7035 POSTER

The Outcome of High Dose Rrate Brachytherapy Combined With External Beam Radiation Therapy in Patients With Prostate Cancer

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Purpose: To determine the effects of high dose rate brachytherapy (HDR-BT) combined with external beam radiation therapy (EBRT), and to evaluate the early and late sequelae.
Patients and Methods: From April 2002 to March 2011, 126 patients with prostate cancer were treated with HDR-BT combined with EBRT. Patients were stratified into three groups: low-risk [20 patients (pts.)](GS: $\leqslant 6$, PSA $\leqslant 10$, T1c-T2a), intermediate-risk [33 pts.] (GS: 7, PSA 10−20, T2b), and high-risk [73 pts.] (GS: 8−10, PSA > = 20, T2c-T3). In all patients EBRT was performed before HDR-BT. Patients in low-risk group, intermediate-risk, and high-risk group were delivered 40 Gy/20 fractions/4 weeks, 46 Gy/23 fractions/4.6 weeks, and 50.4 Gy/28 fractions/5.6 weeks respectively, using a four field technique with a 10 MV photon beam. One to six days after the completion of EBRT, HDR-BT was performed with 18–19.5 Gy/3 fractions/2 days. Clinical Target Volume (CTV) was determined 3−5 mm outside the periphery of the prostate. Proximal part of the seminal vesicle was also included in the CTV in patients with T3. More than 95% of the prescription dose was delivered to the CTV.
Results: The median follow-up was 48.0 months. Biochemical (PSA) failure free survival rate according to the Phoenix definition (nadir + 2 ng/ml) was 95%, 94%, and 94% in low-, intermediate- and high-risk group, respectively. Overall survival rate was 96.0% and cause specific survival rate was 99.2%. Early sequelae were evaluated according to the Common Toxicity Criteria (CTC)-ver 4.0. Early genitourinary toxicity of grade 2, and grade 3 was observed in three and one patient, respectively. All the patients recovered from early toxicity within 12 months. Late genitourinary/gastrointestinal toxicity (rectal damage) of grade 2 appeared in 6 (6.5%)/2 (2.2%) of the patients whose observation period exceeded more than one year after the completion of the treatment.
Conclusions: HDR-BT combined with EBRT showed the excellent effects especially in intermediate- and high-risk group patients with prostate cancer. Biochemical failure and early and late sequelae were acceptable. Especially, HDR-BT had the advantage of avoiding late gastrointestinal toxicity.

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Improved Outcomes With Dose Escalated Hypofractionated Radiotherapy for Prostate Cancer

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Background: Dose escalation of hypofractionated radiotherapy is an area of interest in the non-surgical treatment of prostate cancer. This centre has previously reported outcomes for patients treated with neoadjuvant hormones and 5250 cGy in 20# [1]. We have subsequently dose escalated hypofractionated radiotherapy to 5500 cGy in 20#. We now present the outcome data for patients treated at 5500 cGy in 20# with neoadjuvant hormone deprivation and adjuvant hormone deprivation in some higher risk cases.
Material and Methods: Between 2001 and 2005, 584 patients were treated with T1−T3 prostate cancer. The median age was 67.2 years (range 49−80). The median follow-up was 81 months. All patients received a 3 month course of neoadjuvant hormone deprivation followed by CT planned conformal radiotherapy to the prostate (+/− seminal vesicles) using 5500 cGy in 20 daily fractions. Patients considered at high risk of relapse also received 2 years adjuvant hormone deprivation (147 patients). Outcomes were obtained from serial PSA measurements and casenote review. Standard prognostic indicators were used to classify patients into 'Good' (PSA $\leqslant 10$, Gleason score $\leqslant 6$, and Stage T1/T2), 'Intermediate' (1 raised value) and 'Poor' (2 or more raised values) prognostic groups. PSA relapse was defined as a rise of at least 2 ng/ml above the nadir (Houston criteria). Any patient with uncontrolled PSA at time of death was considered to have prostate cancer present at death for the purposes of actuarial cause specific survival.
Results: See the table.

