Radiotherapy and Oncology 103 (2012) 217–222

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer

Peter J. Hoskin [a], Ana M. Rojas [a,*], Peter J. Bownes [b], Gerry J. Lowe [a], Peter J. Ostler [a], Linda Bryant [a]

[a] Cancer Centre, Mount Vernon Hospital, Northwood, UK; [b] St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK

ARTICLE INFO

Article history:
Received 16 August 2011
Received in revised form 9 December 2011
Accepted 11 January 2012
Available online 16 February 2012

Keywords:
High-dose-rate-brachytherapy boost
Hypo-fractionation
Dose escalation
Prostate cancer
Randomised trial

ABSTRACT

Background: A randomised phase-III trial compared external beam radiotherapy (EBRT) alone with EBRT combined with high-dose-rate brachytherapy boost (HDR-BTb) in localised prostate adenocarcinoma.
Methods: From December 1997 to August 2005, 218 patients were assigned to EBRT alone ($n = 108$) or EBRT followed by a temporary high-dose-rate implant ($n = 110$). Patients were stratified according to tumour stage, PSA, Gleason score and androgen deprivation therapy (ADT). Biochemical/clinical relapse-free survival (RFS) was the primary endpoint. Secondary endpoints were overall survival (OS), urinary and bowel toxicity.
Results: RFS was significantly higher in patients treated with EBRT + HDR-BTb (log rank $p = 0.04$). In multivariate analysis treatment arm, risk category and ADT were significant covariates for risk of relapse. Differences in OS were not significant. Incidence of severe late urinary and bowel morbidity was similar.
Conclusions: EBRT + HDR-BTb resulted in a significant improvement in RFS compared to EBRT alone with a 31% reduction in the risk of recurrence ($p = 0.01$) and similar incidence of severe late urinary and rectal morbidity.

Radiotherapy and Oncology 103 (2012) 217–222

A number of studies provide evidence for the efficacy of dose-escalation in prostate cancer, and mature results from randomised trials show that control of disease improves with increasing radiation dose [1–4]. The low α/β ratio and consequent high sensitivity to dose fractionation of prostate adenocarcinoma means that these tumours should be more sensitive to large radiation doses per fraction than most other malignancies [5,6]. These principles underpin the use of hypo-fractionated schedules to achieve dose escalation. The challenge then is to deliver hypo-fractionated dose escalation within the limits of normal tissue tolerance for the organs at risk; this is optimally achieved with HDR-brachytherapy.

Brachytherapy (BT) is well established as a treatment for localised prostate cancer and has advantages over external beam radiotherapy because of its ability to overcome problems of organ movement, which confound external beam techniques. BT alone with permanent low-dose-rate (LDR) seed implants or high-dose-rate (HDR) afterloading can deliver a high, localised radiation dose to the tumour with excellent biochemical control of disease [6–8]. For intermediate and high-risk disease there are concerns that brachytherapy alone may not adequately treat the peri-prostatic tissues, and therefore it may be used optimally as a boost in combination with external beam radiotherapy. In locally advanced disease HDR brachytherapy has greater flexibility than LDR BT in implanting treatment volume, particularly where larger volumes or seminal vesicles need to be encompassed. It also has a potential biological advantage through the delivery of high doses per fraction. Dose escalation is feasible by combining external beam radiotherapy with high-dose-rate afterloading brachytherapy, which provides optimal intensity modulated conformal radiation dose delivery [6,9].

A prospective randomised trial has been undertaken comparing external beam radiotherapy alone with a combined schedule including an HDR-brachytherapy boost. In 2007 we reported improved biochemical relapse-free survival compared to external beam radiotherapy alone after a median follow-up time of 30 months with less acute rectal toxicity and improved quality of life [10]. This current publication presents survival data and urinary and bowel late adverse events up to 10 years after treatment.

Materials and methods

Patients with a histological diagnosis of carcinoma of the prostate, stage T_1 to T_3, with no evidence of metastatic disease, a PSA <50 μg/l, suitable for radical radiotherapy, fit for general anaesthetic and able to comply with the informed consent procedure were eligible. Prior to randomisation, patients had baseline investigations including pelvic computed tomography (CT) and/or magnetic resonance imaging (MRI), isotope bone scan, chest X-ray and serum PSA. Exclusion criteria were evidence of metastases, PSA

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

0167-8140
doi:10.1016/j.radonc.2012.01.007

Table 1
Scoring system for late urinary and bowel adverse events.

