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Similar effect on rectal dose reduction despite different displacement kits during high dose rate brachytherapy for prostate cancer

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Introduction: It is mandatory to reduce the rectal dose during radiotherapy with high dose rate brachytherapy. Different types of displacement kits have been used in order to increase the distance between the rectum and the prostate.
Material and methods: Two different kind of Water stand-off kit (BK Medical, Denmark) have been used to displace the prostate in selected cases where the dorsal border of the prostate was closer than 10 mm to the ultrasound probe (= rectal inner wall). Both displacement kits use a water balloon which makes it possible to displace the prostate anteriorly, thereby increasing the distance to the rectum. In 20 patients treated with combined external therapy (50 Gy in 25F) and HDR brachytherapy (20 Gy in 2F) a second dose plan was performed based on images of the prostate with the needles in treatment position and the water balloons empty. All dose plans were performed on TRUS images taken with 5 mm interval using BrachyVision v.6.1 (Varian Medical Systems).
Results: The needles stabilize the prostate, but not fully, so the distance between the prostate and the probe is not equally increased to the used amount of water. The prostate was moved on average 2 mm towards the ultrasound probe when the water was removed. On average the maximum dose to the rectum decreased with 20% by withdrawal of the water from the kit during the HDR brachytherapy. Prostate volume exceeding 30 cc gave larger movements compared to smaller volumes, irrespectively of water stand-of kit type. However, the newer kit distributed the amount of water more equally in the balloon.
Discussion: The rectal dose correlate to late side effects from the rectum. According to our intentions the dose to the rectum should not exceed 60% of the prescribed dose to the planning target volume, which is possible if the distance between the posterior border of the prostate and the probe is >10 mm. In cases where this is not possible, a displacement kit can increase the distance during planning, assuming that the prostate is immobilized by the inserted needles and do not move when water is removed. In this trial the displacement kit increased the distance between the rectum and the prostate but the prostate was not completely immobilized by the needles when the water was removed. The overall effect was still positive in terms of increased distance between organs at risk, but to obtain the actual rectal dose an on-line assessment has to be performed.

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HDR brachytherapy as boost combined with external radiotherapy for localised prostate cancer. Long term follow-up compared to nomogram

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Introduction: Different treatments modalities are available for localised prostate cancer (PC). Our 5-year follow-up results, using a combination of high dose rate (HDR) brachytherapy and external beam (EB), have been compared to results calculated from nomograms for radical prostatectomy and conformal external dose escalated radiotherapy (3D ERT).
Material and methods: From May 1998 through Dec 1999, 154 patients with localized PC received neoadjuvant hormonal therapy (TAB) and external radiotherapy (2 Gy×25 F = 50 Gy) combined with transperineal HDR brachytherapy with transrectal ultrasound guidance (10 Gy×2 F = 20 Gy). Six patients were lost of follow-up. Risk factors were defined as PSA >10 mg/L, T-stage 3 (TNM) and poorly differentiated PC (WHO grade III). The likelihood of 5-year PSA relapse free survival after radical prostatectomy and 3D ERT was calculated from Kattan's nomogram according to patient characteristics. When no histopathology was available the results from cytology was transformed as followed; low graded cancer = Gleason score (GS) 4, intermediate graded = GS 6 and high graded cancer = GS 8. Using Kattans nomogram for 3D ERT it was stated that the dose was 88 Gy and neoadjuvant hormonal therapy was given. Results: During a median follow-up of 4.8 years PSA relapse occurred in 25 patients and of these, 7 died from distant metastasis. No patient demonstrated clinical signs of local recurrence in the prostate. The median PSA at follow-up among the relapse-free patients was 0.06 mg/L. The relapse free survival at 5 years follow-up was 82%. Table 1 demonstrate the actual 5 years relapse free survival compared to the results using nomograms.

