BJUI
BJU International

Low-dose-rate brachytherapy for the treatment of localised prostate cancer in men with a high risk of disease relapse

Robert Laing, Jennifer Uribe, Santiago Uribe-Lewis, Julian Money-Kyrle, Carla Perna, Stylianos Chintzoglou, Sara Khaksar and Stephen E.M. Langley

St. Luke's Cancer Centre, Guildford, UK

Objectives

To report clinical outcomes of ^{125}I low-dose-rate prostate brachytherapy (LDR-PB) as monotherapy or combined with androgen-deprivation therapy (ADT) and/or external beam radiotherapy (EBRT) in high-risk localised prostate cancer.

Patients and Methods

Analysis of clinical outcomes from a prospective cohort of patients treated with LDR-PB alone or combined treatment in a single institution. Men with a high risk of disease relapse were identified by the National Institute for Health and Care Excellence (NICE) criteria or by the National Comprehensive Cancer Network (NCCN) criteria. Relapse-free survival (RFS), overall survival (OS), prostate cancer-specific survival (PCSS), and metastases-free survival (MFS), were analysed together with patient-reported symptom scores and physician-reported adverse events.

Results

The NICE and NCCN criteria identified 267 and 202 high-risk patients, respectively. NICE-defined patients had significantly lower pre-treatment PSA levels, Gleason scores <7, and a greater proportion of patients who received LDR-PB monotherapy. At 9 years after implantation RFS was 89% and 87% in the NICE and NCCN groups, respectively (log-rank $P = 0.637$), and OS 93% and 94%, respectively (log-rank $P = 0.481$). All of the survival estimates were similar between LDR-PB monotherapy and combined therapies. Cox proportional hazards regression confirmed RFS was similar between the treatment types. Treatment-related toxicity was also similar between the treatment methods.

Conclusion

LDR-PB is effective at controlling localised prostate cancer in patients with a high risk of disease relapse. As the present study was not randomised, it is not possible to define those patients who need the addition of ADT and/or EBRT. However, the NICE criteria appear suitable to define treatment options where patients could benefit from LDR-PB as monotherapy or combined treatment. This choice should be discussed with the patient taking into account comorbidities and presence of multiple high-risk factors.

Keywords

LDR brachytherapy, prostate cancer, high-risk

Introduction

Low-dose-rate prostate brachytherapy (LDR-PB) using ^{125}I-seed implants is a standard therapeutic approach for low-risk localised prostate cancer and selected intermediate-risk patients [1,2]. Combined therapy, in the form of an LDR-PB boost to external beam radiotherapy (EBRT) with or without androgen-deprivation therapy (ADT), has been recommended as an option for the treatment of patients with prostate cancer with a high risk of disease relapse [1–3]. These recommendations, based on large cohort series, are now supported by Level 1 Evidence from the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) randomised controlled trial [4].

In the ASCENDE-RT trial, National Comprehensive Cancer Network (NCCN) criteria were used to identify men with high- and intermediate-risk disease. With a median follow-up of 6.5 years the trial showed superior relapse-free survival (RFS) after an ^{125}I LDR-PB boost relative to a dose-escalated EBRT boost in 398 patients who had received ADT and EBRT. Genitourinary (GU) toxicity was higher in the LDR-PB-boost trial arm.

Most long-term reports of combined therapy for high-risk disease are prospective studies with exclusive or predominant

use of ^{103}Pd seeds [5–7]. The treatment protocol for high-risk disease with the tri-modal approach, ADT, EBRT and ^{125}I-seed implant boost, described in the ASCENDE-RT trial, is similar to that used in our institution. Herewith we report on clinical outcomes and toxicity profiles of high-risk patients who have been treated in the LDR-PB programme at the Royal Surrey NHS Trust since 1999.