	Moderate	Severe
Urinary endpoints		
Urination frequency day	Up to 1 hourly	0 (diversion)
Urination frequency night	4–5 events	⩾6 events
Incontinence	Intermittent requiring use of appliance Persistent, no treatment or requiring pads	Intermittent requiring catheter Persistent requiring appliance or catheter
Hæmaturia	Intermittent clinical blood loss Daily, microscopic orclinical blood loss	Intermittent, blood clots Daily, blood clots
Dysuria	Score 2	Score 3
Urgency	Score 2	Score 3
Bowel endpoints		
Frequency in 24 h	4–5 events	⩾6 events
Faecal consistency	Semi formed	Liquid
Blood loss (volume)	Intermittent, moderate blood loss Daily, moderate blood loss	Intermittent, gross haemorrhage Daily, gross haemorrhage
Rectal discharge	Intermittent requiring local medication Persistent requiring no treatment or requiring local medication	Intermittent or persistent requiring surgical treatment

Adapted from Dische et al [12].

>50 μg/l, co-existing malignancy, co-existing medical condition that precluded general anaesthesia.

This 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. The trial was overseen by an Independent Data Monitoring Committee and reviewed twice (March 2004 and February 2006).

Randomisation and masking

Patients were entered using a balanced one-to-one randomisation with stratification according to tumour stage, PSA, Gleason score and androgen deprivation therapy. A baseline probability of biochemical relapse-free survival of 60% with external beam therapy alone was assumed. To detect a 20% improvement in response with an a-error of 0.05 and a power of 80% a target accrual of 214 patients was proposed. No blinding was used for treatment delivery or follow-up assessments.

Radiotherapy

The external beam target volume was defined using CT imaging to cover the prostate gland and the proximal seminal vesicles with a 1 cm margin except to the posterior margin, which was reduced to 0.5 cm. The EBRT alone arm received a total dose of 55 Gy prescribed to the intersection point in 20 daily fractions. The HDR-BT boost arm received EBRT to 35.75 Gy in 13 fractions followed by a HDR-BT boost of 2×8.5 Gy in 24 h. Further details of the radiotherapy schedules have been published previously [10].

Androgen deprivation therapy (ADT)

Neo-adjuvant-adjuvant ADT was administered to 76% of patients. Depending on patients' tolerance the intention was to administer this for 6 months in low/intermediate risk, and up to 3-years in high-risk patients.

Endpoints and statistical analyses

The primary endpoint was biochemical relapse free survival (RFS). Secondary endpoints included overall survival (OS), acute and late urinary and bowel toxicity and quality of life. Biochemical relapse was assigned to patients with a rise of 2 μg/l or more above nadir PSA and to those not meeting this criterion but who underwent salvage therapies (such as ADT, radical prostatectomy, brachytherapy, or cryosurgery) as recommended in the RTOG/ASTRO Phoenix guidelines [11]. RFS was taken as time to biochemical recurrence, clinical evidence of local disease, or death from any cause. Imaging, to confirm local relapse, was initiated in patients with rising PSA levels or those with pelvic or musculoskeletal symptoms. Live patients free of local disease were censored at the time of their last follow-up. Time was set to zero for those who died before the first assessment was ever done. OS was taken as time to death; patients still alive were censored at the time last seen. All intervals were calculated from the date of randomisation and analyses were performed on an intention-to-treat basis.

Late urinary and bowel adverse events were evaluated twice a year during the first 5 years and annually thereafter, using an adapted version of the Dische Scales (Table 1) [12]. For analyses of morbidity patients were grouped according to the actual treatment delivered and time to event was calculated from date of first external beam radiotherapy dose.

Statistical comparisons were carried out using version 8.0.2 JMP™, SAS Institute, Cary, NC, USA. Prevalence of GU and GI late events was compared using a contingency platform and Fisher's exact test used to test for significance between schedules. RFS, OS and actuarial estimates of late morbidity were obtained using the Kaplan–Meier method and differences compared using the Mantel–Cox log-rank test. Univariate and multivariate Hazard Ratios (HR) and their 95% confidence intervals (CI) were obtained using Cox's proportional hazard model with treatment arm, risk category and ADT as covariates.

