Podium Session 5: Prostate Cancer
June 26, 2012, 0800-0900

POD-05.01

Effect of Denosumab on Prolonging Bone-metastasis Free Survival in Men with Non-metastatic Castrate-resistant Prostate Cancer Presenting with Aggressive Prostate-specific Antigen Kinetics

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Introduction & Objectives: Denosumab, an anti-RANK-ligand monoclonal antibody, has been shown to prolong bone-metastasis free survival (BMFS) by a median 4.2 months and with a 15% risk reduction vs. placebo in men with non-metastatic castrate-resistant prostate cancer (CRPC) and baseline prostate-specific antigen (PSA) value ≥8.0 ng/mL and/or PSA doubling time (DT) ≤10.0 months. The objective of this analysis was to determine the efficacy of denosumab in men at greatest risk for bone metastases. BMFS was evaluated in a subset of men with PSADT ≤6 months (previous report in Smith MR, et al: J Clin Oncol. 23:2918-2925, 2005).

Methods: 1432 men with non-metastatic CRPC (baseline [median] PSA: 12.3 ng/mL, PSADT: 5.1 months, ADT duration: 47.1 months) were randomized 1:1 to receive monthly subcutaneous denosumab 120 mg or placebo. The first patient enrolled February 2006; primary analysis cut-off was July 2010, when >660 men had developed bone metastasis or died. The primary endpoint was BMFS (time to first bone metastasis or death from any cause). BMFS results are presented for men with baseline PSADT ≤6 months.

Results: Median BMFS in the placebo group of men with PSADT ≤6 months was 6.5 months shorter than for the placebo group in the full population (18.7 months vs. 25.2 months), indicating that these men are at particularly high risk. In this group of men with PSADT <6 months, denosumab prolonged BMFS by a median of 7.2 months and with a 23% reduction in risk compared with placebo (Table 1).

Conclusions: Patients with shortened PSADT are at higher risk of developing bone metastasis and denosumab is markedly effective at prolonging BMFS in this subset of patients.

POD-05.02

Need for Intervention and Survival in a Cohort of Patients on Active Surveillance (AS) for Low-risk Prostate Cancer

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Introduction and Objective: Specific indications for intervention and survival in patients on AS have not been adequately defined. With the growing concern about overtreatment of prostate cancer, AS is increasingly used to manage low risk prostate cancer. However, longterm data on need for intervention and survival is limited. Our objective was to determine the need for intervention, CSS and OS in an AS cohort.

Methods: A historical cohort study of 499 men diagnosed with localized prostate cancer was performed at a single centre between 1997-2009. Although AS had been practiced during this period, in 2008 our group agreed upon inclusion criteria for AS: Gleason 6, Gleason 7 in select patients with low volume, ≤3/12 cores positive with ≤20% in each core, and PSA<10. Only men with AS as initial management were included. Survival analyses were conducted using the Kaplan-Meier method.

Results: Median age at diagnosis was 68.3yr and median fu was 4.8yr. Median PSA at diagnosis was 5.1. 98.2% (490/499) of patients were Gleason 6, 1.8% (9/499) were Gleason 7 and 94.0% (469/499) were stage T1c. Freedom from intervention was 77% at 5yr and 63% at 10yr. Of the 123 patients requiring treatment, 57 (46%) received radiation, 29 (24%) received surgery, 17 (14%) received brachytherapy and 20 (16%) received hormonal therapy. Reasons for intervention included; 46% (56/123) path progression, 29% (36/123) PSA progression, 12% (15/123) patient preference, and 6% (7/123) DRE progression. Metastases-free survival was 99% at 5yr and 97% at 10yr. Freedom from salvage ADT was 99% at 5yr and 91% at 10yr. CSS was 100% at 5 and 10yr. OS was 96% at 5yr and 86% at 10yr.

Conclusions: 63% of patients remained on AS at 10yr. In those treated, pathologic, PSA or DRE progression initiated treatment in 81%. AS is a treatment method which spares the majority of properly selected men from intervention, provides adequate time for intervention if required, and has durable CSS and OS.