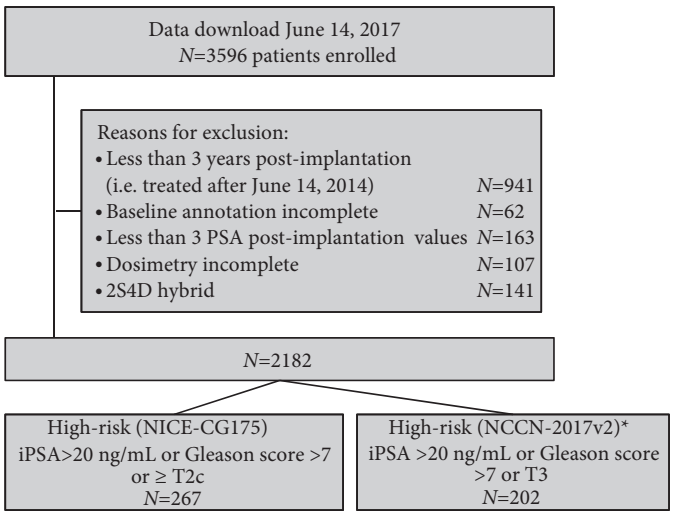
Patients and Methods

Patient Selection and Stratification

Our prospectively maintained database was accessed on 14 June 2017. From 3596 patients enrolled up to that date, we selected for patients with >3 years post-implant, a minimum of four PSA measurements (the pre-treatment initial PSA (iPSA) and three post-implantation values), documented pre-treatment clinical staging, and Gleason score. These selection steps resulted in 2182 consecutive patients available for analyses, of whom 267 (12.2%) were identified as high-risk by the National Institute for Health and Care Excellence (NICE) guideline criteria [8] and 202 (9.3%) by the NCCN criteria [9] (Fig. 1). The selection steps did not significantly alter the proportions of high-risk patients; of 3596 patients enrolled, 3506 were risk-classifiable and of these 457 (13.0%) were high-risk by NICE criteria (P = 0.5) and 359 (10.2%) by NCCN criteria (P = 0.3).

Biochemical failure was defined by a PSA value nadir plus 2 ng/mL (nadir +2) without a return to levels below the nadir +2 level (i.e. not a bounce). Treatment failure was defined as a biochemical failure and/or documented clinical failure. Metastatic status was confirmed by a review of clinical notes of patients with treatment failure.

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram for high-risk patient selection from the prospective cohort. From 3596 patients enrolled up to the data download date, 2182 were identified for further analysis of whom 267 were classified as high-risk by the NICE-CG175 criteria [8] and 202 by NCCN criteria [9]. *Patients with multiple intermediate-risk factors were included.



Therapy

Our brachytherapy technique has been described elsewhere [10,11]. The prescription dose for ^{125}I monotherapy was 145 and 110 Gy as a boost to EBRT. A two-stage technique was used up to 2007 after which the 4D Brachytherapy real-time technique was adopted [10,11].

For patients who received adjuvant EBRT combined with brachytherapy the prescription dose was 45 Gy in 25 fractions delivered to the pelvis by 3D-conformal EBRT. In 2007, the prescription dose changed to 44 Gy in 22 fractions delivered to the prostate and seminal vesicles. Patients with the highest risk (e.g. Gleason >7, T3) received pelvic nodal irradiation to 50.4 Gy in 28 fractions. Patients who received triple therapy (ADT+EBRT+LDR-PB) had 3 months neoadjuvant hormone therapy, which was continued for a further 3 months after implantation. The ideal regimen and duration of ADT combined with brachytherapy has still to be determined, therefore clinicians used the best available evidence at the time. Less than 22% of patients received neoadjuvant ADT for >1 year and no patient received ADT for >3 years.

Patients were prescribed tamsulosin 400 mg daily for the first 3–6 months after implantation. They were encouraged to take a phosphodiesterase type 5 inhibitor if erectile function was sub-optimal and as a preventative approach [12] once or twice per week to maintain nocturnal and early morning erections.

Dosimetry

A post-implantation CT was conducted in all patients for post-implantation dosimetry and quality assurance. Post-implantation dosimetry values were not significantly different between treatment types (not shown).

Toxicity Outcomes

As previously described [13], urinary and bowel toxicity scores were obtained using the international prostate symptom score (IPSS) questionnaire (including the urinary quality-of-life [QoL] domain) and the bowel function subscale of the European Organisation for Research and Treatment of Cancer (EORTC) prostate-specific QLQ-PR25 questionnaire. The International Index of Erectile Function (five-item version, IIEF-5) questionnaire was used for assessment of erectile function. Patients with complete scores documented at baseline and follow-up visits were included in the analysis. The number of patients for each QoL assessment is shown in Table S1. Physician-reported toxicity was assessed by the

Common Terminology Criteria for Adverse Events grading system (CTCAE) version 3 [14].

