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Original Article

Long-term survival after low-dose-rate brachytherapy for prostate cancer: the Royal Surrey experience

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Objectives

To assess the long-term treatment efficacy of low-dose-rate (LDR) brachytherapy for the treatment of localized prostate cancer.

Patients and Methods

Cause-of-death annotation in our prospective database was supplemented with death certificate information obtained via an internal audit of patients treated from 1999 to 2017 with LDR prostate brachytherapy as monotherapy or as combination with androgen deprivation therapy and/or external beam radiotherapy. Overall and disease-specific survival were the primary outcomes, estimated with Kaplan–Meier and competing risks multi-state models. Clinical variables influencing mortality were assessed with Cox proportional hazards regression in a sub-analysis of men to assess the predictive value of prostate-specific antigen (PSA) level at 48 months post implant.

Results

The audit process began in October 2017 and culminated in June 2020 with a curated series of 2936 patients. All-cause and prostate cancer-specific death prevalence were 11% and 2.9%, respectively. The median (range) follow-up time was 10 (3–21) years and the median (range) time to death from any cause was 9 (3–21) years. At 15 years post implant the overall and prostate cancer-specific survival probability were 81% and 95%, respectively. The 15-year cumulative incidence rates of death not due and due to prostate cancer were 14% and 5%, respectively. A greater risk of death due to prostate cancer was conferred by increasing age at therapy (hazard ratio [HR] 1.1, $P < 0.001$), advanced clinical stages relative to T1a-T2a (HR 1.9, $P = 0.048$ for T2b; HR 2.7, $P = 0.023$ for T2c-T3b) and a 48-month PSA level >1.0 ng/mL (HR 6.8, $P < 0.001$).

Conclusion

This study constitutes the largest retrospective analyses of long-term mortality outcomes from prospectively collected prostate brachytherapy data and confirms the excellent treatment efficacy of LDR prostate brachytherapy for localized prostate cancer. T2 clinical stage subdivisions and 48-month PSA level >1.0 ng/mL appear to be strong indicators of prostate cancer-related survival.

Keywords

low dose rate, brachytherapy, prostate cancer, 48-month PSA, stage, long-term survival

Introduction

Low-dose-rate (LDR) prostate brachytherapy, for treatment of localized disease, was first performed at the Royal Surrey Hospital (RSH) in 1999. To date, more than 4500 patients have been registered in our LDR prostate brachytherapy programme, with more than 300 implants consistently delivered per pre-COVID-19 year.

Measuring and demonstrating optimal performance in outcomes is key to maintaining delivery of high-quality care. In compliance with the RSH Cancer Strategy, an internal audit was implemented to obtain up-to-date survival metrics for all patients who had undergone LDR prostate brachytherapy since the inception of the programme. The primary objective was to ascertain the long-term efficacy of LDR prostate brachytherapy. Secondary aims were to determine survival outcomes of patients with features of a high risk of prostate cancer recurrence, and outcomes of patients presenting post treatment with rising PSA levels.

In the present paper, we report the results of the audit, explore factors influencing survival, and compare outcomes

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with those of other longstanding brachytherapy programmes published in the medical literature.

Patients and Methods

Patient Selection, Treatment and Follow-up

Patients enrolled in our prospectively maintained database (BrachyBase) were selected if they had documented pre-treatment PSA, clinical stage and total Gleason score, were >3 years post implant and had at least three post implant PSA follow-up values. Risk of relapse was defined by criteria from the National Institute for Health and Care Excellence [1]. Disease relapse was defined by evidence of clinical progression and/or evidence of biochemical failure (nadir+2 definition).