Outcome measure	5250 cGy in 20#	5500 cGy in 20#	
	Without adjuvant hormones (n = 300)	Without adjuvant hormones (n = 437)	With adjuvant hormones (n = 147)
5 year actuarial cause specific survival rate (CSSR)	83.2%	97.8%	93.4%
5 year PSA relapse rate by prognostic group:			
Good	22.8% (n = 37)	4.0% (n = 78)	(n = 0)
Intermediate	44.3% (n = 103)	19.5% (n = 189)	18.4% (n = 22)
Poor	70.3% (n = 160)	37.8% (n = 170)	28.0% (n = 125)

For 52.5 v 55 Gy (without adjuvant hormones) for both CSSR and PSA relapse $P < 0.0001$.

Conclusions: These outcomes demonstrate substantially improved outcomes in all prognostic groups following a modest dose escalation. This supports evidence of a steep dose-response gradient and a low alpha-beta ratio in this cancer.

References

[1] Higgins GS *et al,*. Int J Radiat Oncol Biol Phys. 2006 Jul 15;65(4):982−9.

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Radiopeptide Therapy of Prostate Cancer Lu-177-RM2 (BAY 1017858) Monotherapy and in Combination With PKI Inhibitors

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Background: The Gastrin Releasing Peptide Receptor (GRPr) is over-expressed in the majority of prostate cancers. We evaluated whether radiolabeled GRPr ligands could be used for radionuclide therapy of prostate cancer.
Methods: We studied the cytotoxic effect of the GRPr antagonist BAY 1017858 (^{177}Lu-DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2, ^{177}Lu-RM2) in PC3 prostate cancer cells in-vitro and in tumour bearing mice. In addition, we evaluated a combination of targeted radiotherapy via ^{177}LuRM2 with the protein kinase inhibitors (PKIs) dasatinib and rapamycin. In vitro studies using different concentrations of the two PKIs were performed to confirm their cytostatic effect on PC3 cells, to measure the influence of the PKIs on ^{177}LuRM2 uptake and to assess the cell survival after the combined treatment (trypan blue exclusion assay). The effect of ^{177}Lu-RM2 alone or in combination with rapamycin or dasatinib (4 or 70 mg/kg for 3d) was assessed. Animals were monitored daily for tumour growth and toxicity. Potential changes in GRPr expression or binding affinity following therapy were studied by small animal PET with ^{68}Ga-RM2.
Results: Following 3d of PKIs treatment, there was a dose-dependent reduction in PC3 proliferation in vitro without evidence for apoptosis or downregulation of GRPr expression/^{177}LuRM2 binding. In vivo, animals treated with six doses of 12 or 24 MBq over 18d showed a significant reduction in tumour mass. PET scans demonstrated that tumour uptake of ^{68}GaRM2 is not significantly changed after treatment with PKIs. Combined treatment group with ^{177}Lu-RM2 (37MBq) plus rapamycin was most effective on survival and tumour growth. Partial remission was observed in >80% of the animals; 30% of the animals achieved a complete remission. No compound-related histopathological changes were observed in the analysed organs of treated mice.
Conclusions: Radiotherapy using the bombesin antagonist ^{177}LuRM2 (BAY 1017858) alone or in combination with rapamycin is a promising strategy for treatment of GRPr expressing prostate cancer.

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The HIPRO (Hypofractionated Dose Escalation Utilising Intensity Modulated Radiotherapy in Carcinoma of the Prostate) Study − Late Toxicity and Outcome at 7 Years

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Background: Increasing radiotherapy dose has improved biochemical control for organ-confined prostate cancer. This is at the expense of prolonged treatment times and late toxicity. Hypofractionation should confer a biological advantage given the low alpha-beta ratio. Intensity modulated radiotherapy (IMRT) allows dose escalation with critical organ sparing. We report 7 year late toxicity and survival data in patients within the