Statistical Analysis

Statistical analyses were performed within R statistical environment (R Foundation for Statistical Computing, Vienna, Austria) [15]. The 'survival' package was used for Kaplan–Meier estimates of RFS, overall survival (OS), prostate cancer-specific survival (PCSS), metastasis-free survival (MFS), log-rank tests and Coxph regression (proportional hazards confirmed with the coxzph test). Survival objects were right censored using the data download date. Categorical data (proportions) were analysed using Fisher's exact test. Unpaired two-tailed *t*-tests were used for continuous data.

Results

We identified 267 and 202 high-risk patients using the NICE and NCCN criteria, respectively (Fig. 1). High-risk patients defined by NICE criteria had lower iPSA levels, a greater proportion of patients with a Gleason score <7, and a greater proportion of patients treated with LDR-PB monotherapy relative to the NCCN-defined group (Table 1). The NICE-defined group also showed that all LDR-PB monotherapy patients had a single high-risk factor, where 59 (90%) were defined as high-risk by a clinical stage T2c, three (5%) by an iPSA >20 ng/mL, two (3%) by a Gleason >7, and two (3%) by a clinical stage T3 (Fig. S1). Conversely, 57 ADT+LDR-PB patients (97%) had a single high-risk factor, where 45 (76%) were high-risk defined by a stage T2c, 11 (19%) by a Gleason >7, and one (2%) by an iPSA >20 ng/mL. Two (3%) ADT+LDR-PB patients had more than one high-risk factor, one a T2c with Gleason >7 and one T3 with Gleason >7 (Fig. S1). For triple therapy (ADT+EBRT+LDR-PB) patients, 114 (80%) had a single high-risk factor, where 46 (32%) were defined as high-risk by a T2c clinical stage, 19 (13%) by a T3 stage, 23 by an iPSA >20 ng/mL, and 26 by a Gleason >7. In all, 27 (19%) patients had two high-risk factors; 20 with a Gleason >7 (of whom nine a T2c and 11 a T3 clinical stage) and seven with an iPSA >20 ng/mL (of whom four and three patients were T2c and T3 clinical stage, respectively). One patient had three high-risk factors (T2c, Gleason >7 and iPSA >20 ng/mL; Fig. S1).

Kaplan–Meier analyses showed 7- and 9-year post-implantation RFS estimates of 91% and 89% in the NICE-defined group, respectively, and 90% and 87% in the NCCN-defined group, respectively (log-rank $P = 0.637$; Fig. 2 – left panel). These estimates included 43 (16%) and 35 (17%) NICE- and NCCN-defined patients, respectively, with a PSA follow-up time <3 years, of whom 10 (4%) and nine (4%) NICE- and NCCN-defined patients, respectively, had treatment failure within the first 3 years after implantation.

RFS estimates were similar between treatment types (Fig. 2 – mid and right panels, and Table 2) and after adjustment for age at therapy, iPSA, Gleason score, clinical stage, and dose received (multivariable Cox proportional hazards regression, Table S2). The proportions of patients with controlled disease (relapse-free) were similar between the three treatment regimens, as were the proportions of patients with metastasis, patients alive with or without disease, prostate cancer-specific or non-specific deaths (Table 2). All death events unrelated to prostate cancer had no evidence of disease progression. OS of all high-risk NICE-defined patients showed 94% and 93% survival at 7 and 9 years after implantation, respectively, and in the high-risk NCCN-defined patients, 94% and 94% survival, respectively (log-rank $P = 0.481$, not shown). OS estimates were similar between treatment types (Table 2), as were PCSS and MFS.

Health-related QoL assessments are shown in Fig. 3. The IPSS and urinary domain scores showed that the acute rise soon after treatment with gradual return to baseline was not different between treatment types. Scores for bowel symptoms were not significantly different between treatments nor were the proportion of patients with preserved potency (defined by an IIEF-5 score >11 at base and post-implantation follow-up).

There were 34 Grade 2 and one Grade 3 adverse events by CTCAE version 3.0 criteria in 27 (10%) patients (not shown). Of Grade 2 events, there were 10 urinary stricture/stenosis, eight GU haemorrhages, five rectal haemorrhages, three urinary incontinence, two cystitis, two dysuria, two severe perineal pain, one proctitis, and one GU obstruction. The single Grade 3 event was a urinary stricture/stenosis. Of the 35 adverse events, 22 occurred after triple therapy, of these nine were urinary stricture/stenosis, six GU haemorrhages, three rectal haemorrhages, one cystitis, one dysuria, one proctitis, and one urinary incontinence. The single Grade 3 event of urinary stricture/stenosis occurred in a patient who received ADT+LDR-PB. The incidence of all GU events was 7.2% for LDR-PB (with or without ADT) and 12.7% for triple therapy (Fisher's $P = 0.2$). The incidence of urinary stricture/stenosis, the most common adverse event, was 1.6% for LDR-PB (with or without ADT) and 6.3% for triple therapy (Fisher's $P = 0.07$).