Our brachytherapy technique and treatment protocol have been described elsewhere [2–4]. Brachytherapy with I-125 delivered 145 Gy for monotherapy or 110 Gy for a boost to external beam radiotherapy (EBRT). A two-stage technique was used up to 2007, after which the 4D Brachytherapy one-stage, real-time technique was adopted [2]. Adjuvant EBRT in combination with brachytherapy was prescribed as 45 Gy in 25 fractions delivered to the pelvis by three-dimensional conformal EBRT. In 2007, the prescription dose changed to 44 Gy in 22 fractions delivered to the prostate and seminal vesicles. The highest-risk patients (e.g. those with PSA >20 ng/mL, Gleason score >7, T3 stage) also received pelvic nodal irradiation to a total dose of 50.4 Gy in 28 fractions. Patients who received androgen deprivation therapy (ADT) in combination with EBRT and LDR prostate brachytherapy (triple therapy) had 3 months neoadjuvant hormone therapy that was continued for a further 3 months post implant. The ideal regimen and duration of ADT in combination with brachytherapy has still to be determined, therefore, clinicians used the best available evidence at the time. Less than one quarter of patients received neoadjuvant ADT for more than 1 year and no patient received ADT for more than 3 years. Patients were prescribed tamsulosin 0.4 mg daily for the first 3–6 months post implant. They were encouraged to take a phosphodiesterase type 5 inhibitor if erectile function was sub-optimal and as a preventative approach [5] once or twice per week to maintain nocturnal and early morning erections.

Patients are followed up at 3-month intervals during the first year post implant, every 6 months up to 2 years, and annually thereafter, by specialist urology nurses, either by means of telephone interviews or in the outpatient clinic as necessary. At each follow-up visit patients are monitored for PSA values.

Audit Process

Although death certificates are documents in the public domain and deceased patients are unable to give informed consent for their use, the duty of confidentiality remains after death.

As such, an application was made to the Health Research Authority's Confidentiality Advisory Group (HRA-CAG) under Section 251 of NHS Act 2006 Health Service (Control of Patient Information) Regulations 2002, which regulates the use of confidential patient information without consent.

After approval from the RSH Patient Safety and Quality/ Clinical Audit Department (Clinical Audit 517), the steps taken for retrieval of death certificate information on patients who had been lost to follow-up and had died between 1999 and 2018 were:

1. Initial query of NHS Spine to ascertain date of death (DoD), where relevant, of all patients registered in BrachyBase;
2. Identify those patients who had been lost to follow-up and whose death certificate information would be sought from NHS Digital. These were patients with a DoD in NHS Spine that lacked a DoD and/or a cause of death in BrachyBase;
3. Approval of the audit methodology from HRA-CAG for the use of confidential patient information without consent;
4. Submission of information from NHS Spine (patient names and dates of birth) to NHS Digital Medical Research Information Service with a view to obtaining information from death certificates where appropriate;
5. On receipt of data from NHS Digital, *de novo* anonymization and update of results in BrachyBase;
6. Statistical analyses and report of survival outcomes.

The audit timeline is shown in Figure S1.

Definition of a Prostate Cancer-related Death

Death certificates in the UK consist of Part I, which specifies underlying causes, and Part II, which documents contributing causes. Turner et al. [6] concluded that UK death certificates accurately identify cause(s) of death in men with prostate cancer, supporting their use in routine statistics. In the present series, prostate cancer-related death was assigned to cases where the International Classification of Diseases-10 code for prostate cancer (C61) was present in any part of the death certificate. This approach may therefore overestimate the number of prostate cancer-specific deaths. Cause of death in BrachyBase is registered as the patient having died *of* prostate cancer, *with* prostate cancer, or of causes unrelated to prostate cancer.

Statistical Analysis

All statistical analyses were performed within R statistical environment [7]. The primary outcomes of interest were

overall survival (OS) and prostate cancer-specific survival (PCSS). The 'survival' package (version 3.1-8) was used to obtain Kaplan–Meier survival probabilities, log-rank tests, multi-state cumulative incidences, and Cox proportional hazards regression (proportional hazards over time assessed with the cox.zph test) [8]. Survival objects were right-censored using the data download date. The multi-state model 1 used death from other cause as the competing risk for prostate cancer-specific death, and the multi-state model 2 included relapse as a transient state, with death after relapse and death before/without relapse as the two absorbing states [9]. The 48-month PSA value sub-analyses included 2285 patients (78%) with ≥3.5 years post implant PSA follow-up and survival. Of these, 1932 (85%) had annotated 48-month (±6 months) PSA values in BrachyBase. For the remaining 353 patients (15%) the 48-month value was derived from their PSA history by linear regression (the median [range] post implant PSA measurement count was 9 [3–22] and all cases had at least one value either side of the 48-month time point).