HIPRO (Hypofractionated Dose Escalation utilising Intensity Modulated Radiotherapy in Carcinoma of the Prostate) study (UKCRN ID 1272).
Materials and Methods: Sixty men, median age 75 years (50−87), with localised adenocarcinoma of prostate (T1−3N0M0) and either Gleason score ⩾7 or PSA 20−50 ng/l received 57 Gy in 19 fractions (n = 30) or 60 Gy in 20 fractions (n = 30) using 5-field inverse-planned IMRT. All patients received neoadjuvant hormone therapy, continuing for up to 6 months after treatment. Late toxicity was assessed at 7 years follow-up using RTOG criteria and a validated LENT/SOMA patient questionnaire. Overall survival, cause-specific survival and biochemical progression-free survival defined using Phoenix criteria (bPFS) were assessed at 5 years.
Results: Median follow-up was 84 months (13−93 months) and forty-four (73%) patients were alive at 7 years. Nine patients (21%) reported RTOG grade 1 bowel or bladder toxicity; there was no grade 2 toxicity or above. There was no difference between the fractionation schedules. LENT/SOMA questionnaires were returned by 31/44 patients. At 7 years, mean and median scores were less than one for bowel and urinary symptoms. Compared with baseline assessment prior to radiotherapy, the proportion of all patients with significant (maximum LENT/SOMA ⩾2) urinary symptoms remained similar (76% vs. 75%), problems with sexual function had decreased (98% vs. 84%) but bowel symptoms increased (25% vs. 62%). At 5 years, overall survival was 83% and 74%, cause-specific survival 83% and 84% and bPFS 50% and 58% in the 57 Gy and 60 Gy groups respectively.
Conclusions: Dose-escalated hypofractionated IMRT for prostate cancer is well tolerated with acceptable levels of late toxicity compared to the published literature. Although this study predominantly included high risk patients (D'Amico classification), survival outcomes are promising. This study served as a precursor for CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer), a large multicentre Phase III clinical trial which will further assess long-term disease control and toxicity with these regimens.

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Establishing a Dose Response Relationship for the Treatment of Prostate Cancer With External Beam Radiotherapy: a Meta-analysis

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Background: Randomized trials have shown the benefit of radiation dose-escalation in prostate cancer, however, the exact quantitative relationship remains unclear. We aim to quantify a relationship between radiotherapy dose and freedom from biochemical failure (FFBF) in low and intermediate risk prostate cancer. To reduce confounding, we used data with a standardised endpoint, mature follow-up, low competing risk of metastatic failure via exclusion of high risk patients, conventional fractionation and separate reporting for outcomes with hormonal therapy.
Materials and Methods: A systemic review of the literature from was carried out in EMBASE, Pubmed and the Cochrane library, as well as proceedings of annual ASTRO meetings and publication bibliographies. Studies that reported the use of radiotherapy alone in 1.8−2 Gy fractions in low and intermediate risk prostate cancer were included. The primary endpoint was Phoenix definition 5-year FFBF. A logistic regression was used to model the dose-response relationship. The dose required to achieve 50% biochemical tumour control (TCD50) and the slope of the dose-response curve at TCD50 (γ50) were calculated.
Results: Data from 14 studies with 2704 patients met the inclusion criteria. The data from 1255 low risk patients (591 patients without hormone therapy and 664 patients treated with hormone therapy) and 1449 intermediate risk patients without hormone therapy were analysed. A strong correlation between radiotherapy dose and FFBF were found in low and intermediate risk patients managed with radiotherapy alone. In low risk patient not treated with hormone therapy the TCD50 is 49.5 Gy and the γ50 is 1.8%/Gy ($p = 0.0003$). At 78 Gy this represents a FFBF of 88.8%. In intermediate risk patients not treated with hormone therapy, the TCD50 is 64.7 Gy and the γ50 is 3.2%/Gy ($p < 0.0001$). At 78 Gy this translated into a FFBF of 84.5%. Hormonal therapy had a borderline significant effect in low risk patients with a relative risk reduction of 27% in FFBF at 78 Gy ($p = 0.07$), equivalent to an absolute risk reduction of 3%.
Conclusions: A strong correlation was found between radiation dose and biochemical outcome in both low and intermediate risk patients. There is a FFBF benefit for hormonal therapy for men with low risk disease, but in absolute terms this is small in the presence of dose escalated radiotherapy. With image guided radiotherapy and conformal planning techniques providing more accurate prostate dose delivery than what was achieved in some of the studies included in this analysis, the models may underestimate FFBF rates achievable in the modern era.

