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Analysis of acute and late morbidity and biochemical control for intermediate to high risk prostrate cancer treated with androgen deprivation, HDR and 3D/IMRT: update of a phase I-II dose escalation trial

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Background: Prostate tumors exhibit a high sensitivity to fractionation due to low alpha/beta ratios and may be radioresitant to convention fractionation. HDR regimens may provide superior or equal tumor control over other approaches with possibly lower late sequelae.

Purpose: To evaluate GU and GI morbidity and biochemical control (bNED) of intermediate-high risk prostate cancer patients treated with androgen deprivation (AD), transrectal ultrasound assisted High Dose Rate (HDR) brachytherapy and conformal external radiotherapy as part of an HDR dose escalation trial.

Material and Methods: from April 1999 to October 2002, a total of 127 patients with intermediate or high-risk prostate cancer were enrolled on a dose escalation trial. Criteria included one or more of the following: PSA > 10, Gleason > 6, Bulky T2-T3 clinical stage, 4-6 core biopsies with bilobar disease. Patients with intermediate risk disease received 4-6 months of AD, and 9-12 months for high-risk disease. Patients underwent a single TRUS implant followed by 3 divided fractions of HDR Iridium-192 delivered over 24 hours, followed by 3D-CRT or IMRT to the prostate and/or lymph nodes to doses between 50-54 Gy. Patients were divided into 4 dose arms of HDR including 16.5 Gy (N= 38), 18 Gy (N= 48), 19.5 Gy (N=30) and 21 Gy (N=11). Dose constraints were placed on the urethra (125% of prescription) and anterior rectal wall (70% of prescription) with point dose calculations. 112 patients in Groups 1-3 with a minimum follow-up time of 6 months were analyzed. Pre and post treatment IPSS score were obtained in all patients. Scoring for GU and GI symptoms was based on the current RTOG morbidity scale. Biochemical failure was defined by the ASTRO consensus statement. Kaplan Meier methodology was used to estimate actuarial bNED.

Results: The overall median age was 68. The overall median follow-up for evaluable patients was 24 months, with a median follow-up for each HDR dose arm of 41 mos, 23 mos, and 10 mos, respectively. Overall Pre- and post treatment median PSA levels were 9 and 0.2 ng/mL at last follow-up. The median PSA value decreased from 9 to 0.2 in Arm 1 (med f/u 39 mos), from 9 to 0.3 in Arm 2 (med f/u 21 mos) and from 10 to 0.1 in Arm 3 (med f/u 12 mos). The 4- year actuarial biochemical control rate for all patients was 96%. The crude biochemical control for Arms 1 through 3 was 97%, 94%, and 100% respectively (p = NS). No difference in bNED has been observed to date in pts (17%) treated to LN bearing regions or by dose levels. Overall pre-and post median IPSS scores were 5 and 5 respectively, with no difference observed (p=. 42) Pre- IPSS median scores for Arm 1, 2 and 3 were 3, 8, and 7.5 (p = 0.005) with a difference seen in group 1 vs. 2and 3. However, the Post-IPSS median scores for Arms 1-3 were 6, 4, and 5 with no difference seen. (p = 0.42) The GU grade 2 morbidity at 12 months for arms 1 through 3 were 10%, 6% and 30% (p = 0.05) and the Grade 2 GI morbidity at 12 months for Arms 1-3 were 3%, 0% and 0% respectively (p = 0.10) Within Arm 1, with median follow-up of 41 mos, the Grade 2 Gu and GI morbidity is 9% and 0%. For Arm 2, with a median follow-up of 23 mos, the Grade 2 GU and GI morbidity is 7% and 0%. 3 out of 112 (3%) have developed urethral strictures to date. The 4 year-actuarial risk of a urethral stricture is 14%. All 3 occurred in arm 1 at 13 mos, 36, mos and 48 mos respectively. In multivariate analysis to determine patient and dosimetric risk factors at 12 mos predictive for Grade 2 or higher GU and GI morbidity, no one factor was predictive.

