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POD-1.01

A randomized, double-blind, placebo-controlled trial of denosumab in men with nonmetastatic prostate cancer receiving androgen deprivation therapy

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Introduction and Objective: Androgen deprivation therapy (ADT) for prostate cancer is associated with osteoclast activation, accelerated bone loss and increased risk of fracture. The formation, function and survival of osteoclasts are dependent on the receptor activator of NF-kB ligand (RANKL). The purpose of this study was to investigate the effects of denosumab, a fully human monoclonal antibody against RANKL, on bone mineral density (BMD) and fractures in men receiving ADT for prostate cancer.

Materials and Methods: This was a phase-3, randomized, double-blind, controlled study. Men receiving ADT for nonmetastatic prostate cancer received subcutaneous denosumab 60 mg (n = 734) or placebo (n = 734) every 6 months for 3 years. All subjects were instructed to take daily supplements of calcium and vitamin D. Stratification factors included duration of prior ADT (≤ 6 v. > 6 mo) and age (< 70 v. ≥ 70 yr). The primary end point was percentage change from baseline at month 24 in lumbar spine BMD. Key secondary end points included subject incidence of new vertebral fracture and fracture at any site over 36 months.

Results: At 24 months, lumbar spine BMD increased by 6.7% in the denosumab group compared with placebo ($p < 0.0001$), with significant differences between treatment arms observed as early as 1 month. Denosumab significantly increased BMD at the total hip (4.8% v. placebo) and femoral neck (3.9% v. placebo) ($p < 0.0001$). Denosumab was associated with a 62% reduction in vertebral fracture (adjusted $p = 0.01$) at 36 months, with marked reduction evident within the first year. A 28% reduction in fracture at any site was observed, but not statistically significant (adjusted $p = 0.10$). The rates of adverse events (AEs) (87% denosumab, 87% placebo), serious AEs (35% denosumab, 31% placebo), and deaths (6% denosumab, 6% placebo) were similar across treatment arms. None of the deaths in the denosumab arm was considered treatment-related.

Conclusion: In conclusion, subcutaneous administration of denosumab twice yearly significantly increased BMD at all measured skeletal sites and significantly reduced the incidence of vertebral fracture over 36 months in men with nonmetastatic prostate cancer receiving ADT.

POD-1.02

Two years biochemical failure-free survival following high-intensity focused ultrasound for localized prostate cancer: prospective single centre study of 196 patients

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Introduction and Objective: High-intensity focused ultrasound (HIFU) is an emerging ablative modality for the treatment of localized prostate cancer with limited reports on oncological outcome. We prospectively analyzed our 2 years results.

Patients and Methods: Two hundred fifty-three consecutive patients (January 2006–June 2008) were treated with a single session of HIFU (Ablatherm integrated imaging model system). Follow-up (median 12, range 3–24 mo) included PSA measurement every 3 months. Patients who received prior radiation or hormonal therapy and patients for whom at least 2 consecutive PSA measurements were not available were excluded. Biochemical failure (BCF) is reported using the Stephenson (PSA > 0.4 ng/mL and rising), Horwitz (2 consecutive increases of at least 0.5 ng/mL) and Phoenix (nadir + 2 ng/mL) definitions.

Results: One hundred ninety-six patients (age 64, standard deviation [SD] 8) met the inclusion criteria for analysis. Seventy-five had low and 121 had intermediate D'Amico's risk stratification disease. Mean and median absolute PSA nadir levels were 0.28 (SD 0.53) and 0.06 ng/mL, respectively. It was achieved in median time of 3 months and remained unchanged in 70% of the patients throughout the follow-up. Overall, 2 years BCF-free rates were 70% (62%–78%), 86% (81%–91%) and 96% (91%–99%) according to the Stephenson, Horwitz and Phoenix definitions, respectively, with no significant differences between risk groups. Predictors of BCF were absolute nadir (HR 3.0 [2.3–3.8]) and pretreatment PSA (HR 1.1 [1.0–1.2]).

Conclusion: Short-term results by various BCF definitions (including postradical prostatectomy ones) are promising with similar results for patients with low and intermediate risk. Pre-HIFU PSA and post-HIFU PSA nadir levels predict BCF. Biochemical failures usually occur in the first year and plateau thereafter.

POD-1.03

Preliminary results of high-intensity focused ultrasound treatment of prostate cancer: early Canadian experience

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Introduction and Objective: High-intensity focused ultrasound (HIFU) is a noninvasive technique that uses precision ultrasound waves to destroy tissue. HIFU is now approved in Canada for the treatment of prostate cancer. This study evaluates the early Canadian experience using HIFU to treat prostate cancer in terms of outcomes and complications

Materials and Methods: Ninety-five patients were treated between March 2006 and December 2007. Follow-up occurred at 3-month intervals and included serial PSA measurements, assessments of erectile function and continence rates with the IIEF and EPIC questionnaires respectively. Early and late complications were also studied.

