) but not fractures of the hand, skull, ribs, or feet. Independent predictors ($p < 0.05$) of fragility fracture included increasing age (HR 1.79 for 75-84 year olds and HR 3.23 for 85+ compared to 65-74 year olds), prior use of bone-thinning medications (HR 1.25), chronic kidney disease (HR 1.33), prior dementia (HR 2.14), prior fragility fracture (HR 3.43), a prior diagnosis or treatment for osteoporosis (HR 1.39), and regular access to a primary care physician (HR 0.82). The same variables were independent predictors of any fracture.
Conclusions: Continuous ADT use for at least 6 months in older men is associated with an increased risk of a variety of fractures and fractures requiring hospitalization. Increasing age and prior osteoporotic fracture are common and important clinical factors that may warrant greater consideration of anti-osteoporotic therapies in these men.

POD-01.07

Evaluation of Long-Term Prostate-Specific Antigen Control during Degarelix Treatment and in Patients Switched from Leuprolide to Degarelix

Klotz L[1], Olesen TK[2], Persson B-E[3]
[1]Division of Urology, University of Toronto, Toronto, ON; [2]Ferring Pharmaceuticals Inc, Parsippany, NJ, USA; [3]Ferring Pharmaceuticals, Saint-Prex, Switzerland

Introduction and Objective: Previous 1-year trial results (CS21) comparing leuprolide, a gonadotropin-releasing hormone (GnRH) agonist, to degarelix, a new generation GnRH antagonist, demonstrated several differences which appear to favor degarelix such as: time to suppression of testosterone, luteinizing hormone and prostate-specific antigen (PSA); level of FSH and alkaline phosphatase suppression, musculoskeletal adverse events (AEs), time to PSA recurrence and PSA progression-free survival (PFS). Here we report long-term effects on PSA control and musculoskeletal AEs in patients on continuous degarelix treatment compared to patients switched from leuprolide to degarelix.
Methods: There were 610 patients with histologically confirmed prostate cancer (all stages) were randomized to leuprolide 7.5 mg/month, degarelix 240 mg/80 mg (starting dose/monthly maintenance dose) or degarelix 240/160 mg (CS21). After 1 year, patients were offered entry into an extension trial (CS21A). 135 leuprolide patients were re-randomized to degarelix 240/80 mg or 240/160 mg treatment. 251 degarelix patients continued on their respective dose. PSA PFS was defined as time to first PSA recurrence (2 consecutive increases in PSA of ≥50% compared with nadir and ≥5 ng/mL on 2 consecutive measurements at least 2 weeks apart) or death.
Results: During the first year (CS21), risk of PSA recurrence or death was significantly less in patients receiving degarelix 240/80 mg versus leuprolide ($p = 0.05$; log-rank). After up to 3 years total exposure, PSA PFS hazard rate for continuous degarelix went from 0.11 during the first year (CS21) to 0.14 thereafter (CS21A) ($p = 0.45$) while a significant decrease from 0.20 to 0.09 was observed in leuprolide patients switched to degarelix ($p = 0.01$). Musculoskeletal AEs were 17% during the first year (CS21) and 16% thereafter (CS21A) for continuous degarelix while a decrease from 26 to 18% in was observed for leuprolide patients switched to degarelix.
Conclusions: Extension trial data of patients initially treated for 1 year with leuprolide who then switched to degarelix showed an improved control of PSA and fewer musculoskeletal AEs. The differences may reflect the different mode of action of degarelix compared to leuprolide.