Table 1: Probability of 5-years realapse free survival

	Actual	Nomogram		
	HDR+3D ERT	No. patients	Surgery	3D ERT
No risk factor	0.95	37	0.83	0.89
One risk factor	0.90	52	0.64	0.76
Two risk factors	0.72	53	0.40	0.60
Three risk factors	0.33	2	0.20	0.46
Total	0.82	154	0.56	0.71

Conclusion: HDR brachytherapy as a boost combined with EB and TAB demonstrates good clinical results in patients with localised PC even though the majority have one or several risk factors. Nomograms, which have been developed in order to provide some guidance for decision-making, may be used comparing different treatments modalities, as results from randomised clinical studies are lacking. Patients with several risk factors, including T-stage 3, would probably have less favourable results after surgery. Combining EB and HDR boost provides a biologically higher dose to the prostate than any 3D ERT technique can deliver, which probably is beneficial to high risk PC.

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PSA bouncing after short-term androgen deprivation and 3-D conformal radiotherapy for localized prostate adenocarcinoma and the relationship with the kinetics of testosterone

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Background: To assess the factors effecting PSA bounce and to identify any possible relationship with biochemical control after 3-D conformal radiotherapy (3D-CRT) and total androgen deprivation (TAD) for prostate cancer by evaluating four previously described PSA bounce definitions.
Material and Methods: Between January 1998 and January 2001, 83 consecutive patients with clinically localized prostate cancer were treated by 3D-CRT with neoadjuvant 3 months and/or 6 months adjuvant TAD. All patients had a pretreatment PSA level, at least eight post-external beam radiotherapy (EBRT) PSA and testosterone levels and minimum two years of follow-up. Total radiotherapy dose was 73.6 Gy at ICRU reference point. Four previous definitions of PSA bounce were used: Critz definition (⩾0.1 ng/mL), Cavanagh definition (⩾0.2 ng/mL), Hanlon definition (⩾0.4 ng/mL) and Rosser definition (⩾0.5 ng/mL) according to original methodology performed to report PSA bounce. Biochemical failure was defined in accordance with the ASTRO consensus guidelines.
Results: The median follow-up time was 40 months. PSA bounce was recorded as follows: Critz definition, 33 patients (40%); Cavanagh definition, 21 patients (25%); Hanlon definition, 11 patients (13%); and Rosser definition, 7 patients (8%). In multivariate analysis, pre-EBRT PSA level and the duration of TAD for Critz definition; age, pre-EBRT PSA and the duration of TAD for Cavanagh definition; age and duration of TAD for Hanlon definition; age and pre-biopsy PSA for Rosser definition were significant independent prognostic factors determining PSA bounce. A significant increase of mean testosterone level in bouncers was detected at the 6th-9th and 18th-21st months. PSA bounce did not predict for PSA failure in multivariate analysis.
Conclusions: We observed no correlation between biochemical failure and PSA bounce. The longer duration of TAD and older age were found to be inversely proportional with PSA bouncing in this cohort. Notably, recovery of testosterone might cause PSA bouncing.

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Dose escalated conformal radiotherapy (DECRT) in elderly men with prostate cancer

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Background: There is little literature on the safety of DECRT in the elderly. This study evaluates the toxicity and efficacy of DECRT for localized prostate adenocarcinoma in men aged 75 years and older.

Materials and methods: The prostate cancer database at the Ottawa Hospital Regional Cancer Centre was examined for relevant demographics, tumour features, treatment parameters, toxicity, and efficacy outcomes. Patients were grouped according to Canadian Consensus Guidelines into low risk (LR) (PSA$\leqslant$10& T1-T2a & Gleason $\leqslant$6) high risk (HR) (PSA >20 &/or T3/T4 &/or Gleason >7) or intermediate risk (IR). Radiotherapy: Initially, three gold fiducial intraprostatic markers were implanted under Ultrasound guidance to ensure accurate targetting of the prostate on the LINAC. Patients were positioned prone with HIP FIX® immobilization. Patients were treated with a 6 field 3DCRT technique using 18 MV photons. Planning Target Volume 1 (PTV1) included Prostate $\pm$ Seminal Vesicles with a 1 cm volume margin. PTV2 was Prostate +5 mm margin. PTV1 was treated to 5600 cGy/28 fractions prescribed to the isocentre and PTV2 dose ranged from 1,000 cGy/5 to 2,000 cGy/10.
Weekly orthogonal portal films were taken and repeat CT planning was carried out if prostate motion greater than 1.0 cm was noted prior to the boost phase. Concurrent and adjuvant hormones for 6–36 months were used in IR and HR patients.
Results: Between 1998 and 2001, 71 men were treated. 84.5% were 75–80 years old and 15.5% were over 80. Median follow up is 44.7 months (range 1.6–71). Risk distribution was LR: 15.5%, IR: 50.7%, HR: 33.8%. 60/71(84.5%) received hormones. The total dose delivered was 66 Gy in one (1.4%), 70 Gy in 2 (2.8%), 72 Gy in 24 (33.8%), 74 Gy in 41 (57.7%) and 76 Gy in 3 (4.2%). RTOG GI and GU toxicity is listed in the table.