Discussion

Our present results compare favourably with respect to ASCENDE-RT, where the primary endpoint was biochemical progression-free survival with failure events identified by a PSA value over a nadir +2 ng/mL threshold. The 7– and 9-year Kaplan–Meier biochemical progression-free survival estimates were 83% and 78%, respectively for high-risk patients defined by NCCN criteria [16]. In our present cohort of high-risk patients the 7- and 9-year Kaplan–Meier RFS estimates were 90% and 89%, respectively in patients who

Table 1 Patients' characteristics.

Variable	NICE-defined patients	NCCN-defined patients	*P*
Number of patients	267	202	
Median (range)			
Age, years	66 (49–81)	66 (49–81)	0.983
Follow-up*, years	9.6 (3–18.1)	8 (3–18.1)	0.185
PSA follow-up†, years	5.8 (1–15.7)	5.1 (1.2–15.7)	0.793
iPSA level, ng/mL	8.75 (1.1–73)	10.95 (2.2–73)	0.04
N (%)			
iPSA, ng/mL			
<10	158 (59)	93 (46)	0.131
10–20	73 (27)	73 (36)	0.153
>20	36 (13)	36 (18)	0.308
cT Stage			
T1c–T2a	37 (14)	37 (18)	0.314
T2b	28 (10)	28 (14)	0.393
T2c	166 (62)	101 (50)	0.185
T3	36 (13)	36 (18)	0.308
Gleason score			
<7	99 (37)	34 (17)	<0.001
7	108 (40)	108 (53)	0.099
>7	60 (22)	60 (30)	0.182
Treatment type			
LDR-PB	66 (25)	26 (13)	0.01
ADT+LDR-PB	59 (22)	39 (19)	0.576
ADT+EBRT+LDR-PB	142 (53)	137 (68)	0.111

**Time from implantation to data download date; †Time from implantation to last available PSA level follow-up date.*

received combined ADT+EBRT+LDR-PB whether defined as high-risk by NICE or by NCCN criteria (Table 2).

We found no difference in any of the survival estimates between treatment types. Monotherapy used in 66 (25%) patients performed equally efficiently to double- or triple-therapy patients (Fig. 2). Of note, 40 of the 66 (61%) monotherapy patients were in fact intermediate-risk disease by NCCN criteria (i.e. only one intermediate risk factor). This result may indicate that monotherapy could be a treatment option for selected patients with high-risk prostate cancer defined by a clinical stage T2c (i.e. by the NICE-CG175 definition [8]) with low-risk iPSA levels and Gleason scores or with a single intermediate- or high-risk factor.

A comparison of GU and gastrointestinal morbidity between ASCENDE-RT and our present study is limited by differences in morbidity scoring systems. The ASCENDE-RT trial used a modified Late Effects Normal Tissue Task Force – Subjective, Objective, Management, Analytic (LENT-SOMA) scale to report adverse events [17], whereas we used the CTCAE-version 3 score. ASCENDE-RT reported a significant increase in acute Grade 2 GU morbidity in the LDR PB boost arm (30% Grade 2 crude incidence vs 16% in the dose-escalated EBRT arm). We saw no statistically significant difference in the incidence of GU adverse events between LDR-PB, with or without ADT, and triple therapy (7.2% vs 12.7%, respectively). GU toxicity has been linked to a high brachytherapy radiation dose delivered to the membranous urethra in the GU diaphragm region [18]. Our favourable GU toxicity results may therefore be explained by a reduced dose to the membranous urethra as delivered by the 4D-Brachytherapy technique [19], which utilises both stranded and loose seeds, as well as real-time intraoperative dose planning.

