Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

A modelled comparison of prostate cancer control rates after high-dose-rate brachytherapy (3145 multicentre patients) combined with, or in contrast to, external-beam radiotherapy

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Prostate cancer
Radiotherapy
High dose-rate brachytherapy
Biochemical relapse free survival

ABSTRACT

Background and purpose: To analyse biochemical relapse-free-survival results for prostate cancer patients receiving combined external beam and high-dose-rate brachytherapy, in comparison with expected results using projections based on dose/fractionation/response parameter values deduced from a previous external-beam-alone 5969-patient multicentre dataset.

Material and methods: Results on a total of 3145 prostate cancer patients receiving brachytherapy (BT) as part or all of their treatment were collected from 10 institutions, and subjected to linear-quadratic (LQ) modelling of dose response and fractionation parameters.

Results: Treatments with BT components of less than 25 Gy, 3–4 BT fractions, doses per BT fraction up to 6 Gy, and treatment times of 3–7 weeks, all gave outcomes expected from LQ projections of the external-beam-alone data (α/β = 1.42 Gy). However, BT doses higher than 30 Gy, 1–2 fractions, 9 fractions (BT alone), doses per fraction of 9–15 Gy, and treatment in only 1 week (one example), gave local control levels lower than the expected levels by up to ~35%.

Conclusions: There are various potential causes of the lower-than-projected control levels for some schedules of brachytherapy: it seems plausible that cold spots in the brachytherapy dose distribution may be contributory, and the applicability of the LQ model at high doses per fraction remains somewhat uncertain. The results of further trials may help elucidate the true benefit of hypofractionated high-dose-rate brachytherapy.

High-dose-rate brachytherapy (HDR-BT) is being used increasingly as a boost to conventional external-beam treatments [e.g. 1–9], although it is also used as a short-course monotherapy [e.g. 10]. In a recent biomathematical modelling analysis of external-beam treatment outcome results from 5969 patients in 7 institutions worldwide using different fractionation schedules, an α/β ratio of 1.4 (0.9–2.2 95% CI) Gy was deduced characterising the fractionation sensitivity of prostate cancer [11]. Control rates were higher in low risk groups than in high risk groups as expected, and higher by about 5% in patients also receiving androgen deprivation treatment, but the α/β ratio did not differ significantly between risk groups (Fig. 1).

The analysis has now been extended to consider patients receiving a brachytherapy boost after a course of external beam radiotherapy (EBRT), or HDR-BT alone in one dataset, in a total of 3145 patients among 10 institutions. The results from those patient groups were compared with expected results, using projections based on dose/fractionation/response parameter values deduced from the previous external-beam-alone datasets [11].

Materials and methods

Clinical material and data collection

Twenty-seven datasets were assembled from 10 institutions worldwide in Sweden, United States, Germany, United Kingdom, Brazil, Spain, Japan, and Australia. The institutions were different from those which supplied external-beam-alone data for the previous analysis [11]. All institutions were requested to provide recently updated information concerning the patients' outcome (5-year bRFS according to the Phoenix or ASTRO criteria). Risk grouping was undertaken according to the National Comprehensive Cancer Network (NCCN) guidelines risk group classification. The prescribed

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http://dx.doi.org/10.1016/j.radonc.2014.01.008
0167-8140/

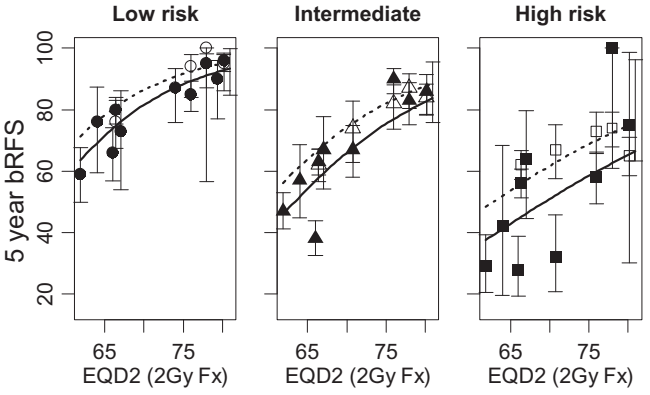

Fig. 1. Previously fitted biochemical relapse-free survival (bRFS) fraction at 5 years for external beam treatments. Data and model derivation are described in [11] and are plotted by risk groups and androgen deprivation (AD) status. The lines show the fit from a LQ model, and the points the outcomes according to the Phoenix criterion from each series used to derive the model. Risk grouping was undertaken according to the National Comprehensive Cancer Network (NCCN) guidelines risk group classification. Error bars represent 95% CI on the binomial proportions in each group. Broken lines and filled symbols are for AD treated patients and solid lines/open symbols are non-AD treated. Doses are normalised to 2 Gy fractions (EQD2) using the fitted α/β value of 1.42 Gy.

total doses of radiotherapy, the doses per fraction of EBRT and HDR-BT, the number of fractions, and the overall treatment time in weeks were recorded in the database (Table 1). Androgen deprivation (AD) status was very variable among authors and complete information was not available. Briefly, in three series (Rotterdam, Oakland, and Berlin) patients were hormone-free; in five series (Gothenburg, Northwood, Oviedo, Osaka, and Melbourne) 70–80% of patients received short neoadjuvant and concomitant AD; in one series (Kiel) only 37% of patients were under AD conditions; and in one other series (Sao-Paulo) patients were allowed to receive neoadjuvant treatment by the referring urologist (data unknown) but not concomitant AD during radiotherapy. Further details of the treatments are available from references [1–10].