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Treatment of Prostate Cancer With Intensity Modulated Radiation Therapy Using an Empty Bladder Protocol − Treatment Outcomes and Toxicity Profile

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Background: To examine the acute and late toxicities, and biochemical relapse-free-survival (bRFS) after moderate dose-escalation using Intensity Modulated Radiation Therapy (IMRT) in Stage cT1−4cN0 prostate cancer patients on an empty-bladder protocol.
Materials and Methods: We retrospectively analyzed all (n = 95) patients with prostate cancer treated with IMRT at the National Cancer Centre Singapore from 2004 to 2006 using a modified bladder-filling protocol. Patients were instructed to empty their bladder before simulation and treatment. After completion of treatment, patients were scored for late-urinary and bowel toxicities using the Common Terminology Criteria for Adverse Events version 3.0. Late toxicity data was compared to that published from other IMRT studies using a full-bladder protocol. Overall-Survival (OS) and bRFS were estimated by the Kaplan–Meier method.
Results: Ninety-one patients (95.8%) completed IMRT. Median age was 68 years (range = 51−82). 71% of patients had clinical stage cT1 and cT2 disease. Median presenting PSA was 13.8 ng/dL (range = 2.5–483). Median Gleason score was 7 (range 4−10). Fifty-eight patients (70%) received 74 Gy to the prostate gland. 4.8% and 50% of patients exceeded the dose-constraints for rectum and bladder, respectively. Median follow-up time was 51 months (range = 3.6–144). Twelve (14.5%) and 10 (12.8%) patients had hematuria and rectal bleeding. 5-year OS and bRFS was 89.7% and 80.5%.
Conclusions: Moderate dose-escalation with IMRT using a modified empty-bladder protocol is feasible and produces late-toxicity rates and treatment outcomes comparable to treatments using a conventional full bladder protocol.

Table: Comparison of treatment outcomes and toxicity profile of patients in study with published results

	Current study	MSKCC (Alicikus et al., 2010)	MSKCC (Zelefsky et al., 2008)			Koh et al., 2009	Storey et al., 2000		Al-Mamgani et al., 2008	
Radiation technique	IMRT	IMRT	3D CRT, IMRT (n = 170)	3D CRT	3D CRT	IMRT	3D CRT	3D CRT	3D CRT, IMRT (n = 41)	3D CRT
Bladder during RT	Empty	Empty	Empty	Empty	Empty	Full	Full	Full	Full	Full
No. of patients	91	170	741	358	472	76	91	98	333	331
Median follow-up, months	50.3	99	120	78		7.9	42	40	71	70.3
Radiation dose, Gy (fraction size)	66−74 (2)	81 (1.8)	81 (1.8)	70.2 (1.8)	75.6 (1.8)	73.8 (1.8)	78 (2)	70 (2)	78 (2)	68 (2)
Survival rate, %										
5-year OS, %	91.3	–	–	–	–	–	–	–	–	–
7-year OS	–	–	–	–	–	–	–	–	75%	75%
5-year bRFS, %	73.2	–	85%	61%,	74%	–	–	–	67%	61%
7-year bRFS, %	–	–	78%	68%	50%	–	–	–	56%	45%
10-yr Risk groups										
Fav		81%								
Mod		78%								
Poor		62%								
G.U. Toxicity										
⩾Gr 2, %	15.4	9	20	10	15	3.9	20	9	40%	41%
⩾Gr 3, %	2.2	5	5	3	3	1.3	–	–	12%	13%
G.I. Toxicity										
Gr 1	12.1	19	–	–	–	–	–	–	–	–
⩾Gr 2, %	1.1	2	5	7	18	2.6	21	14	35%	25%
⩾=Gr 3, %	0	1	1	1	1	1.3	–	–	4%	6%