	GI pts.			GU pts.		
Grade	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3
Acute	9	8	2	13	2	0
Chronic	9	2	0	9	8	1

No patient has died of prostate cancer. 88.7% remain alive and 11.3% have died for reasons other than prostate cancer. 87.3% remain biochemically free of recurrence and 95.8% have no clinically apparent local failure. The biochemical and local failures have occurred in 0/11 LR, 4/36 IR and 4/24 HR pts. To date, no significant differences in disease free or overall survival have emerged between the risk categories.
Conclusions: This study demonstrates the feasibility, tolerability and efficacy of DECRT in elderly men with prostate cancer.

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The impact of fractionation on acute toxicity in radical radiotherapy for bladder cancer

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Background: The aim of the study is to evaluate the relationship between the fractionation schedule and acute bladder and bowel toxicity in patients with bladder cancer treated with radical radiotherapy.
Methods and Material: A total of 480 patients with T2, T3 bladder cancer, treated with radical radiotherapy between 1975 and 1995, comprise the study group. Radiotherapy was performed with 9–23 MV X photons in 313 patients (65%) or with ^{60}Co photons in 167 patients (35%). The PTV in all patients included the bladder with a margin, but, 299 patients (62%) received initially pelvic irradiation. Mean total radiation dose to the PTV was 65.5 Gy (59.2–72 Gy). Radiotherapy was performed using various fractionation schedules, as follows: conventional fractionation (CF) – once a-day with df-1.6–2.5 Gy, split-course fractionation (SCF) – once a-day with df – 1.6–2.5 Gy, accelerated hyperfractionation (AHF) – twice a-day with df 1.2–1.5, and accelerated hyperfractionated boost (AHB) – pelvis irradiated once a-day with df-2.0 Gy; boost irradiated twice a-day with df-1.3–1.4 Gy. Acute radiation toxicity was assessed with RTOG/EORTC scale. The comparison of the bladder and bowel toxicity was performed among various fractionation schedules.
Results: Acute bladder toxicity was similar with respect to various fractionation schedules; no acute bladder toxicity was observed in 41% to 49% of patients, Grade 1 toxicity ranged from 34% to 37%, and $\geqslant$Grade 2 bladder toxicity ranged from 17% to 26% of patients. The differences were not significant. However, acute bowel toxicity was significantly different in various fractionation schedules ($p = 0.000$). Grade 0 bowel toxicity was observed in 75% of patients in SCF group, 67% in CF, 60% in AHB and 31% in AHF group. Acute $\geqslant$Grade 2 bowel toxicity was observed in 5% of patients in SCF group, 11% in CF, 16% in AHB and 46% in AHF group.
Conclusion: Acute bowel toxicity is highly correlated with fractionation schedule and increases with acceleration of the radiation therapy.