Results: There were 95 patients treated by 5 urologists. The mean age of patients was 64 (range 46–91) years. The majority of men treated had Gleason 6 (n = 53) disease. The remainder had Gleason 7 (n = 35), Gleason 8 (n = 5) and Gleason 9 (n = 2). Hormone injection before treatment to reduce prostate volume or for cancer treatment occurred in 10 men. Salvage HIFU following radiation failure was performed in 7 men. Prostate volume in the pretreatment group was 30.5 (range 14.4–73) mL. Early complications included catheter-related issues in 10 patients, retention in 16 patients and 1 patient had urosepsis. Late complications included need for cystoscopy (n = 25), TURP (n = 6), VIU/dilatation (n = 10) and self-catheterization (n = 1). Serious complications included fistula in 1 patient and bladder neck contractures in 5 patients. Post-HIFU with a minimum

6 months follow-up (mean 10.62 mo), 17% (10/59) of men had moderate to severe erectile dysfunction (IIEF ≤ 11). With a minimum of 6 months follow-up (mean 8.85 mo), 36.6% (15/41) of the men had any degree of incontinence according to their EPIC scores. Recurrence of cancer following HIFU was diagnosed in 7 men. Salvage treatment included radical prostatectomy (n = 3), radiation therapy (n = 2), repeat HIFU (n = 1) and hormone therapy (n = 1).
Conclusion: In our early experience, HIFU treatment for prostate cancer appears effective and safe with low rates of complications and failure when compared with standard therapies. Further studies are required to examine long-term outcomes with HIFU (Table 1).

Table 1. POD-1.03. Descriptive statistics for PSA, EPIC and IIEF

Time, mo	PSA, ng/mL			EPIC (score/9)			IIEF (score/25)		
	n	Median	Range	*n*	Median	Range	*n*	Median	Range
0	95	5.33	0.19–14.5	51	8.45	5–9	75	19.1	3–25
3	81	0.28	0.01–12	32	7.41	3–9	48	18.5	3–25
6	74	0.46	0.01–6.65	35	6.77	2–9	52	18.0	5–25
9	55	0.33	0.01–8.4	20	6.95	2–9	29	17.49	5–25
12	42	0.72	0.01–6.65	7	7.00	4–9	24	17.42	5–25
18	27	0.68	0.01–7.18	3	6.67	5–9	12	18.0	5–24
24	13	0.30	0.03–1.33	—	—	—	2	20.5	17–24

POD-1.04

Radical prostatectomy with neoadjuvant docetaxel and androgen deprivation therapy for high-risk localized prostate cancer: 5-year outcomes

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Introduction and Objective: Previous studies have shown significant relapse rates for patients with high-risk prostate cancer, leading to many patients undergoing radiotherapy if high-risk features are present. We report 5-year oncological outcomes for this group of patients, who were treated with combined neoadjuvant androgen deprivation therapy (ADT) and docetaxel followed by radical prostatectomy.
Materials and Methods: All patients who underwent radical prostatectomy between July 2002 and December 2003 by a single surgeon were reviewed. From this cohort, 27 patients were identified who were defined as high risk (either PSA > 20, and/or clinical stage > T2c, and/or Gleason ≥ 8), who had combined neoadjuvant ADT and docetaxel. Parameters evaluated included PSA, Gleason score, % involvement of biopsy cores, use of adjuvant therapy, pathological parameters and PSA recurrence. None of the 27 patients have been lost to follow-up. Biochemical disease-free survival was estimated using the Kaplan–Meier method.
Results: The mean age was 58.3 years, mean preoperative PSA was 14.4 and the median biopsy Gleason score was 8. The majority of patients (66.7%) had 1 high-risk feature; 25.9% and 7.4% had 2 and 3 high-risk features, respectively. Median follow-up was 64 months. Two patients had positive lymph nodes, 5 patients had seminal vesicle involvement and 5 patients (18.5%) had positive margins. Gleason score was downgraded in 18.5%, and upgraded in 18.5%. Pathological stage was pT2 in 41% and pT3 in 52%. Five patients underwent adjuvant radiotherapy, and 3 patients had salvage radiotherapy. One patient had a non–prostate cancer or –treatment related death. A total of 11 patients (40.7%) have had biochemical failure. Five-year actuarial biochemical disease-free survival was 62%.
Conclusion: At a median follow-up of 64 months, 59.3% of patients remain free of biochemical relapse. Radical prostatectomy with combined neoadjuvant androgen deprivation therapy and docetaxel provides good 5 year oncological outcomes in select high-risk patients.