Table 1 Baseline demography.

Variable	
Number of cases	2936
Median (Q1–Q3) age at implant, years	66 (60–70)
PSA, *n* (%)	
<10 ng/mL	2242 (76)
10–20 ng/mL	633 (22)
>20 ng/mL	61 (2)
Clinical stage, *n* (%)	
T1a-T2a	2071 (71)
T2b	585 (20)
T2c-T3b	280 (10)
Gleason score, *n* (%)	
<7	1582 (54)
=7	1249 (43)
>7	105 (4)
Relapse risk, *n* (%)	
Low	954 (32)
Intermediate	1592 (54)
High	390 (13)
Treatment type, *n* (%)	
LDR prostate brachytherapy	1910 (65)
ADT+LDR prostate brachytherapy	608 (21)
ADT+EBRT+LDR prostate brachytherapy	418 (14)

ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; LDR, low-dose-rate; Q1–Q3, first and third quartile.

Results

We identified 388 deceased patients, of whom 272 had an unknown cause of death (Figure S1). Of the 272 patient records that were submitted to NHS Digital for the death certificate search, 162 (60%) had a matching certificate from an automated matching process. After additional manual tracing, 254 cases (93%) had a matching certificate. Of the 18 cases where the death certificate could not be traced, a review of clinical notes was undertaken to investigate causes of death. Of these, four patients were still alive as evidenced by follow-up visits in BrachyBase and seven patients had a cause of death identified from the clinical notes. For the remaining seven patients, we were not able to obtain further information and they were excluded from the audit. After updating BrachyBase with newly identified dates and causes of death and curation to completeness for biochemical failure assessment, 2936 patients were eligible for outcomes analyses of 329 deaths.

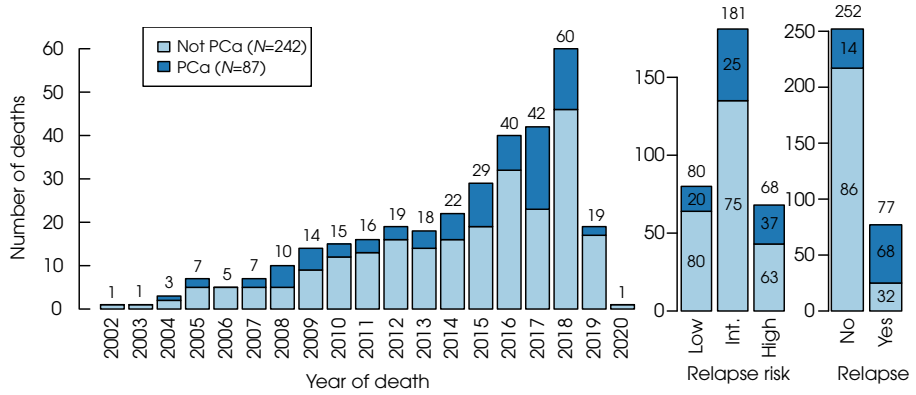
The median age at implant was 66 years (Table 1). The majority of patients had a baseline PSA value below 10 ng/mL (76%), a clinical stage T2a or below (71%), and a Gleason score < 7 (54%). Fifty-four percent of patients included in this audit were at intermediate risk and 13% were at high risk of recurrence [1]. Brachytherapy was performed as monotherapy in 65% of the cases, 21% of patients received ADT and 13% underwent triple therapy consisting of ADT, EBRT and a brachytherapy boost.