Results from radiation and surgical approaches to treatment of patients with high-risk prostate cancer are difficult to compare in the absence of prospective randomised trials, differences in risk stratification criteria, and definition of biochemical failure. Additionally, patients treated with EBRT or LDR-PB are often older, have more comorbidities and worse prognostic features. Results from the Prostate Cancer Study Group published in 2012 [20] compared outcomes from studies involving high-risk patients treated with surgery (N = 5149), EBRT (N = 3828), and brachytherapy (with or

Fig. 2 RFS. Kaplan–Meier analyses of RFS in high-risk disease defined by NICE and NCCN criteria (left panel) and by treatment types (mid and right panel). See Table 2 for breakdown of estimates by treatment type.

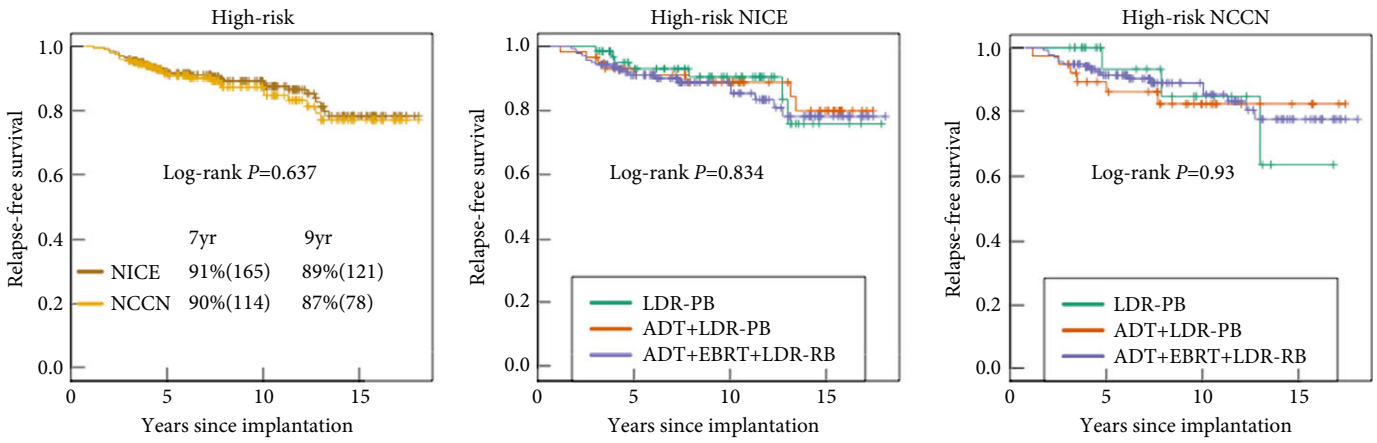
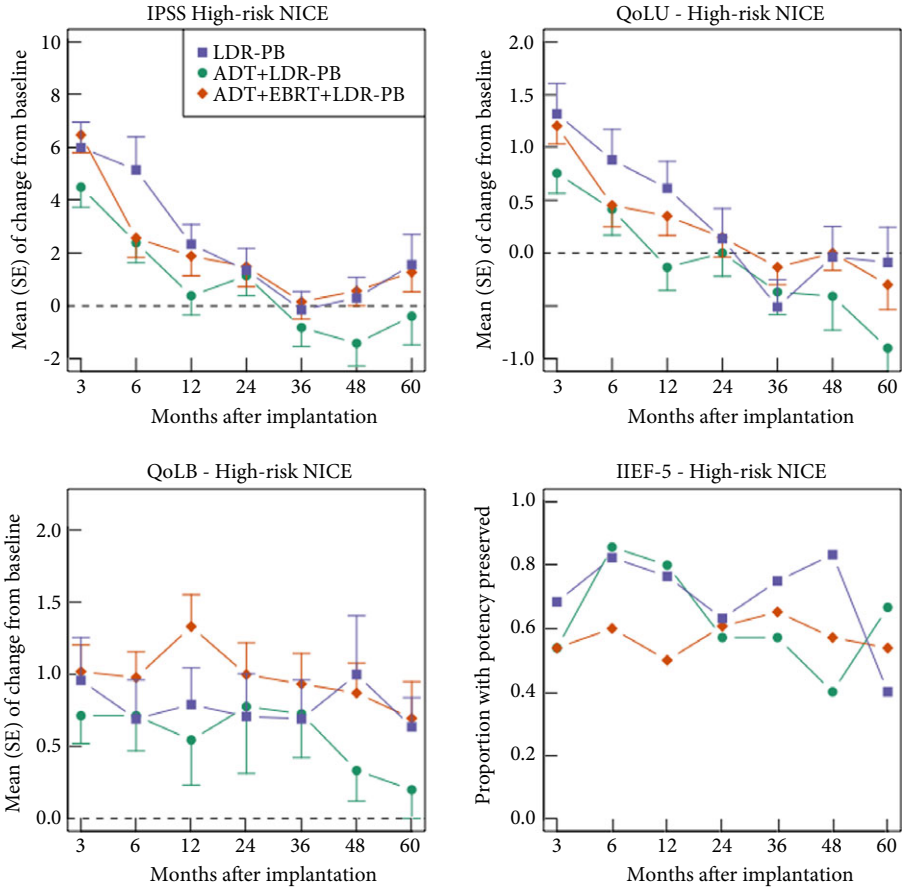