Conclusion: With longer follow-up time and clinical experience, dose escalation with HDR Ir-192 fractionated brachytherapy using a single implant resulted in acceptable Grade 2-3 GU morbidity. Minimal Grade 2 GI sequelae was observed overall (3%) and was only seen in Arm 1. We have not seen an increase of urethral strictures to date in Arms 2 and 3. Overall crude and actuarial biochemical control is excellent. Delayed failures in Arm 1 with addition of short course AD have yet to be realized (med f/u 41 mos) which is encouraging. Accrual to Arm 4 is completed.

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What to do with asymptomatic prostate cancer patients with rising PSA after curative treatment with external beam radiotherapy (RT)?

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Purpose: To describe the characteristics and outcomes of hormonally treated and non-treated asymptomatic prostate cancer patients with biochemical relapse (BR) post-RT

Material and methods: There were 528 prostate cancer patients staged as T1-3N0M0 treated in our institution between January 92 and February 99 with RT (no surgery). A total of 207 patients (39%) had BR defined as 3 consecutive PSA rises separated by at least 3 months (date of BR was considered the 1st of the 3 rises). Of these 207 patients, 140 (68%) were asymptomatic and had either no CT or bone scans or had negative scans. 62 of them (44%) received hormonal treatment and the remaining 78 (56%) were followed without further treatment. We compared the baseline characteristics and outcomes of these two groups using χ^2 or Mann-Whitney test as appropriate.

Results: The Table below shows the characteristics and outcome of the two groups along with p values. At a median follow-up time of almost 7 years for both groups, no patient has died from prostate cancer.

Patient Characteristics	Treated N = 62	Not treated N = 78	P values
Median age (years)	70	70	0.82
Median total dose of RT	65 Gy	67 Gy	0.08
Median Gleason Score	6	6	0.21
Median initial PSA (ng/ml)	17	14	0.69
Most common stage	T2b	T2b	0.86*
Neoadjuvant hormones (yes)	40%	45%	0.59
Median nadir PSA after RT	1.1	0.5	<0.0001
Median PSA at BR	2.2	1.2	<0.0001
Deaths (undue to prostate ca)	2/62	7/78	
Median total follow-up time	81 months	77 months	0.36
Median time for BR (month)	23	31	0.003
Median time post BR(month)	60	43	
Median PSA at last follow-up	1.8	3.4	

*Mann-Whitney test; all others were $\chi 2$

Conclusions: 1.) Asymptomatic patients with rising PSA after radiotherapy may not develop clinically progressive disease for a long time. It is not clear when they should start hormonal therapy. 2) The definition of BR as 3 consecutive PSA rises may be inappropriate to use in the growing number of patients treated with neoadjuvant hormonal therapy. 3) Some prognostic factors that could be considered in future studies are the median nadir PSA after RT, median PSA at BR and median time for BR as suggested by the univariable analysis; 4) Randomized trials of immediate versus delayed hormonal therapy are urgently needed in this population of asymptomatic patients with rising PSA post-RT.

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Disease presentation and development in bladder cancer is related to outcome following radical cystectomy

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Background: Approximately 75% of patients with bladder tumours present with non-invasive (Ta) or superficial invasive disease in lamina propria (T1). The recurrence rate is high, but only a minority will progress and become muscle invasive. In 25% of the patients with bladder tumours the first appearance is a muscle invasive tumour. Disease course was related to outcome following radical cystectomy.

Patients and methods: From 1/92 to 12/98, 208 consecutive patients with muscle invasive bladder cancer undergoing radical cystectomy was retrospectively followed from the time of diagnosis until death. Median follow up was 6.4 years (range, 3.4-10.4). The primary diagnosis, clinical and pathological T classification made it possible to separate the patients into 2 groups of tumour presentation and development. I: patients with de novo muscle invasive tumour (n=136) and II: patients with initial superficial bladder tumour progressing to muscle invasive bladder cancer (n=72).

Results: In univariate analyses T classification (organ confined vs. non-organ confined), N classification (N0 vs. N+) and tumour presentation and development showed to be significant predictors for survival. The 5-year