POD-1.05

Clinical results of long-term follow-up of a large active surveillance cohort

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Introduction and Objective: In 1995, a prospective phase-2 trial of active surveillance was initiated at our centre. This approach was offered to men with favourable risk prostate cancer as an alternative to radical intervention. Patients were closely followed with serial PSA and periodic biopsy, and intervention was offered based on PSA kinetics or grade progression. Our initial results were reported in 2002 on 231 patients. This report is our second analysis of this group, which now constitutes 453 men.
Materials and Methods: A prospective, single-arm cohort study. Patients with favourable clinical parameters (screen diagnosed patients with Gleason ≤ 6, PSA ≤ 10) were managed with active surveillance. Initially, a subset of men older than 70 were included with Gleason 3 + 4 or PSA 10–15. In 2000, the study was restricted to favourable risk disease. Definitive intervention was offered to those patients with a PSA doubling time of less than 3 years, Gleason score progression (to 4 + 3 or greater), or unequivocal clinical progression. PSA doubling time was calculated using the general linear mixed model.
Results: Since November 1995, 453 patients have entered the program. Median age is 70 (range 45–86). Median follow-up is 7.2 (range 1–13) years. Overall survival is 83%, and prostate cancer survival is 99% (5 of 453 patients have died of prostate cancer). Thirty-five percent of patients have been reclassified as higher risk and offered definitive therapy. The commonest indication for treatment was a PSA DT less than 3 years (14%) or Gleason upgrading (6%). Of 137 patients treated radically, the PSA failure rate was 52%. Patients with biochemical failure after radical therapy constitute 15% of the overall cohort. The ratio of nonprostate cancer to prostate cancer mortality was 16:1.
Conclusion: A policy of watchful waiting with selective delayed intervention based on defined criteria of disease reclassification as higher risk is feasible and is associated with a low prostate cancer mortality in the intermediate time frame. Patients with favourable risk parameters at baseline who subsequently demonstrate a PSA doubling time less than 3 years or pathological progression to Gleason 4 + 3 represent a high-risk cohort, reflected in a 52% rate of biochemical progression after radical therapy. This strategy offers the benefit of an individualized approach based on the demonstrated risk of clinical or biochemical progression with time and, thus, it may decrease the burden of therapy in patients with indolent disease, while providing definitive therapy for those with biologically active disease.

POD-1.06

Extent of lymphadenectomy and biochemical recurrence after radical prostatectomy: a multicentre study

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Introduction and Objective: Extended lymphadenectomy (PNLD) in radical prostatectomy (RP) has been shown to increase the number of total metastatic lymph nodes (LN) detected. The aim of this study was to analyze its impact on PSA failure (PSAF).
Material and Methods: The databases of the RPs from 3 different urological departments have been retrospectively compared. Centre A performed only perineal prostatectomies (PP) with no PNLD and the 2 others retropubic RPs. Centre B performed a standard PNLD (obturator, external iliac LN) and Centre C an extended PNLD (obturator, external and internal iliac LN). Patients were divided into low-, intermediate- and high-risk cancers

according to the D'Amico risk stratification based on preoperative characteristics. Demographics, clinical and pathological characteristics were first analyzed. PSA failure was then calculated with and without eliminating patients who received adjuvant radiotherapy and/or hormone therapy.
Results: A total of 3328 patients were included. Centre A had 756, Centre B 1363 and Centre C 1209 patients meeting all entry criteria for the study. Median follow-up was 6.4 years. Baseline demographic and pathological characteristics were different for the 3 cohorts. Multivariate analysis was used to adjust for presurgical risk factors as well as surgical pathological features of the primary. The median of LN removed was 0, 6 and 14 and the percentage of pN+ was 0%, 2.3% and 13.6%, for Centre A, B and C, respectively. Centre B had 103 high-risk patients and Centre C 116, but Centre A had very few. The median time to PSAF for high-risk patients was 7.8 years for patients with extended PNLD (C) and 3.6 years after standard PNLD (B). The 10-year biochemical-free recurrence was 42% for the extended PNLD patients compared with 25% for those who had a standard PNLD.
Conclusion: In our study, extended lymphadenectomy nearly doubled the number of nodes removed and significantly increased the number of pN+ detected. Extended lymphadenectomy significantly reduced biochemical recurrences after RP and more than doubled the median time to PSA recurrence in high-risk patients.