POD-05.03

A Population-based Analysis of Pathological Outcomes Following Radical Prostatectomy in Academic vs. Non-academic Institutions

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Table 1. POD-05.01

Population	Sample Size	BMFS Median (Months)	BMFS Treatment Difference (Months)	Hazard Ratio	95% Confidence Interval	*p*-value
All Patients	D: 716 P: 716	D: 29.5 P: 25.2	4.2	0.85	0.73–0.98	0.028
PSADT <6 months	D: 419 P: 427	D: 25.9 P: 18.7	7.2	0.77	0.64–0.93	0.0064

D=Denosumab; P=Placebo.

Introduction and Objectives: Radical prostatectomy (RP) is a common urological procedure in the treatment of prostate cancer (PCa). With increasing sub-specialization within tertiary care hospitals, RP outcomes may be superior in academic rather than at nonacademic institutions.[1] We report on pathological outcomes between academic and non-academic institutions.
Methods: Retrospective chart review of 1080 men diagnosed with PCa between 2003 - 2008 who were treated with RP. Pathological outcomes were compared between oncology fellowship trained academic (FTA) vs. non-fellowship trained academic (NFTA) vs. non-academic (NA) urologists. Multi-variable logistic regression analysis was used to adjust for confounding variables and included the following factors: age at prostatectomy, urologist type (FTA, NFTA, NA), Gleason sum, nodal status, ratio of positive to total cores at biopsy, lymphovascular invasion and pathological stage. Surgeon intensity, defined as the average number of cases per year, was also examined
Results: Overall margin positivity was 49.4%. The rate of positive margins was different between FTA, NFTA and NA urologists (p=0.0003). Pathological stage and the ratio of positive core biopsies were also associated with margin positivity (p= 0.0042 and p=0.0056, respectively). NFTA and NA urologists were more likely to have positive margins compared to FTA urologists (OR 2.429; 95% CI: 1.355 - 4.355 and OR 2.219; 95% CI: 1.564 - 3.149, respectively). However, the rate positive margins between NFTA and NA urologists was not significant (OR = 1.09; 95% CI 0.6385 - 1.8764, p=0.7425).
Conclusions: Increased sub-specialization within tertiary centres correlates with reduced rates of margin positivity. The outcomes of margin positivity in our cohort will require further investigation to discern oncological impact.

POD-05.04

Between-surgeon Variation in Outcomes of Radical Prostatectomy for Clinically Localized Prostate Cancer: Analysis of 1014 Consecutive Men Treated at the University of Alberta

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Introduction and Objectives: We determined whether between-surgeon variation (known as heterogeneity) in outcomes of radical prostatectomy exists for urologic surgeons practicing at a Canadian academic centre.
Methods: A prospective analysis of data from the University of Alberta Radical Prostatectomy Database was performed. Between September 2007 and August 2010, 1019 consecutive men underwent radical prostatectomy for clinically localized prostate cancer by 1 of 8 urologic surgeons. All patients followed a common postoperative clinical care pathway. The outcomes were biochemical recurrence (BCR), positive surgical margins (PSM), and complications within 90 days of surgery. BCR was defined as a PSA ≥ 0.1 ng/ml followed by a subsequent confirmatory value or initiation of salvage therapy. Complications were analyzed and graded according to the Clavien system. Multivariable random effects models were used to evaluate heterogeneity in outcomes after adjustment for case mix.
Results: Data were evaluable for 1014 out of 1019 patients. The median follow-up duration was 21 months (IQR 12 to 29). There was no significant between-surgeon variation in BCR (random effects variance <0.001, p=0.99). However, there was significant between-surgeon variation in PSM (random effects variance=0.049, p=0.03) and complications within 90 days of surgery (random effects variance=0.148, p<0.001). Two surgeons had adjusted PSM rates ≤21% whereas four surgeons had adjusted PSM rates ≥30%. Three surgeons had adjusted 90-day complication rates ≤23% whereas three surgeons had adjusted 90-day complication rates ≥39%.
Conclusions: A patient's likelihood of achieving optimal cancer control and perioperative outcomes differs depending on which of two urologic surgeons performs his radical prostatectomy. Research examining the mechanism(s) underlying surgical heterogeneity in outcomes of radical prostatectomy is urgently needed.