The median (range) time from implant to the data download date was 10 (3–21) years (Table S1). The median (range) time from implant to the last recorded PSA follow-up date was 6 (1–19) years. The median (range) time to disease relapse for patients with low, intermediate and high risk of relapse was 7 (1–16) years, 5 (0–14) years and 4 (1–13) years, respectively. The median time to death from causes other than prostate cancer was 8 (1–19) years and to death from prostate cancer 9 (2–17) years. The median (range) time from the last recorded visit to the data download date was 1 (0–17) years for patients who are alive, 1 (0–14) years for patients who died from causes other than prostate cancer, and 3 (0–11) years for deaths due to prostate cancer.

All patients had a minimum of three post implant PSA measurements plus the baseline. To assess robustness of PSA follow-up, and hence the estimation of biochemical control, the PSA follow-up value counts were compared to the patient's survival time (this is the number of years from LDR prostate brachytherapy to death, relapse, or to the data download date). Figure S2 shows that patients who have relapsed and are still alive have had a PSA follow-up very close to that expected in a per-protocol follow-up. In all other patients, PSA follow-up measurement count was reduced in the longer term, but was significantly positively correlated to survival.

Figure 1 shows causes of death (not due to prostate cancer or due to prostate cancer) by year of death, risk of relapse classification, and relapse status. The number of deaths increased over the years as is expected from growth and duration of the brachytherapy programme. Seventy-four percent of deaths were not due to prostate cancer and 26% were due to prostate cancer. Fifty-five percent (181 of 329) of deaths were patients with an intermediate risk of relapse

Fig. 1 Cause of death distribution by year of death (left panel), relapse risk classification (mid panel, Int. = intermediate), and relapse status (right panel). Number of deaths and proportion per category are above and inside bars, respectively. PCa, prostate cancer.



(Fig. 1, mid panel) which was equally proportional to the number of intermediate-risk patients treated (Table 1). Most deaths (252 of 329, 77%) occurred in patients with no evidence of relapse (Fig. 1, right panel) of which 35 (11% of all deaths) were classified as due to prostate cancer. Evidence of relapse was present in 25 (8% of all deaths) patients who died from causes other than prostate cancer.

The probabilities of OS and PCSS are shown in Fig. 2. At 15 years post implant, the OS and PCSS rates were 81% and 95%, respectively. Table 2 shows a summary of 10- and 15-year estimates by relapse risk and treatment type. The 15-year cumulative incidence of death from prostate cancer was 5% with competing risk by death from other causes, which showed an incidence of 14% (multi-state model 1). In a model where relapse is a transient state and death with or without relapse the two absorbing states (multi-state 2) the 15-year incidence rate of death after relapse was 4%, the incidence of death without relapse was 15%, and the incidence of relapse 10%.

The use of 48-month PSA level as a biochemical definition of cure after prostate brachytherapy was recently reported [10, 11]. Specifically, patients with a 48-month PSA ≤0.2 ng/mL had 10- and 15-year freedom-from-relapse rates of 98% and 95%, respectively [11]. We therefore investigated whether long-term PCSS may also be predicted by a 48-month PSA value. In this sub-analysis we considered 2285 patients who had survived more than 3.5 years from implant and had more than 3.5 years of PSA follow-up.

The 48-month post implant PSA level was ≤0.2 ng/mL in 1362 patients (59%), >0.2 and ≤0.5 ng/mL in 479 patients (21%), >0.5 and ≤1.0 ng/mL in 221 patients (10%), and >1.0 ng/mL in 223 patients (10%; Table S2). The median survival time was similar between the 48-month groups, irrespective of the cause of death, but the prevalence of prostate cancer-specific death was greater in patients with a PSA >1.0 ng/mL relative to cases with values ≤1.0 ng/mL (10% and ˜1%, respectively; Table S2). This was reflected in a considerably larger 15-year cumulative incidence of prostate cancer-specific death in patients with a 48-month PSA >1.0 ng/mL relative to patients in the lower PSA level groups (12% vs a maximum of 2.8%, respectively; Figure S3).