Results

Between December 1997 and August 2005 a total of 218 patients were randomised to receive either EBRT or EBRT + HDR-BTb. Two patients were excluded from analysis. In one, the pre-treatment scan showed bone metastases and he was withdrawn from the trial that same day. Another refused treatment allocated and received HDR-BT as monotherapy. In addition, two patients randomised to EBRT plus HDR-BTb, were treated with EBRT alone (failure to insert catheters in one and the other had a previous TURP). For the purposes of late morbidity they were analysed as

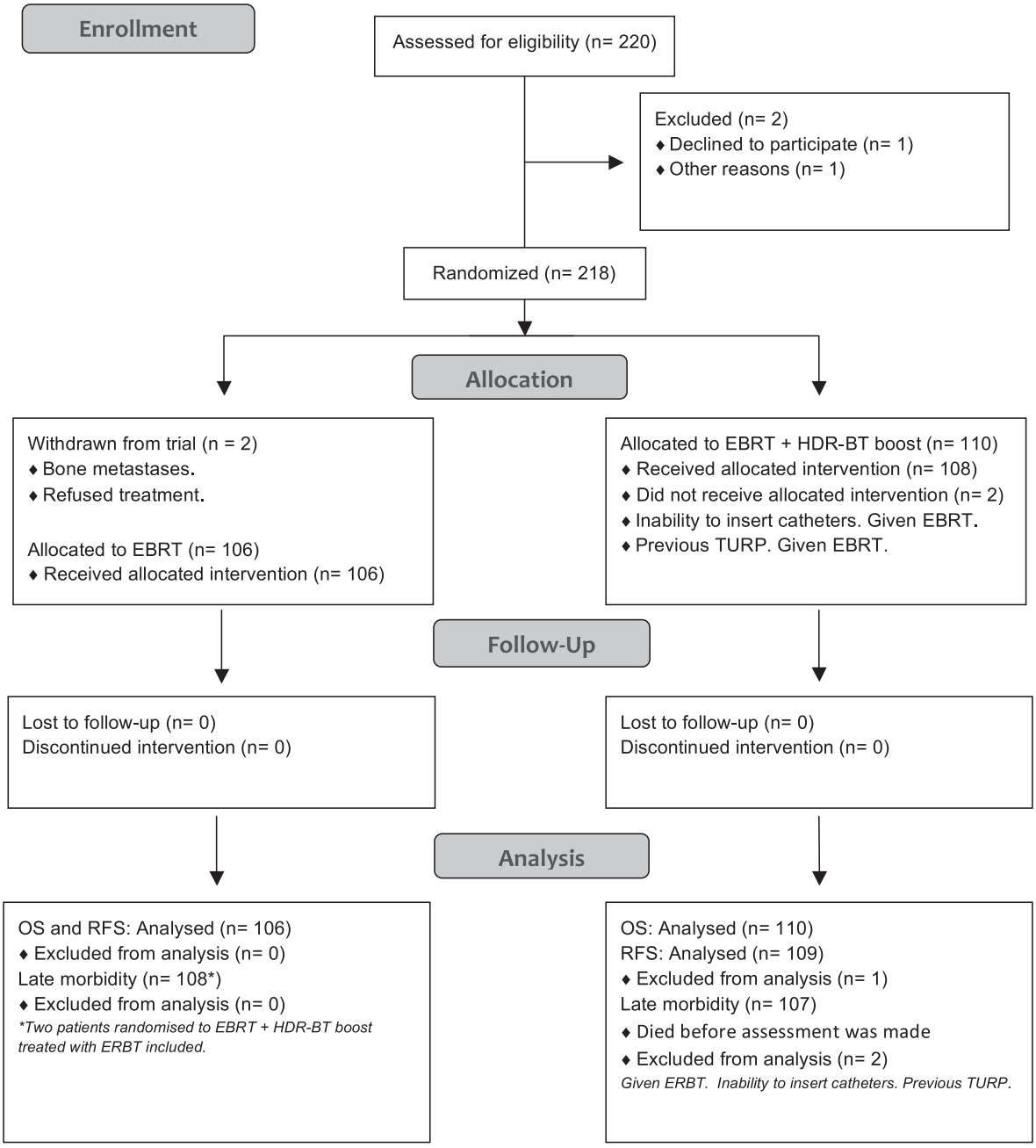

Fig. 1. Consort diagram. *Abbreviations:* EBRT, external beam radiotherapy; EBRT + HDR-BT boost, external beam radiotherapy combined with high-dose-rate brachytherapy as boost; TURP, trans-urethral resection of the prostate.

part of the EBRT alone arm. Fig. 1 (CONSORT diagram) shows number of patients enrolled, randomised, treated and finally analysed. The median follow-up time is 85 months for both arms. Demographic details are listed in Table 2.

Fig. 2 shows Kaplan–Meier curves for biochemical relapse-free and overall survival for patients treated with EBRT alone and EBRT + HDR-BT boost for all risk groups. After 4 years there was a noticeable improvement in RFS for EBRT + HDR-BTb, with a median time to relapse of 116 months compared to 74 months for EBRT alone. The 5-, 7- and 10-year estimates are 75%, 66% and 46% for EBRT + HDR-BTb compared to 61%, 48% and 39% for EBRT alone (log rank $p = 0.04$). In univariate and multivariate analysis treatment arm and risk category were significant covariates for risk of biochemical relapse as was ADT (the latter only in multivariate analysis). At this time any confounding effect of ADT use should have subsided.

Differences in overall survival between treatment arms were not statistically significant. Five-, 7- and 10-year survival estimates were 88%, 81% and 67% for EBRT + HDR-BT boost and 89%, 88% and 79% EBRT alone (log rank $p = 0.2$). In all, 45 patients have died, 26 in the experimental arm and 19 in the EBRT alone arm. The primary cause of death was metastatic disease (fourteen), cardiovascular (nine), second primary (nine), respiratory (four), cerebrovascular (three), mixed (five patients presented a combination of cardiovascular, renal and gastrointestinal complications) and neurological (one).