POD-05.05

Population-based Study of Long-term Rates of Surgery for Urinary Incontinence following Radical Prostatectomy for Prostate Cancer

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Introduction and Objectives: Urinary incontinence can be a significant complication of radical prostatectomy, and can be treated with post-prostatectomy surgical procedures. The long-term rates of patients undergoing these surgeries, which include the insertion of an artificial urinary sphincter (AUS) or a urethral sling, have not been well-described. We examined the long-term rates of post-prostatectomy incontinence surgery and factors that influences the rates.
Methods: We conducted a population-based study of 25,346 men who underwent radical prostatectomy for prostate cancer in Ontario, Canada, between 1993-2006. We used hospital and cancer registry administrative data to identify patients from this cohort who later underwent surgery for urinary incontinence.
Results: Of the 25,346 patients, 703 (2.8%) underwent an insertion of an AUS and 282 (1.1%) underwent a urethral sling procedure, a mean of 3.9 years after the prostatectomy. The probability of patients undergoing an AUS/sling procedure increased over time from prostatectomy. The 5, 10 and 15-year Kaplan-Meier rates of undergoing an AUS/sling procedure were 2.6% (95%CI:2.4%-2.8%), 3.8% (95%CI:3.6%-4.1%), and 4.8% (95%CI:4.4%-5.3%), respectively. Factors that were predictive of surgery for incontinence were age at radical prostatectomy (HR=1.24 per decade, 95%CI=1.11-1.38, p=0.0002), radiotherapy after surgery (HR=1.61, 95%CI=1.36-1.90, p<0.0001) and surgeon volume (performance of ≥49 prostatectomies per year) (HR=0.59, 95%CI=0.46-0.77, p<0.0001).
Conclusions: Five percent of patients who undergo a radical prostatectomy are expected to undergo surgery for urinary incontinence over a 15 year period. Increasing patient age, radiation treatment, and low surgeon volume are all associated with significantly higher risk.

POD-05.06

A Randomized Trial Comparing External Beam Radiation and Cryotherapy in Localized Prostate Cancer: 10 Year Follow-up

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Introduction and Objectives: Localized prostate cancer can be treated using various modalities, but head-to-head comparisons of treatments are infrequent. We conducted a randomized unblinded, non-inferiority trial to compare cryoablation and external beam radiation therapy in treating localized disease.
Methods: From December 1997 through February 2003, 244 men with newly diagnosed localized prostate cancer were randomly assigned to cryoablation or radiotherapy (122 to each arm). All patients received neoadjuvant antiandrogen therapy. The revised primary endpoint was disease progression at 36 months based on: (a) radiological evidence of metastatic disease or b) initiation of further antineoplastic therapy or c) biochemical failure defined as a rise of PSA above nadir + 2. Secondary endpoints were overall survival, disease-specific survival, and prostate biopsy at 36 months.
Results: Median follow-up is 119 months. Overall and disease specific survival is the same in both groups. Disease progression at 120 months was: 37% in the cryoablation arm and 46% in the radiation therapy arm (difference = 9%, N.S: PSA >1.0 ng/ml); At 36 months biopsy more radiotherapy patients had a cancer positive biopsy (28.9%) compared with cryoablation patients (7.7%). Adverse events (grade 3) occurred in 10.3% of cryotherapy and 12.3% of radiation patients.
Conclusions: At 10 years follow-up, there continues to be no significant difference between the two treatment modalities. While significantly fewer positive biopsies were documented following cryoablation than radiotherapy, this has not resulted in a higher prostate cancer specific mortality. Prostate cancer specific mortality is similar to other prospective randomized trials in the management of localized prostate cancer.