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Original article

High-dose-rate brachytherapy with two or three fractions as monotherapy in the treatment of locally advanced prostate cancer

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ABSTRACT

Background: To evaluate late urinary (GU) and gastrointestinal (GI) adverse events (AEs) and biochemical control of disease after high-dose rate brachytherapy (HDR-BT) in locally advanced prostate cancer.

Patients and methods: 227 consecutive patients were treated with 3×10.5 Gy ($n = 109$) or 2×13 Gy ($n = 118$) HDR-BT alone. Biochemical failure was assessed using the Phoenix definition of PSA nadir + 2 μg/l and late AEs using the RTOG scoring system and the International Prostate Symptom Score (IPSS).

Results: Kaplan–Meier estimates and prevalence of late events indicate that urinary, bowel and IPSS symptoms are higher after 31.5 Gy than after 26 Gy, however differences are significant only for Grade 1 and 2 urinary toxicity. Kaplan–Meier estimates of morbidity are consistently and considerably higher than time-point estimates of prevalence; which reflects the transient nature of most symptoms. At 3 years 93% and 97% of patients treated with 26 and 31.5 Gy, respectively, were free from biochemical relapse ($p = 0.5$) and 91% for the latter regimen at 5 years. In univariate and multivariate analysis risk-category was the only significant predictor of relapse ($p < 0.03$).

Conclusion: These HDR-BT schedules achieved high levels of biochemical control of disease in patients with advanced prostate cancer with few severe complications seen throughout the first 3 years.

Brachytherapy (BT) has the ability to deliver a high, localised radiation dose to the tumour while minimising normal tissue toxicity and achieves excellent outcome for patients with carcinoma of the prostate [1,2]. Low-dose-rate (LDR) BT is most frequently used in low risk disease [3] and high-dose-rate (HDR) BT predominantly as boost after external beam radiation therapy to treat intermediate and high-risk patients [4–7]. HDR monotherapy has been evaluated primarily in favourable-risk disease [8–10].

Unlike many other tumour types, prostate carcinomas appear to have a high sensitivity to radiation dose fractionation and therefore more sensitive to large doses per fraction than most other malignancies. HDR-BT monotherapy should effectively exploit this radiobiological advantage [2,11,12]. To investigate the efficacy and evaluate the possible therapeutic benefit of hypofractionation in intermediate to high-risk disease a dose escalation study of HDR-BT monotherapy in advanced prostate cancer has been ongoing in our centre since 2003. Earlier reports on dose escalation protocols showed good biochemical control and manageable early and late urinary and bowel adverse events [13]. This present report compares 26 Gy delivered in 2 fractions with 31.5 Gy in 3 fractions.

Patients and methods

Two hundred and twenty-seven patients, with histologically proven prostate adenocarcinoma were sequentially enrolled to this study, which received ethical approval through the UK Integrated Research Application System. Written informed consent was mandatory. Patients with localised T_{1c} to T_{3b} tumours, based on digital rectal examination and pelvic magnetic resonance imaging (MRI) were included. Exclusion criteria were PSA $\geqslant$ 40 μg/L, evidence of metastases on isotope bone scan or pelvic MRI, a previous TURP and those unfit for a general or spinal anaesthetic.

Treatment schedule

The technique of HDR iridium (^{192}Ir) after-loading used has been previously described [14]. Briefly, after implantation computed tomography imaging (CTI) and MRI were obtained and registered. The clinical target volume (CTV) was defined by the prostate capsule and extended to cover extra-capsular and seminal

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vesicle disease. The planning target volume (PTV) was a 3 mm volumetric expansion from the CTV, constrained to the anterior rectal wall. The dose was prescribed to the PTV as a minimum peripheral dose. On the day of implant, patients received the first fraction of the 3×10.5 or 2×13 Gy-schedule. The second and third fraction was delivered on the following day, with a minimum of 6 h between fractions 2 and 3. A CT scan was obtained before the second and third fraction, and appropriate adjustments made to dwell positions to optimise dose distribution compensating for any changes in implant dosimetry [15]. Constraints for the rectal D_{2cc} were 8 Gy with a V_{10Gy} of zero; urethral $D_{10} < 12$ Gy and $D_{30} < 11.5$ Gy; normal tissue constraints were kept constant for both the two and three fraction schedules.

Androgen deprivation therapy (ADT)

Neo-adjuvant-adjuvant androgen deprivation therapy was administered to 75% (26 Gy group) and 88% (31.5 Gy series) of patients following a policy of administration for 6 months in low/intermediate risk, and up to 3-years in high-risk patients. Details of ADT administration are summarised in Table 1.

Endpoints and statistical analysis

Late urinary and gastrointestinal adverse events were evaluated using the RTOG scoring system and the International Prostate Symptom Score (IPSS). Time to biochemical/clinical failure was assessed using the RTOG/ASTRO Phoenix definition of PSA nadir plus 2 μg/L. After the initial assessment of early morbidity, follow-ups took place at 6 months after treatment and bi-annually for the first 5 years and annually thereafter.