Fig. 3 shows Kaplan–Meier curves for incidence of severe urinary and bowel adverse events recorded from 6 months to 8 years

Table 2
Demographic details of patients given external beam radiotherapy alone (arm 1) or with a boost of high-dose-rate brachytherapy (arm 2).

Variable	Category	Arm 1 (n = 106) n (%)	Arm 2 (n = 110) n (%)
Age	Median	70	70
	Range	47–80	47–80
Follow-up time (months)	Median	85	85
	Mean	88	86
	Range	9–147	8–144
T stage	T_1	27 (25)	29 (26)
	T_2	55 (52)	47 (43)
	T_3	24 (23)	34 (31)
Gleason	<7	48 (45)	46 (42)
	7	40 (38)	44 (40)
	⩾8	18 (17)	20 (18)
PSA (μg/l)	<10	36 (34)	35 (32)
	10–20	43 (41)	45 (41)
	>20	27 (25)	30 (27)
Risk Group[a]	Low	7 (7)	2 (2)
	Intermediate	43 (40)	48 (44)
	High	56 (53)	60 (54)
ADT	No	26 (25)	25 (23)
	Yes	80 (75)	85 (77)
ADT (duration)			
6 months	Low	2 (29)	1 (50)
6 months	Intermediate	26 (60)	29 (60)
⩽3 years	High	52 (93)	55 (92)

Abbreviation: ADT, androgen deprivation therapy.
[a] Risk Group: identified using the National Comprehensive Cancer Network Guidelines.

after EBRT treatment. The 5- and 7-year incidence for patients with any severe urinary symptom is 26% and 31% for those treated with EBRT + HDR-BT compared with 26% and 30% for those given EBRT alone (log rank $p = 0.5$). The incidence of severe bowel events was considerably lower (7% and 6%, respectively, at 5 and 7 years; log rank $p = 0.8$). A large number of patients had transient urinary and bowel morbidity. This is reflected in the analysis of morbidity using prevalence. Over the first 8 years from treatment the highest prevalence of severe urinary events was 14% and lowest 4% for EBRT + HDR-BTb and 10% and 0% for EBRT alone. The difference was significant only at 5.5 year (14% vs 0%, $p = 0.02$, respectively). Table 3 summarises the 5 and 7 years Kaplan–Meier rates and prevalence of severe adverse events, and for urethral strictures managed surgically.