Table 2 Summary of status and survival estimates by risk classification group and treatment type.

	NICE-defined patients			NCCN-defined patients		
	LDR-PB (*N* = 66)	ADT+LDR-PB (*N* = 59)	ADT+EBRT+LDR-PB (*N* = 142)	LDR-PB (*N* = 26)	ADT+LDR-PB (*N* = 39)	ADT+EBRT+LDR-PB (*N* = 137)
N (%)						
Relapse-free	59 (89)	51 (86)	123 (87)	23 (88)	33 (85)	119 (87)
Relapse	7 (11)	8 (14)	19 (13)	3 (12)	6 (15)	18 (13)
Metastasis	1 (2)	5 (8)	10 (7)	1 (4)	5 (13)	10 (7)
Alive	61 (92)	54 (92)	132 (93)	25 (96)	37 (95)	130 (95)
Deceased	5 (8)	5 (8)	10 (7)	1 (4)	2 (5)	7 (5)
AWOD	60 (91)	50 (85)	127 (89)	24 (92)	33 (85)	124 (91)
AWD	1 (2)	4 (7)	5 (4)	1 (4)	4 (10)	6 (4)
DPCa	1 (2)	3 (5)	6 (4)	0 (0)	2 (5)	5 (4)
DNPCa.NEP	4 (6)	2 (3)	4 (3)	1 (4)	0 (0)	2 (1)
DNPCa.EP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Estimate (95% CI); *N* at risk						
RFS*						
7 year	93 (100–87); 43	91 (99–84); 44	90 (95–85); 78	93 (100–82); 13	86 (98–76); 27	90 (96–85); 74
9 year	91 (99–83); 32	89 (98–81); 35	89 (95–83); 54	85 (100–67); 9	83 (97–71); 18	89 (95–83); 51
OS*						
7 year	95 (100–89); 43	95 (100–89); 46	93 (98–88); 81	100 (100–100); 14	94 (100–87); 30	92 (98–87); 76
9 year	95 (100–89); 34	95 (100–89); 37	91 (97–86); 56	100 (100–100); 11	94 (100–87); 21	92 (98–87); 53
PCSS*						
7 year	98 (100–95); 43	96 (100–91); 46	95 (99–91); 81	100 (100–100); 14	94 (100–87); 30	94 (99–90); 76
9 year	98 (100–95); 34	96 (100–91); 37	95 (99–91); 56	100 (100–100); 11	94 (100–87); 21	94 (99–90); 53
MFS*						
7 year	98 (100–95); 41	95 (100–89); 42	94 (99–90); 76	95 (100–85); 13	92 (100–84); 27	94 (98–90); 71
9 year	98 (100–95); 31	90 (99–81); 33	94 (99–90); 51	95 (100–85); 9	84 (99–72); 18	94 (98–90); 48

*DPCa, death from prostate cancer; DNPCa.EP, Death not due to prostate cancer with evidence of progression; DNPCa.NEP, Death not due to prostate cancer and no evidence of progression; AWD, alive with disease; AWOD, alive without disease. *Log-rank P value not significant (>0.05) for the comparison between treatment types in NICE or NCCN-defined groups.*

Fig. 3 Health-related QoL assessments by treatment type. IPSS, urinary and bowel QoL (QoLU and QoLB, respectively) assessments show the mean and standard error (SE) of the change in scores at the follow-up visits relative to baseline. For erectile function the plot shows the proportion of potent patients (IIEF-5 score >11) at follow-up relative to the number of potent patients at baseline. All time points showed a non-significant *P* value (>0.05) for the comparison between treatment types (Student's *t*-test in IPSS, QoLU and QoLB plots and by Fisher's test in the IIEF-5 plot).



without ADT and/or EBRT, $N = 4390$). For high-risk patients, PSA relapse-free progression was superior after EBRT combined with brachytherapy relative to brachytherapy alone, surgery alone, or EBRT alone. However, Ciezki et al. [21] recently reported in a large non-randomised study of 2557 high-risk patients defined by NCCN criteria that LDR-PB ^{125}I-seed implantation can be superior to EBRT or radical prostatectomy for disease control of high-risk prostate cancer with reduced toxicity.

