Radiotherapy and Oncology 110 (2014) 110–113

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Dosimetric predictors of biochemical control of prostate cancer in patients randomised to external beam radiotherapy with a boost of high dose rate brachytherapy

Peter J. Hoskin, Ana M. Rojas *, Peter J. Ostler, Robert Hughes, Linda Bryant, Gerry J. Lowe

Cancer Centre, Mount Vernon Hospital, Middlesex, UK

ARTICLE INFO

Article history:
Received 15 August 2012
Received in revised form 28 August 2013
Accepted 31 August 2013
Available online 4 October 2013

Keywords:
High-dose-rate-brachytherapy
Dosimetry
Biochemical control
Prostate cancer
Randomised trial

ABSTRACT

Background: To correlate dose and volume dosimetric parameters (D_{90} and V_{100}) with biochemical control in advanced prostate cancer treated with high-dose rate brachytherapy (HDR-BT).
Methods: One hundred and eight patients received external beam radiotherapy (EBRT) to 35.75 Gy in 13 fractions followed by HDR-BT of 2 × 8.5 Gy. Kaplan–Meier freedom-from-biochemical relapse (FFbR; nadir + 2 μg/L) fits were grouped by the first (Q1), second (Q2) and third (Q3) D_{90} and V_{100} quartiles. Groups were compared with the log-rank test. Univariate and multivariate Hazard Ratios (HR) for D_{90} and V_{100} and other co-variates (PSA, androgen deprivation therapy (ADT) were obtained using Cox's proportional hazard model.
Results: FFbR was significantly higher in patients whose D_{90} and V_{100} were at or above the second and third quartile (log rank $p \leqslant 0{\cdot}04$). In multivariate analysis D_{90}, V_{100} were significant covariates for risk of relapse.
Conclusions: Dichotomising the data using 6 levels of response (above and below Q1, Q2 and Q3) showed a progressive and continuous improvement in biochemical control of disease across the entire dose (and volume) range. The data show that a minimum D_{90} of 108% of the prescribed dose should be the target to achieve.
 Radiotherapy and Oncology 110 (2014) 110–113

A radiation-dose response for prostate cancer using external beam irradiation has been demonstrated with dose escalation studies approaching 90 Gy made possible with the application of intensity modulated radiotherapy (IMRT) which enables such doses to be achieved within normal tissue tolerances [1,2]. An alternative means of dose escalation has been demonstrated using HDR-BT in addition to external beam [3–6]. However brachytherapy remains one of the 'craft' subspecialties in oncology with each individual implant critically dependent upon the skill and expertise of the operator alongside meticulous attention to dosimetry and quality assurance. There is an extensive literature from low dose rate (LDR) permanent implant treatments in early prostate cancer demonstrating the impact of implant quality and dosimetry in predicting outcome [7–12].

To date there is no analysis correlating HDR-BT implant quality and dosimetric parameters with FFbR. We therefore have taken the results from a published prospective randomised trial that compared EBRT with EBRT + HDR-BT and using the dose-volume histogram explored the relation between implant quality and FFbR in the arm receiving EBRT + HDR-BT [13].

Materials and methods

Details of patient selection, trial randomisation procedures, number of patients randomised, treated and in analysis and CONSORT diagrams have been published previously [13]. The single-centre trial was performed in compliance with the Declaration of Helsinki and approved by the local research Ethics Committee. Written informed consent, prior to randomisation, was mandatory.

Radiotherapy

The techniques used have been described in detail previously [4,13]. Briefly, The external beam PTV was defined using CT planned volumes to cover the prostate gland with a 1 cm margin except posteriorly where the margin was reduced to 5-mm. The EBRT (using megavoltage 6–10 MV photons) delivered a dose of 35.75 Gy, prescribed to the intersection point in 13 fractions, treating daily Monday to Friday followed within no more than 6 days by the high dose rate (HDR) brachytherapy boost. The HDR-boost CTV was defined to cover the entire gland and the seminal vesicles if involved. The dose per fraction to the brachytherapy CTV was 8.5 Gy peripheral dose. The rectal dose constraint was <6.7 Gy to 2 cc with no area receiving 8.5 Gy

* Corresponding author. Address: Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, UK.
E-mail addresses: arc03@btconnect.com, arc@macunlimited.net (A.M. Rojas).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.08.043

and the urethral constraint <10 Gy to 10% of the urethra. A second fraction was given the following day to deliver a total dose of 17 Gy in two fractions in 24 h.

Endpoints and statistical analyses

Baseline demographics were compared using a contingency platform or one-way ANOVA and statistical differences made using Chi-square and Fisher's exact tests.

Dose–volume histograms were produced by Brachyvision (Varian Medical Systems, Crawley, Sussex). From these D_{90} (Gy), the minimum dose to 90% of the prostate volume, and V_{100} (%), the volume that received 100% of the prescribed iso-dose were derived. The first (Q1), second (Q2) and third (Q3) quartiles for D_{90} and V_{100} were obtained using a distribution analysis.

Biochemical relapse was assigned to patients with a rise of 2 μg/l or more above nadir PSA as recommended in the RTOG/ASTRO Phœnix guidelines [14]. Freedom from biochemical relapse (FFbR) rates were obtained using the Kaplan–Meier method and differences compared using the log-rank test. Univariate and multivariate hazard ratios (HR) were obtained using Cox's proportional hazard model with the patients' and tumour features summarised in Table 1 as covariates.