Cox proportional hazards regression adjusted for age at treatment, pre-treatment (initial) PSA, total Gleason score, clinical stage, treatment type and 48-month PSA level (Fig. 3) showed that the risk of death from *all causes* significantly increased with increasing age at brachytherapy (hazard ratio [HR] 1.1, 95% CI 1.1–1.2), advanced clinical stages relative to T1a-T2a (HR 1.5, 95% CI 1.1–2.0 for T2b and HR 1.7, 95% CI 1.2–2.6 for T2c-T3b) and by a PSA at 48 months >1.0 ng/mL (HR 1.97, 95% CI 1.3–2.9). The pre-treatment PSA, total Gleason score or treatment type were not associated with death from any cause. Age and triple therapy were the only factors associated with increased risk of death not due to prostate cancer, whereas the risk of death due to prostate cancer was significantly greater with increasing age at implant (HR 1.1, 95% CI 1.1–1.2), advanced clinical stages relative to T1a-T2a (HR 1.9, 95% CI 1.0–3.7 for T2b and HR 2.7, 95% CI 1.1–6.3 for T2c-T3b), and by a 48-month PSA >1.0 ng/mL (HR 6.8, 95% CI 3.7–12.8).

Discussion

It was possible to obtain causes of death in all but seven of the 272 cases queried. The causes of death from the death certificates, whether primary or contributing, were assessed. Altogether 329 deaths were confirmed, of which 242 were not due to prostate cancer and 87 were due to prostate cancer. With a more complete annotation of mortality events, the audit instilled precision on the survival metrics.

These outcomes are consistent with results reported by other series with 10 or more years of follow-up (Table 3). Goy

Fig. 2 Top panels: survival outcomes with the Kaplan–Meier (K-M) method for overall (OS) and prostate cancer-specific survival (PCSS). Bottom panels: competing risks probabilities for death due to prostate cancer (PCa) or due to other causes, or for deaths with or without relapse (Dw/woR, respectively). For the K-M plots the grey shade represents the 95% confidence interval. LDR-PB, low-dose-rate prostate brachytherapy.