Statistical Analysis

A conventional LQ model was utilised for tumour control at 5 years versus dose, of the form:

$$P = \exp(-\exp(k - \alpha D - \alpha(\beta/\alpha)D^2/N)) \quad (1)$$

where P is the tumour control probability (bRFS); D, the total dose; N, the number of fractions; k can be interpreted as the natural logarithm of an effective target cell number; α, dose–response slope for very small fractions; β/α, the ratio that characterises dose-fractionation sensitivity. Previous work has determined optimal parameter estimates based on a large series of EBRT data [11] with outcomes based on the Phoenix criteria. The estimates of k and α were specific to each risk group, with α also differing according to AD status, but a common estimate of β/α was determined to be the best fit to the data.

It proved impossible to directly fit the LQ model to the HDR-BT data alone or in conjunction with the EBRT data. Therefore we compared the observed HDR-BT data to what would be expected by direct extrapolation of the EBRT data using equation (1) and the previously reported fitted parameter values [11]. As AD status was not available in the present dataset, parameters for non-AD patients were used, potentially giving a small underestimate of the predicted outcomes. Firstly, we present the 5-year control rates with binomial confidence intervals as a function of the dose normalised to 2 Gy fractions (EQD2), using the previously derived α/β estimate of 1.42 Gy alongside the fitted parameter values for EBRT. Secondly, for each HDR-BT series we utilised the (risk-group-specific) dose–response curve to estimate the EBRT dose increment (D_{eff}) that would give the observed control rate – that is, the difference between the total dose delivered as EBRT

Table 1
Radiotherapy prescription parameters, patients and risk groups, and outcome.

Centre	Risk	EBRT fractionation			BT fractionation			Overall time (weeks)	Outcome			EQD2 (Gy)
		N_{ext}	d_{ext} (Gy)	D_{ext} (Gy)	N_{BT}	d_{BT} (Gy)	D_{BT} (Gy)		N	Type*	Control (%)	
Gothenburg-S (University of Gothenburg) [1]	Low	25	2	50	2	10	20	7	80	A	92	116.7
	Intermediate	25	2	50	2	10	20	7	87	A	88	116.7
	High	25	2	50	2	10	20	7	47	A	56	116.7
Rotterdam-NL (Daniel den Hoed Cancer Center) [2]	Low	25	1.8	45	3	6	18	7	212	P	97	81.4
	Intermediate	25	1.8	45	3	6	18	7	53	P	99	81.4
Berlin-D (Charité Hospital) [3]	Low	25	1.8	45	2	9	18	6	90	A	81	97.1
	Intermediate	28	1.8	50.4	2	9	18	6	53	A	65	102.2
Oakland-CA, US (California Endocurietherapy Cancer Center) [4]	Low	20	1.8	36	4	5.75	23	7	70	P	93	82.1
	Intermediate	20	1.8	36	4	5.75	23	7	92	P	93	82.1
	High	20	1.8	36	4	5.75	23	7	92	P	83	82.1
Kiel-D (University Hospital Schleswig–Holstein) [5]	Low	25	2	50	2	15	30	5.5	23	P	91	193.8
	Intermediate	25	2	50	2	15	30	5.71	119	A	82	193.8
	High	25	2	50	2	15	30	5.71	123	A	68	193.8
Northwood-UK (Mount Vernon Cancer Centre) [6]	Intermediate	13	2.75	35.75	2	8.5	17	3.29	48	P	84.3	92.8
	High	13	2.75	35.75	2	8.5	17	3.34	59	P	70.7	92.8
Sao-Paulo-Brazil (AC Camargo Hospital) [7]	Low	25	1.8	45	4	4	16	7	77	A	94	67.7
	Intermediate	25	1.8	45	4	5	20	7	65	A	82	79.9
	High	25	1.8	45	4	4	16	7	67	P	72	67.7
Oviedo-E (Hospital Universitario Central de Asturias) [8]	Intermediate	23	2	46	1	15	15	5	420	P	88	117.9
	High	23	2	46	2	11.5	23	5	959	P	78	132.7
Osaka-Japan (Osaka University) [10]	Low	0	0	0	9	6	54	1	15	A	91	117.0
	Intermediate	0	0	0	9	6	54	1	32	A	92	117.0
	High	0	0	0	9	6	54	1	75	A	67	117.0
Melbourne-Victoria, Australia (Albert Hospital) [9]	Intermediate	23	2	46	3	6	18	6	70	P	86	85.0
	Intermediate	23	2	46	4	5	20	6	19	P	86	83.5
	High	23	2	46	3	6	18	6	78	P	77	85.0
	High	23	2	46	4	5	20	6	20	P	77	83.5

* A = ASTRO criterion; P = Phoenix.

Please cite this article in press as: Roberts SA et al. A modelled comparison of prostate cancer control rates after high-dose-rate brachytherapy (3145 multicentre patients) combined with, or in contrast to, external-beam radiotherapy. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.01.008