A recent review of surgical series [3] reported biochemical RFS rates ranging from 27% to 55% at 10 years after treatment (defined with a 0.2 ng/mL cut-off). Our present results show 89.2% RFS 10 years after implantation by the Phoenix (nadir +2) definition and that 92% of relapse-free patients with an available PSA 10 years after implantation had a PSA level of ≤0.2 ng/mL (Fig. S2).

The high-risk prostate cancer population is heterogeneous. Our present data indicate that monotherapy is an option for high-risk patients with low iPSA and Gleason scores, where RFS estimates were similar to patients who underwent triple therapy.

Our present prospective study is unable to determine the extent to which brachytherapy contributed to outcomes in the triple therapy patients. However, ASCENDE-RT now clearly shows that clinical outcome is dependent upon the addition of an LDR-PB component to the radiation delivery.

In conclusion, LDR-PB should be offered to patients with high-risk prostate cancer. The choice between monotherapy and combined treatment should be discussed with the patient taking into account comorbidities and presence of multiple intermediate- or high-risk factors. The NICE criteria identify greater numbers of 'favourable' high-risk disease patients and, as shown by the long-term clinical outcomes we report here, the NICE criteria can be used to determine suitable treatment options where patients could benefit from LDR-PB as monotherapy or in combined treatment.

Acknowledgements

Robert Laing and Stephen E.M. Langley conceived and designed the study. Robert Laing, Jennifer Uribe, Julian Money-Kyrle, Sara Khaksar, Stylianos Chintzoglou and Stephen E.M. Langley acquired data. Santiago Uribe-Lewis, Jennifer Uribe, Robert Laing and Stephen E.M. Langley analysed and interpreted data. Santiago Uribe-Lewis performed statistical analyses. Santiago Uribe-Lewis, Jennifer Uribe, Robert Laing and Stephen E.M. Langley wrote the manuscript with critical revisions from all authors.

Conflict of Interest

Robert Laing and Stephen E.M. Langley report personal fees, non-financial support and other from BXTAccelyon, outside the submitted work. Jennifer Uribe, Santiago Uribe-Lewis, Julian Money-Kyrle, Carla Perna, Sara Khaksar, and Stylianos Chintzoglou have nothing to disclose.

References

1 **Davis BJ**, **Taira AV**, **Nguyen PL et al.** ACR appropriateness criteria: permanent source brachytherapy for prostate cancer. *Brachytherapy* 2017; 16: 266–76

2 **Mottet N**, **Bellmunt J**, **Bolla M et al.** EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017; 71: 618–29

3 **Spratt DE**, **Soni PD**, **McLaughlin PW et al.** American Brachytherapy Society Task Group Report: combination of brachytherapy and external beam radiation for high-risk prostate cancer. *Brachytherapy* 2017; 16: 1–12

4 **Morris WJ**, **Tyldesley S**, **Rodda S et al.** Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; 98: 275–85

5 **Stock RG**, **Cesaretti JA**, **Hall SJ**, **Stone NN**. Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormonal therapy. *BJU Int* 2009; 104: 1631–6

6 **Lee WR**, **Sharkey J**, **Cowan JE**, **DuChane J**, **Carroll PR**, **CaPSURE Investigators**. Prostate brachytherapy: a descriptive analysis from CaPSURE. *Brachytherapy* 2007; 6: 123–8

7 **Sylvester JE**, **Grimm PD**, **Blasko JC et al.** 15-year biochemical relapse free survival in clinical Stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007; 67: 57–64

8 **NICE**. Prostate Cancer: Diagnosis and Management. Clinical guideline [CG175], 2014. Available at: https://www.nice.org.uk/guidance/cg175. Accessed April 2018

9 **NCCN**. NCCN Clinical Practice Guidelines in Oncology – Prostate Cancer, 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed April 2018