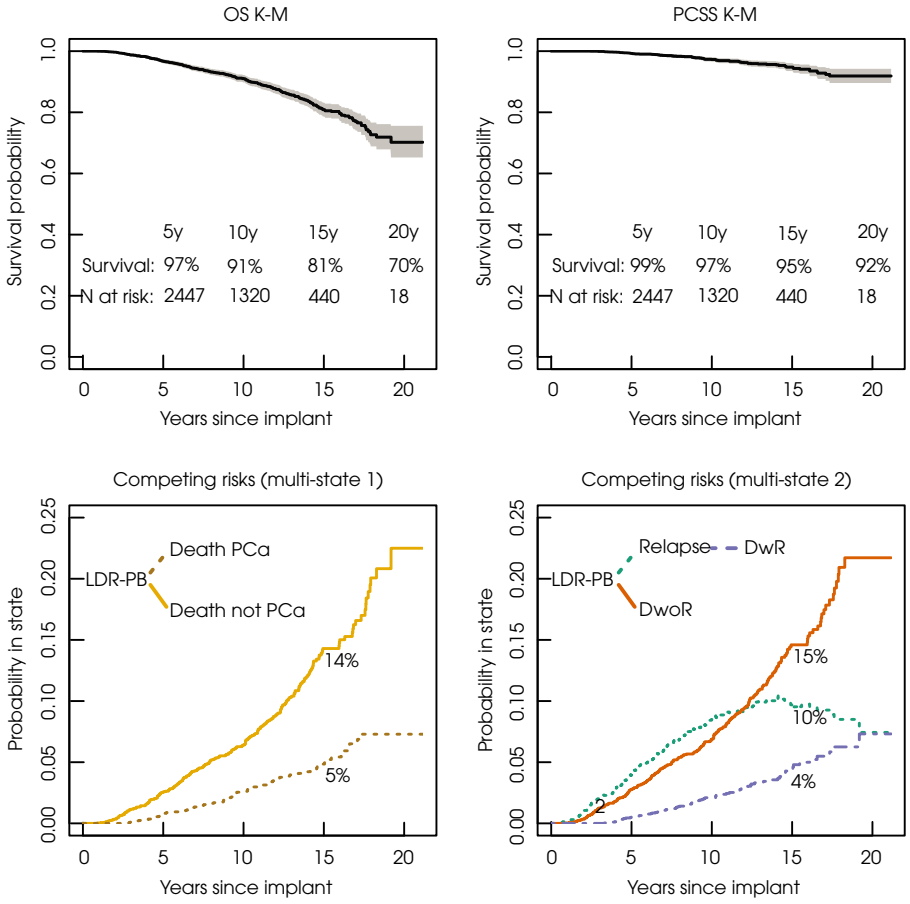


Table 2 Summary of 10- and 15-year overall and prostate cancer-specific survival estimates by relapse risk and treatment type.

	10-year			15-year			Log-rank *P* value	
	OS, %	PCSS, %	Number at risk	OS, %	PCSS, %	Number at risk	OS	PCSS
Risk of relapse								
Low	95	99	562	87	97	179	<0.001	<0.001
Intermediate	89	97	581	79	95	198		
High	87	94	177	71	88	63		
Treatment type								
LDR prostate brachytherapy	92	98	562	84	96	179	0.001	<0.001
ADT+LDR prostate brachytherapy	90	97	581	76	93	198		
Triple	87	95	177	76	91	63		

ADT, androgen deprivation therapy; LDR, low-dose-rate OS, overall survival; PCSS, prostate cancer-specific survival.

et al. [12] reported 10-year 86% OS and 97% PCSS for brachytherapy monotherapy of intermediate-risk disease (defined as T2b-c), comparable with 10-year 91% OS and 97% PCSS estimates in the present population, in which 34% of patients received LDR prostate brachytherapy as monotherapy for intermediate-risk disease (defined as T2b).

Interestingly, Goy et al. found clinical stage and Gleason score were prognostic factors for PCSS, as well as the Charlson comorbidity score to a lesser extent.

Lazarev et al. [13] reported 15-year 81% OS and 98% PCSS, also comparable with our 15-year estimates of 81% OS and

Fig. 3 Forest plots of multivariable Cox regression in the 48-month PSA sub-analysis for all cause death (overall survival model), death from causes other than prostate cancer (PCa), or death due to PCa (competing risks multi-state model 1). *P* = p value.