Discussion

This prospective randomised trial in localised prostate cancer compared EBRT alone with EBRT combined with a boost of HDR-BT. It confirms reports from other studies that an improvement in biochemical and/or clinical relapse-free survival is achieved with radiation dose escalation [1–4,13]. This is however the first randomised prospective trial, which has addressed dose escalation using an HDR brachytherapy boost. A number of criticisms can be levied at this study. It is a single centre trial with a relatively slow accrual rate although there was no overt patient selection outside the trial entry criteria. There were changes in EBRT technique and, by current standards, the control arm is a relatively low-dose treatment. Issues of organ movement with EBRT, not addressed at the time, and implant technique have been discussed in depth previously [10,14]. The radiotherapy schedule and techniques were contemporary with those in widespread use in the UK reflecting contemporary practice.

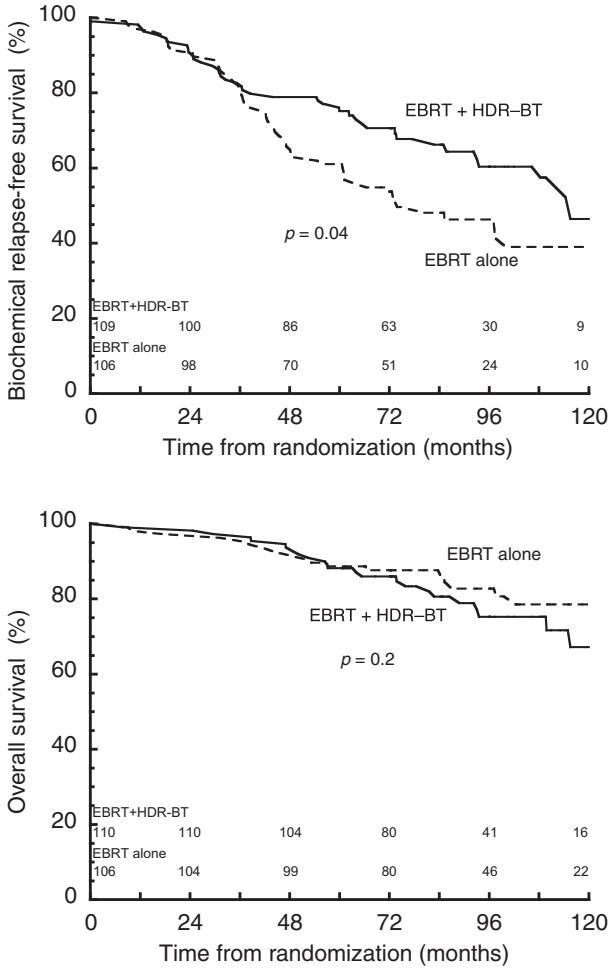

Fig. 2. Kaplan–Meier survival curves for patients free of biochemical and or clinical failure (top panel) and overall survival (bottom panel). Solid line: external-beam radiotherapy plus high-dose-brachytherapy boost (EBRT + HDR-BTb). Dashed line: external-beam radiotherapy alone (EBRT). Number of patients at risk is shown against each time interval.

Table 3
Five- and 7-year Kaplan–Meier rates of biochemical relapse free survival (bRFS) and overall survival (OS), Kaplan–Meier rates and prevalence of severe genitourinary and gastrointestinal adverse events.

Endpoint	Analytical procedure	At 5 years	At 7 years	p value
bRFS				
Arm 1	K–M	61%	48%	0.04
Arm 2		75%	66%	
OS				
Arm 1	K–M	89%	88%	0.2
Arm 2		88%	81%	
Genito-urinary				
Arm 1	K–M	26%	30%	0.5
Arm 2		26%	31%	
Genito-urinary				
Arm 1	Prevalence	9%	4%	5 year: 1.0
Arm 2		8%	11%	7 year: 0.4
Urethral strictures				
Arm 1	K–M	2%	2%	0.1
Arm 2		6%	8%	
Gastro-intestinal				
Arm 1	K–M	6%	6%	0.8
Arm 2		7%	7%	
Gastro-intestinal				
Arm 1	Prevalence	0%	2%	7 year: 1
Arm 2		0%	0%	

Abbreviation: K–M, Kaplan–Meier estimate.