Statistical comparisons were carried out using JMP™, SAS Institute, Cary, NC, USA. Differences in patients' baseline demographics and tumour features were compared using χ^2 and Kruskal–Wallis tests for categorical and continuous covariates, respectively. Analyses were performed as per protocol with time to event calculated from day of first implant. Estimates of freedom from biochemical relapse (FFbR) and late morbidity were obtained using the Kaplan–Meier method and differences compared with the Mantel–Cox log-rank test. Univariate and multivariate hazard ratios (HR) were obtained using Cox's proportional hazard model with patient and tumour features summarised in Table 1 as covariates. For multivariate modelling a stepwise reduction method was used. Prevalence of late effects was calculated using the actual number of patients seen at the particular follow-up and a χ^2 test used to compare differences between dose groups. Where appropriate, the defined level of significance was adjusted using Bonferroni's correction method to compensate for multiple comparisons.

Table 1
Demographics and prognostic features.

Variable	Category	26 Gy $n = 113$	31.5 Gy $n = 107$
[a]Age (years)	Median	69	69
	Mean	69	69
	Range	51–80	55–81
Follow-up times (months)	Median	31	71
	Range	6–54	18–88
[a]IPSS	Mild	61 (52)	55 (50)
	Moderate	43 (36)	36 (33)
	Severe	6 (5)	5 (5)
	Not known	8 (7)	13 (12)
T stage	T_{1c} – T_{2a}	35 (31)	16 (15)
	T_{2b-c}	45 (40)	49 (46)
	T_{3a-b}	33 (29)	38 (36)
	Not known	0	4 (3)
Gleason score	<7	23 (20)	29 (27)
	7	78 (69)	72 (67)
	⩾8	12 (11)	6 (6)
PSA range	<10 μg/L	44 (39)	43 (40)
	10–20 μg/L	44 (39)	38 (36)
	>20 μg/L	25 (22)	26 (24)
[b]Risk group	Low	2 (2)	1 (1)
	Intermediate	58 (51)	49 (46)
	High	53 (47)	57 (53)
PSA (μg/l)	Mean ± 95% CI	14.3 ± 1.7	14.6 ± 1.7
No ADT	Low	0	0
	Intermediate	17 (61)	10 (77)
	High	11 (39)	3 (23)
Given ADT	Low	2 (2)	1 (1)
	Intermediate	41 (48)	39 (42)
	High	42 (49)	54 (57)
ADT	Duration (months)	14.2 ± 3.1	11.6 ± 2.3

Abbreviation: PSA: prostate specific antigen. ADT: androgen deprivation therapy.
[a] Includes 5 patients given 26 Gy and 2 given 31.5 Gy with a pre-treatment PSA ⩾ 40 μg/L (excluded from time to biochemical relapse endpoint).
[b] Categories of risk of biochemical relapse were identified using the National Comprehensive Cancer Network classification (www.nc.org). Numbers in brackets are percentages.

Results

Between August 2005 and August 2012, 118 patients were treated with 26 Gy and 109 patients with 31.5 Gy. Five patients in the former and two in the latter schedule had a pre-treatment PSA ⩾ 40 μg/L (protocol exclusion criteria) and therefore not included in the evaluation of biochemical failure. Table 1 summarises demographic and tumour features for these groups. Differences in the distribution of co-variates between groups were not significant ($p < 0.01$ considered significant).

Time-incidence plots of GI and GU events are shown in Fig. 1 and IPSS moderate or worse (scores ⩾ 8) and severe (scores ⩾ 20) symptoms are shown in Fig. 2 for each schedule. Except for the IPSS ⩾ 8-group, actuarial estimates for toxicity were consistently higher in patients treated with 31.5 Gy, however these were significant only for Grade 1 or worse (mild) and Grade 2 or worse (moderate) GU events ($p \leqslant 0.001$ considered significant). In Table 2 Kaplan–Meier estimates of GU, IPSS and GI adverse events at 3 years are contrasted with prevalence rates at the same follow-up interval. Two striking differences are seen between the two methods of analyses: prevalence estimates are considerably lower than Kaplan–Meier estimates (up to 30 times lower) and similar for both dose groups.

Median follow-up for the whole series is 47 months. Fig. 3 shows estimates of freedom from biochemical failure for the two schedules as function of radiation dose; these were not significant ($p = 0.5$). At 3 years 93% of patients were free of relapse after 26 Gy and 97% of those treated with 31.5 Gy. The five-year recurrence-free estimate for the combined group is 90%. After excluding the 3 patients with low-risk disease from the fitting procedure, Fig. 3 also shows that freedom from biochemical recurrence was significantly higher in patients with intermediate risk disease compared to those with high-risk disease ($p = 0.03$). Of the co-variates listed in Table 1 risk category was the only significant predictor of relapse in either univariate or multivariate analysis (Hazard Ratio: 0.295; $p = 0.01$).

Discussion

This paper adds to the current literature on the role of HDR brachytherapy with androgen deprivation therapy in high and intermediate risk localised prostate cancer.

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