Where appropriate, the defined level of significance was adjusted using Bonferroni's correction method to compensate for multiple comparisons.

Results

Between 1997 and 2005 218 patients were randomised to EBRT or EBRT + HDR-BT. After randomisation two patients were excluded from analysis. A further two, randomised to EBRT + HDR-BT, were treated with EBRT alone. As in the analysis of late effects, these patients form part of the EBRT alone arm [13]. Long-term relapse-free and overall survival, early and late adverse events have been published previously [4,13].

Dosimetry parameters were unavailable in 13 patients because of failure to retrieve archival material, thus of a total of 108 patients treated with EBRT + HDR-BT only 95 form part of this analysis. ADT was administered to 79% of the 95 patients following a policy of administration for 6 months in low/intermediate risk, and up to 3-years in high-risk patients.

Patients were divided into groups above or below the median D_{90} and V_{100} value. The demographic features and known predictors of response are summarised in Table 1 for the whole group and for those at <median D_{90} and $\geqslant D_{90}$. With the exception of ADT, the groups were evenly balanced.

Table 2 shows the mean D_{90} and V_{100} values for patients with and without relapse. It also shows the 1st, 2nd and 3rd quartile cut-off levels of dose and volume. Mean values for both dosimetric parameters were significantly higher in patients free from relapse ($p < 0.0001$).

Fig. 1 shows Kaplan–Meier time incidence curves for FFbR in patients above and below the median D_{90} and median V_{100} level. A significantly higher proportion of patients whose D_{90} and V_{100} levels $\geqslant$ median value were free from relapse (92% and 94% at 5-years; $p \leqslant 0.01$; respectively). Fig. 2 compares these curves with those generated using the 1st and 3rd quartile D_{90} and V_{100} levels as cut-off points to rank time spent free from biochemical relapse. The Kaplan–Meier analysis demonstrates a progressive dose (and volume) related increase in probability of biochemical control of disease.

In univariate analysis D_{90}, V_{100}, were significant predictors of biochemical relapse (Table 3). There was a strong correlation between D_{90}, and V_{100} (Spearman's $\rho = 0.97$; $p < 0.0001$) so that both cannot be included simultaneously in the multivariate fitting procedure. In multivariate analysis $D_{90} < 8.8$ Gy and $V_{100} <$ median were associated with a significantly higher risk of relapse. High PSA level (>20 μg/L) and ADT were of borderline significance ($p = 0.01$ considered significant).

Table 1
Demographics and prognostic features in patients treated with external beam radiotherapy followed by a boost of high-dose-rate brachytherapy ranked by median D_{90}.

Variable	Category	All ($n = 95$) n (%)	<median (46) n (%)	⩾median (49) n (%)	[a]p
Age	Median	69	69	68	0.6
	Mean	67.8	68.5	67.2	
	Range	47–79	56–78	47–79	
T stage	T_1	23 (24)	15 (33)	8 (16)	0.1
	T_2	41 (43)	19 (41)	22 (45)	
	T_3	31 (33)	12 (26)	19 (39)	
Gleason	<7	39 (41)	22 (48)	17 (35)	0.3
	7	39 (41)	15 (33)	24 (49)	
	⩾8	17 (18)	9 (19)	8 (16)	
PSA μg/l	<10	33 (35)	17 (37)	16 (33)	0.8
	10–20	36 (38)	16 (35)	20 (41)	
	>20	26 (27)	13 (28)	13 (26)	
Risk group	Low	1 (1)	1 (2)	0	0.5
	Intermediate	41 (43)	20 (44)	21 (43)	
	High	53 (56)	25 (54)	28 (57)	
ADT	No	20 (21)	14 (30)	6 (12)	0.04
	Yes	75 (79)	32 (70)	43 (88)	
ADT (duration)					
6 months	Low	1	1	0	
6 months	Intermediate	24 (59)	7 (35)	17 (81)	0.004
⩽3 years	High	50 (94)	24 (96)	26 (93)	1

Abbreviation: PSA, prostate specific antigen; ADT, androgen deprivation therapy.
[a] $p < 0.006$ considered significant.

Discussion

This analysis, based on patients participating in the randomised trial of EBRT without and with a boost of HDR-BT, demonstrates that implant dosimetry is a good, reliable predictor of treatment outcome; similar findings have been reported for cervical cancer [15,16]. D_{90} and V_{100} have been shown to be a significant predictor of biochemical failure in patients treated with low-dose rate (LDR) permanent implants [7–12] although D_{90} was not predictive in patients treated with EBRT and LDR implants [9]. More recently,

Table 2
Mean D_{90} and V_{100} in patients with and without biochemical control of disease. First, second and third quartile (Q) values for D_{90} and V_{100}.

Dosimetric variable	Mean (95% CI)	p	Quartiles (all patients; $n = 95$)		
			1st Q	2nd Q	3rd Q
D_{90}					
With relapse ($n = 24$)	7.9 Gy 7.6–8.3	<0.0001	7.9 Gy	8.8 Gy	9.2 Gy
No relapse ($n = 71$)	8.6 Gy 8.3–8.9 Gy				
V_{100}					
With relapse ($n = 24$)	84.7% 81.7–87.7%	<0.0001	85.4%	92.2%	95.2%
No relapse ($n = 71$)	90.8% 88.8– 92.7%				

CI: confidence interval.