After a median follow-up time of 7.1 years, an 18% increase in RFS was obtained relative to EBRT alone, reflecting a 31% reduction in the risk of recurrence ($p = 0.01$) and no evidence of an increase in long-term severe urinary or rectal morbidity, demonstrating an overall therapeutic gain (Table 3). Results of treatment outcome and late normal tissue complications are shown in Supplementary Tables 4 and 5 for a series of EBRT plus HDR-BT boost schedules where a biological effective dose (BED) calculation can be obtained and have a median follow-up of at least 4 years [6,15–27]. The BED_{2Gy}, calculated using an α/β of 1.5 and 3 Gy for tumour response and 3 and 5 Gy for late effects, was used to identify and compare regimens delivering similar BED_{2Gy}. Using tumour $\alpha\beta$ ratios of 1·5 and 3 Gy the BED_{2Gy} for the experimental arm is 92 and 80 Gy and for the control arm 67 and 63 Gy, respectively (Supplementary Table 4).

A diversity of radiotherapy schedules have been investigated in the last 10 years or so to explore the feasibility and efficacy of EBRT combined with a boost of HDR-BT (Supplementary Table 4). Comparisons between series are fraught with methodological difficulties; for example the use of prostate versus pelvic external beam irradiation, unreported dose inhomogeneities across the target volume with brachytherapy, varying risk categories treated and reported, absence or use of androgen deprivation and length of follow-up, etc. In addition, the use of different criteria to define time to biochemical failure, the use of time to biochemical failure and biochemical relapse-free survival (bRFS) as interchangeable endpoints and the fact that some studies include clinical relapse as part of the bRFS endpoint further confound the issue. Bearing in mind these caveats, a comparison with series that have similar follow-up times, radiotherapy techniques and endpoints show that a RFS of 75% at 5 years and 66% at 7 years, as reported here, is somewhat low compared with schedules of comparable or even lower biological dose effectiveness (Supplementary Table 4). These results may reflect not only the relatively low dose with EBRT, but the fact that over half of patients were in the high-risk category with an entry criteria which allowed PSA up to 50 μg/l. Since the two arms are well balanced for these predictive parameters through the randomisation these drawbacks should not detract from the advantage seen with HDR brachytherapy.

Because of the continually evolving nature of radiation damage, late effects are difficult to record and report and morbidity can vary substantially throughout the follow-up period, particularly with