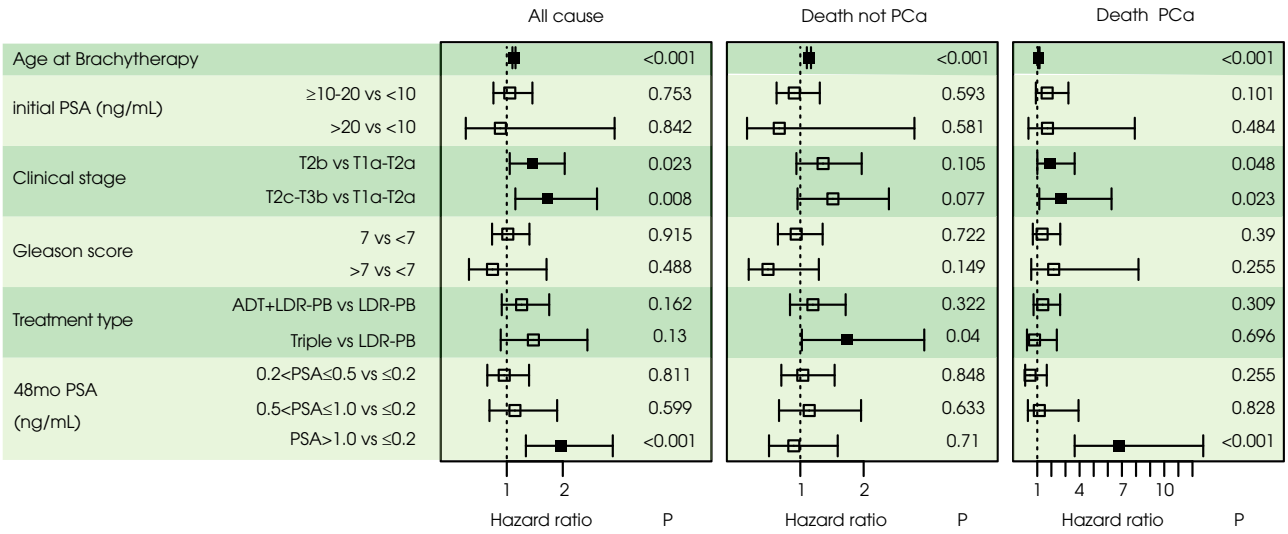


Table 3 Comparison of outcomes with those from other reports with long-term (≥10-year median) follow-up duration.

	This report	Goy et al. [12]	Lazarev et al. [13]	Sylvester et al. [14]
Year of publication	-	2020	2018	2011
Number of cases	2936	110	757	215
Median age at treatment, years	66	65.3	65	70 (mean)
Median follow-up length, years	10	9.8	12.5	11.7
Risk group stratification, %				
Low	32	0	49	74
Intermediate	54	100	23	21
High	13	0	29	5
Treatment type, %				
LDR-PB	65	73	46	100
ADT+LDR prostate brachytherapy	21	13	27	0
EBRT+LDR prostate brachytherapy	0	14	4	0
Triple	14	0	23	0
All cause deaths, %	11.2	11.8	11.4	-
PCSD, %	2.9	2.7	1.5	-
OS, %				
10 years	91	86	-	-
15 years	81	-	81	37
PCSS, %				
10 years	97	97	-	-
15 years	95	NA	98	84

95% PCSS; however, most of their patients were in the low-risk group (49%). Only age and advanced clinical stage (T3a-T3b) were found to increase the risk of OS, from a considerable number of covariates. Sylvester et al. [14] reported the outcomes of I-125 LDR prostate brachytherapy monotherapy in predominantly low-risk patients. The 15-year OS was 37%, a survival rate that was to be expected from a 70-year-old man in the general population. The prevalence of all-cause death and prostate cancer-specific death was similar to that in all studies at ˜11%. The prevalence of prostate cancer-specific deaths was low in Lazarev et al. (1.5%), which is probably an underestimation due to exclusion of events that occurred before their 10-year survival cut-off. Goy et al. reported 2.7% prostate cancer-specific deaths.

In the present analysis, 87 patients (2.96%) died from prostate cancer (Fig. 1), which is probably an overestimation from assignment by death certificate information. Turner et al. [6] found 8% of deaths categorized as 'due to other causes' by review of clinical vignettes had been assigned as

'due to prostate cancer' by death certificates (death certificate specificity of 92%), and that 9% of deaths classified as 'due to prostate cancer' by the clinical reviewers were assigned to other causes by death certificates (death certificate sensitivity of 91%). In the present study, 35 prostate cancer deaths had no evidence of relapse; of these, 29 (8.8% of all deaths) were newly assigned from death certificates obtained by the audit.