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Assessment of late morbidity after 3D conformal radiotherapy for prostate cancer

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Purpose: To assess the safety of dose escalation with 3D conformal radiotherapy (CRT) in prostate cancer patients and to determine the predictive factors for late genitourinary (GU) and gastrointestinal (GI) toxicity.
Materials and methods: Between September 1998 and November 2003, 252 patients were treated for prostate cancer with 3D CRT in a single institution to a median dose of 72 Gy (69–73.8 Gy). The median age was 71 (51–83). Seventy-two percent of the patients were clinically staged as localized, whereas 28% presented with locally advanced disease. The Gleason score was 2–6 in 43%, 7 in 44% and 8–10 in 13% of the patients. Initial PSA level was less than 10 ng/ml in 53%, between 10–20 ng/ml in 26% and higher than 20 ng/ml in 21%. Favourable risk patients according to Roach formula received treatment to the prostate alone, whereas patients with a risk of >15% of seminal vesicle involvement were treated to the prostate and seminal vesicles to 55.8 Gy and then boosted to the prostate. High risk patients with a risk of >15% lymph node involvement received a whole pelvic irradiation to 45 Gy as the initial part of their treatment. The dose is prescribed to the minimum isodose line (95%) that covers the planning target volume (PTV). Patients were evaluated every 3–6 months after the completion of radiotherapy. RTOG/EORTC late toxicity criteria was used. Univariate estimates of morbidity were calculated with Kaplan-Meier methods and comparisons were made with the long-rank statistics. Cox multivariate regression analysis was used to establish the independent predictors of morbidity. Potential risk factors like age, diabetes, colitis, number of radiation portals, pelvic RT, higher radiation dose, presence of acute toxicity, previous history of TUR-P, time on adjuvant hormones, as well as dose-volume histogram (DVH) features for rectum and bladder were evaluated.
Results: After a median follow-up of 36 months (18–75) the incidence for Grade 3 GI and GU late toxicity was 3.2% and 3.8%, respectively. The actuarial incidence of Grade 2 and higher GI and GU morbidity was 18% and 12% at 5 years, respectively. The independent predictors for Grade 2 and higher GI toxicity were history of colitis ($p = 0.0362$) and presence of acute Grade 2 and 3 GI side effects ($p = 0.0135$). We could not identify any significant clinical nor treatment related risk factors for late GU morbidity. DVH features V70, V60, V50 for rectum and bladder were also not significant in univariate analysis.
Conclusions: We confirm that 3D CRT is a safe method to escalate the dose in prostate cancer patients. As reported also by other institutions colitis could be a predictor for late GI morbidity, therefore patients with a history of colitis should be evaluated for other treatment modalities.

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Biochemical outcome following interstitial low dose rate (LDR) prostate brachytherapy in intermediate and high risk patients

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Introduction: We report biochemical outcome data for intermediate and high risk patients who underwent prostate brachytherapy (BXT) using stranded I-125 implant (RapidStrand), with up to 73 months follow up.
Patients and methods: We have prospectively collected data on PSA outcomes on 600 patients treated to date. Between March 1999 and April 2003, 111 intermediate and 43 high risk patients were treated. Minimum follow up was 24 months (range 24–73 months). Risk status was determined using the Seattle Prognostic Index. Patients received either BXT alone, three months of neoadjuvant androgen deprivation (NAAD) followed by brachytherapy, or 3 months NAAD, 45 Gy pelvic external beam radiotherapy (EBRT) and BXT.
Results: The mean age of patients was 63 years. Within the intermediate group 50% had a PSA >10, 25% had a gleason score $\geqslant$7, and 30% were stage T2c or higher. Within the high risk group 86% had a PSA>10, 65% had a gleason $\geqslant$7, and 76% were stage T2c or higher. Actuarial biochemical free survival (bNED) at 73 months for the intermediate group was 93% and the high risk group also 93%. When stratified by treatment group, intermediate risk patients had actuarial bNEDs of 93% for BXT alone ($n = 15$), 94% for NAAD and BXT ($n = 67$), and 90% for NAAD, EBRT and BXT ($n = 29$). In the high risk group bNEDs were 100% for BXT alone ($n = 2$), 83% for NAAD and BXT($n = 7$) and 94% for NAAD, EBRT and BXT ($n = 34$). Three year median PSA for the intermediate risk group was 0.3 ($n = 47$) and 0.1 ($n = 24$) for the high risk group.