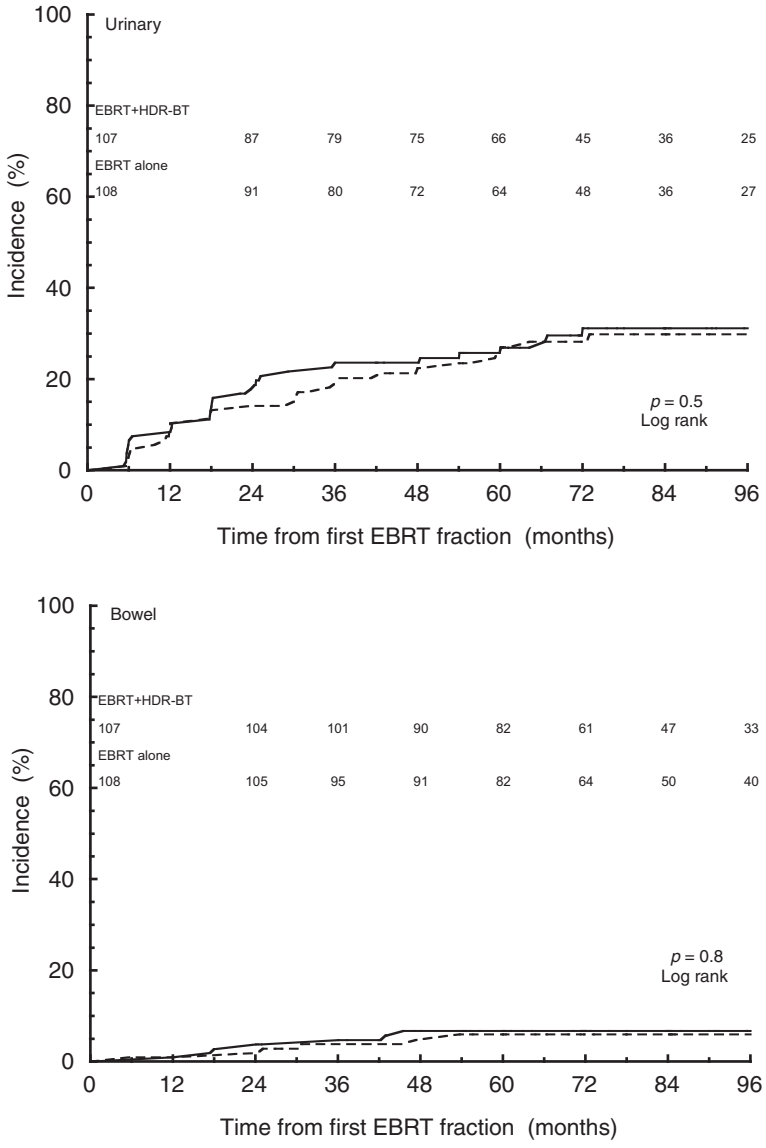

Fig. 3. Incidence of severe Grade 3 urinary (top) and bowel events (bottom) from 6 months to 8 years after radiotherapy. Solid line: external-beam radiotherapy plus high-dose-brachytherapy boost (EBRT + HDR-BTb). Dashed line: external-beam radiotherapy alone (EBRT).

long follow-up. Differences in the scoring systems, methods of analyses, variability in timing and frequency of follow-ups also confound cross-comparisons between series. Both actuarial 5-year rates and prevalence seen in this present study (Table 3) are somewhat higher than those reported by others (Supplementary Table 5), which may be partly explained by the issues discussed above and by the fact that many adverse events in this series were transient in nature and therefore the Kaplan–Meier method will overestimate the occurrence. Kaplan–Meier rates for strictures managed surgically in patients treated with EBRT + HDR-BT are similar to that reported by others (Table 3 and Supplementary Table 5). Importantly in this randomised series there is no evidence of an increase in urethral stricture formation, severe late urinary, or bowel adverse events when EBRT is combined with a boost of HDR-BT (Table 3).

In conclusion this randomised trial has demonstrated that HDR brachytherapy combined with external beam radiotherapy is effective in achieving dose escalation in the radical radiotherapy of intermediate and poor risk localised prostate cancer. The clear dose response seen by Martinez et al. [6] supports not only the role of escalated radiation and use of hypo-fractionated regimes but also the concept of a much lower $\alpha\beta$ ratio for prostate cancer than for normal genitourinary and rectal epithelia [6,28]. The radiobiology of prostate cancer suggests that using large doses per fraction could be an efficient means of achieving radiation dose escalation and for the patient and healthcare system is highly cost effective. With a substantial increase in biochemical relapse-free survival, reduced acute morbidity and no increase in severe late toxicity these results confirm that HDR-BT should be considered in future programmes aimed at dose escalation and a future randomised trial should compare this with optimal high dose intensity modulated external beam radiotherapy.

Conflicts of interest

No potential conflict of interests.

Acknowledgements

The authors are grateful to Professor Soren Bentzen for providing statistical advice during the protocol design. Funding came from the UK Department of Health, Mount Vernon Cancer Research Funds and the National Cancer Research Network, Mount Vernon Hospital. The funding bodies had no role in the design, data acquisition, analysis, interpretation of the data, in the writing of the report, or in the decision to submit the paper for publication.

Trial registration: Trial registration number ISRCTN98241100, registered with ISRCTN at http://www.controlled-trials.com/isrctn/

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2012.01.007.