We identified a clear increase in the risk of long-term mortality with 48-month PSA levels >1.0 ng/mL. PSA is a reliable marker of response to therapy and the 48-month time point as a predictor of long-term PCSS is particularly useful in the context of LDR prostate brachytherapy because the value lies beyond biochemical failure 'bounces' that can occur 2–3 years post implant and that resolve spontaneously. Crook et al. [10] showed that the proportion of patients with a PSA <0.2 ng/mL at 48 months was on average 77.1%, but considerable variation was reported for the individual validation cohorts, ranging from 54.6% in the Australian cohort to 85.7% in the ASCENDE-RT cohort. The proportion in the present study, at 59%, falls within this range. No other study, to our knowledge, has reported a relationship between mortality in prostate cancer patients and their 48-month PSA values. The mode of response of the mortality outcomes, where only values >1.0 ng/mL at 48 months conferred an increased risk, differed to that seen for relapse-free survival, where the Kaplan–Meier analyses showed a more gradual response to the 48-month PSA level groups (Figure S3). Of patients with a 48-month PSA >1 ng/mL (n = 223), 14 relapsed before 4 years after brachytherapy. Of these, three (16%) died from prostate cancer, two (11%) died from other causes, and nine (47%) are still alive. The association between a 48-month PSA >1 ng/mL and prostate cancer mortality seems unlikely to be attributable to early treatment failure. The 48-month subset analysis also showed that triple therapy increased the risk of death not due to prostate cancer relative to brachytherapy monotherapy. Further analyses are required to fully understand the clinical significance, if any, of this association.

Recently, Van den Broeck et al [15] showed in a systematic review that biochemical failure occurring ≤18 months after radiotherapy and a Gleason score >7 had a negative impact on survival. Their observations are currently undergoing formal validation with patient-level analyses. Importantly, use of a short time to biochemical failure requires ruling out a PSA bounce. In the present series, we identified 19 patients with biochemical failure ≤18 months post implant, however, the goodness of fit of the multivariable Cox regression model improved when using a ≤24-month cut-off, where 47 cases were available. The risk of death was indeed strongly increased in patients with a short interval to biochemical failure, but it was not specific to the cause of death, and the Gleason score did not have an impact on long-term mortality (Figure S4).

The definition of risk categories continues to evolve and there is an emerging argument for using a more granular classifier, based primarily on the five-tier International Society of Urological Pathology grading system, to reduce under-/overtreatment [16]. There is no evidence, however, from the present study or others [13] to indicate that Gleason score is a significant predictor of long-term mortality. The T2 clinical stage subdivisions show a clear signal of being independent predictors imparting risk to differing extents with regard to prostate cancer-specific mortality. Thus, risk classification strategies should include a distinction for the T2 subclassifications.

In conclusion, the present study constitutes the largest retrospective analyses of long-term mortality outcomes from prospectively collected prostate brachytherapy data and confirms the excellent treatment efficacy of LDR prostate brachytherapy for localized prostate cancer. Further analyses are needed to confirm the 48-month PSA subgroup results.

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Conflict of Interest

Santiago Uribe-Lewis and Jennifer Uribe report personal fees from BXTAccelyon Limited and Theragenics Corporation, outside the submitted work. Robert Laing and Stephen Langley report personal fees, non-financial support and other from BXTAccelyon Limited, outside the submitted work. Vincent Bourke, Claire Deering, Donna Higgins, Sheel Mehta, Christos Mikropoulos, Sophie Otter, Carla Perna and Sara Khaksar have nothing to disclose.

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Abbreviations: ADT, androgen deprivation therapy; CoD, cause of death; DoD, date of death; EBRT, external beam radiotherapy; HR, hazard ratio; HRA-CAG, Health Research Authority's Confidentiality Advisory Group; iPSA, initial pre-treatment PSA; LDR, low-dose-rate; LDR-PB, low-dose-rate prostate brachytherapy; OS, overall survival; PCSS, prostate cancer-specific survival; RSH, Royal Surrey Hospital.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Audit timeline.
Figure S2. Extent of PSA follow-up.
Figure S3. Outcome response to 48-month PSA levels for all cause (overall) survival, competing risks cumulative incidence of death not due or due to prostate cancer (PCa), and relapse-free survival (RFS).
Figure S4. Forest plot of multivariable Cox regression for all cause death, deaths unrelated to prostate cancer (PCa), or due to PCa with time to biochemical failure (bF) as covariate..
Table S1. Interval times summary.
Table S2. Demography of 48-month PSA level group patients.