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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

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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