References

[1] Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;72:980–8.
[2] Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007;8:475–87.
[3] Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67–74.
[4] Zietman AL, DeSilvio ML, Slater JD, Rossi Jr CJ, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005;294:1233–9.
[5] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–31.
[6] Martinez AA, Gonzalez J, Ye H, Ghilezan M, Shetty S, Kernen K, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int J Radiat Oncol Biol Phys 2011;79:363–70.
[7] Koukourakis G, Kelekis N, Armonis V, Kouloulias V. Brachytherapy for prostate cancer: a systematic review. Adv Urol 2009:1–11.
[8] Yoshioka Y, Konishi K, Oh RJ, Sumida I, Yamazaki H, Nakamura S, et al. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. Radiother Oncol 2006;80:62–8.
[9] Martinez AA, Gustafson G, Gonzalez J, Armour E, Mitchell C, Edmundson G, et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:316–27.
[10] Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiother Oncol 2007;84:114–20.
[11] Roach 3rd M, Hanks G, Thames Jr H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74.
[12] Dische S, Warburton MF, Jones D, Lartigau E. The recording of morbidity related to radiotherapy. Radiother Oncol 1989;16:103–8.
[13] Kwok Y, Yovino S. Update on radiation-based therapies for prostate cancer. Curr Opin Oncol 2010;22:257–62.
[14] Hoskin PJ, Bownes PJ, Ostler P, Walker K, Bryant L. High dose rate afterloading brachytherapy for prostate cancer: catheter and gland movement between fractions. Radiother Oncol 2003;68:285–8.
[15] Arruda-Viani GA, Pellizzon AC, Guimaraes FS, Jacinto AA, Dos Santos Novaes PE, Salvajoli JV. High dose rate and external beam radiotherapy in locally advanced prostate cancer. Am J Clin Oncol 2009;32:187–90.
[16] Astrom L, Pedersen D, Mercke C, Holmang S, Johansson KA. Long-term outcome of high dose rate brachytherapy in radiotherapy of localised prostate cancer. Radiother Oncol 2005;74:157–61.
[17] Chen YC, Chuang CK, Hsieh ML, Chen WC, Fan KH, Yeh CY, et al. High-dose-rate brachytherapy plus external beam radiotherapy for T1 to T3 prostate cancer: an experience in Taiwan. Urology 2007;70:101–5.
[18] Demanes DJ, Rodriguez RR, Schour L, Brandt D, Altieri G. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. Int J Radiat Oncol Biol Phys 2005;61:1306–16.
[19] Duchesne GM, Williams SG, Das R, Tai KH. Patterns of toxicity following high-dose-rate brachytherapy boost for prostate cancer: mature prospective phase I/II study results. Radiother Oncol 2007;84:128–34.
[20] Eulau SM, Van Hollebeke L, Cavanagh W, Gottesman JE, Mate TP. High dose rate 192Iridium brachytherapy in localized prostate cancer: results and toxicity with maximum follow-up of 10 years. Int J Radiat Oncol Biol Phys 2000;48:149.
[21] Galalae RM, Kovacs G, Schultze J, Loch T, Rzehak P, Wilhelm R, et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:81–90.
[22] Hsu IC, Cabrera AR, Weinberg V, Speight J, Gottschalk AR, Roach 3rd M, et al. Combined modality treatment with high-dose-rate brachytherapy boost for locally advanced prostate cancer. Brachytherapy 2005;4:202–6.
[23] Kalkner KM, Wahlgren T, Ryberg M, Cohn-Cedermark G, Castellanos E, Zimmerman R, et al. Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: a 6-year follow-up. Acta Oncol 2007;46:909–17.
[24] Kaprealian T, Weinberg V, Speight JL, Gottschalk AR, Roach III M, Shinohara K, et al. High-dose-rate brachytherapy boost for prostate cancer: comparison of two different fractionation schemes. Int J Radiat Oncol Biol Phys 2012;82:222–7.
[25] Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:204–12.
[26] Neviani CB, Miziara MA, De Andrade Carvalho H. Results of high dose-rate brachytherapy boost before 2D or 3D external beam irradiation for prostate cancer. Radiother Oncol 2011;98:169–74.
[27] Zwahlen DR, Andrianopoulos N, Matheson B, Duchesne GM, Millar JL. High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. Brachytherapy 2010;9:27–35.
[28] Dasu A. Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? Clin Oncol (R Coll Radiol) 2007;5:289–301.