10 **Langley SE**, **Uribe J**, **Uribe-Lewis S et al.** Comparative analysis of clinical outcomes and procedural costs between the conventional two-stage technique and 4D brachytherapy for early prostate cancer. *Clin Oncol (R Coll Radiol)* 2018; 30: 57–64

11 **Langley SE**, **Laing RW**. 4D Brachytherapy, a novel real-time prostate brachytherapy technique using stranded and loose seeds. *BJU Int* 2012; 109(Suppl. 1): 1–6

12 **Zelefsky MJ**, **Shasha D**, **Branco RD et al.** Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. *J Urol* 2014; 192: 868–74

13 **Henderson A**, **Laing RW**, **Langley SE**. Quality of life following treatment for early prostate cancer: does low dose rate (LDR) brachytherapy offer a better outcome? A review *Eur Urol* 2004; 45: 134–41

14 **National Cancer Institue, Cancer Therapy Evaluation Program**. Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed April 2018

15 **R Core Team** *R: A Language and Environment for Statistical Computing*, Vienna, Austria: R Foundation for Statistical Computing, 2017 Available at: http://www.r-project.org/. Accessed April 2018

16 **Morris WJ**. Is ASCENDE-RT Still Pertinent? Is LDR-PB Obsolete? 2016. Available at: https://www.prostatebrachytherapy.org.uk/2016-presentations/J-Morris 170516.pdf. Accessed April 2018

17 **Rodda S**, **Tyldesley S**, **Morris WJ et al.** ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; 98: 286–95

18 **McLaughlin PW**, **Liss AL**, **Nguyen PL et al.** ACR appropriateness criteria® locally advanced, high-risk prostate cancer. *Am J Clin Oncol* 2017; 40: 1–10

19 **Nobes JP**, **Khaksar SJ**, **Hawkins MA**, **Cunningham MJ**, **Langley SE**, **Laing RW**. Novel prostate brachytherapy technique: improved dosimetric and clinical outcome. *Radiother Oncol* 2008; 88: 121–6

20 **Grimm P**, **Billiet I**, **Bostwick D et al.** Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int* 2012; 109(Suppl. 1): 22–9

21 **Ciezki JP**, **Weller M**, **Reddy CA et al.** A comparison between low-dose-rate brachytherapy with or without androgen deprivation, external beam radiation therapy with or without androgen deprivation, and radical prostatectomy with or without adjuvant or salvage radiation therapy for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; 97: 962–75

Correspondence: Robert Laing, St. Luke's Cancer Centre, Royal Surrey Hospital, Guildford, GU2 7XX, UK.

e-mail: robertlaing@nhs.net

Abbreviations: ADT, androgen-deprivation therapy; ASCENDE-RT, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (trial); CTCAE, Common Terminology Criteria for Adverse Events (grading system); EBRT, external beam radiotherapy; EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer quality of life questionnaire prostate specific 25-item; GU, genitourinary; IIEF-5, five-item version of the International Index of Erectile Function; iPSA, initial PSA; LDR-PB, low-dose-rate prostate brachytherapy; MFS, metastases-free survival; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; OS, overall survival; PCSS, prostate cancer-specific survival; QoL, quality of life; RFS, relapse-free survival.

Supporting Information

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

Figure S1. Risk stratification criteria breakdown of NICE-defined high-risk patients. (A) Jitter plot for pretreatment initial PSA (iPSA) levels, Gleason score and clinical stage (cStage) of NICE-defined high-risk patients treated with low-dose-rate prostate brachytherapy (LDR-PB) monotherapy, androgen-deprivation therapy (ADT) and brachytherapy (ADT+LDR-PB) or ADT and external beam radiotherapy (EBRT) with a brachytherapy boost (ADT+EBRT+LDR-PB). B. Summary table of number of high-risk factors by treatment modality.

Figure S2. 10-year RFS and 0.2 ng/mL PSA cut-off in NICE-defined relapse-free patients. A. Kaplan–Meier RFS estimates at 5 and 10 years after implantation. Dashed lines represent the 95% CI. B. Bar plot for the proportion of patients with a PSA ≤0.2 ng/mL at ≥5 years after implantation.

Table S1. Number of high-risk NICE patients with complete values at baseline and follow-up time points by treatment type.

Table S2. Relapse-free survival (RFS) Cox proportional hazards regression.