BJUI
BJU International

Long-term oncological outcomes and toxicity in 597 men aged ≤60 years at time of low-dose-rate brachytherapy for localised prostate cancer

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

St Luke's Cancer Centre, Guildford, Surrey, UK

Objectives

To report oncological and functional outcomes of men treated with low-dose-rate (LDR) prostate brachytherapy aged ≤60 years at time of treatment.

Patients and Methods

Of 3262 patients treated with LDR brachytherapy at our centre up to June 2016, we retrospectively identified 597 patients aged ≤60 years at treatment with ≥3-years post-implantation follow-up and four prostate-specific antigen (PSA) measurements, of which one was at baseline. Overall survival (OS), prostate cancer-specific survival (PCSS) and relapse free survival (RFS) were analysed together with prospectively collected physician-reported adverse events and patient-reported symptom scores.

Results

The median (range) age was 57 (44-60) years, follow-up was 8.9 (1.5-17.2) years, and PSA follow-up 5.9 (0.8-15) years. Low-, intermediate- and high-risk disease represented 53%, 37% and 10% of the patients, respectively. At 10 years after implantation OS and PCSS were 98% and 99% for low-risk, 99% and 100% for intermediate-risk, and 93% and 95% for high-risk disease, respectively. At 10 years after implantation RFS, using the PSA level nadir plus 2 ng/mL definition, was 95%, 90% and 87% for low-, intermediate-, and high-risk disease, respectively. Urinary stricture was the most common genitourinary adverse event occurring in 19 patients (3.2%). At 5 years after implantation erectile function was preserved in 75% of the patients who were potent before treatment.

Conclusion

LDR brachytherapy is an effective treatment with long-term control of prostate cancer in men aged ≤60 years at time of treatment. It was associated with low rates of treatment-related toxicity and can be considered a first-line treatment for prostate cancer in this patient group.

Keywords

brachytherapy, age, survival, toxicity, #ProstateCancer, #PCSM

Introduction

Prostate cancer is the most common cancer in males in the UK, where 46 690 men were newly diagnosed with prostate cancer in 2014, of these 11% were aged <60 years at time of diagnosis [1]. Life expectancy in the UK in 2013–2015 reached 40.4 years for a man aged 40 years and 22.5 years for a man aged 60 years [2]. Thus a man aged between 40 and 60 years may be expected to live beyond 80 years. The impact of any therapeutic method in terms of disease control and treatment-related side-effects could therefore have long reaching consequences. Lifestyle priorities may differ in younger patients. Considerations such as preservation of erectile function and urinary continence are likely to be foremost in the selection of a treatment method.

Radical prostatectomy (RP) used to be the preferred option recommended for younger men based on the premise that long-term outcomes for brachytherapy were unknown and that radiation-based treatments could be used as salvage option in case of primary treatment failure. As long-term data have become available, studies have shown that low-dose-rate (LDR) brachytherapy is a treatment option that affords equivalent, or superior long-term oncological control [3].

Clinical guidelines for the treatment of localised prostate cancer have been published by several authoritative bodies and concur in recommending brachytherapy as a treatment option either as monotherapy, or combined with hormone therapy (HT) and/or external beam radiation therapy (EBRT),

BJU International © 2017 BJU International | doi:10.1111/bju.13946
Published by John Wiley & Sons Ltd. www.bjui.org

depending on pre-treatment risk stratification and a life-expectancy of >10 years [4–7]

The prostate brachytherapy programme at our hospital commenced in 1999; from the outset a prospective, customised web-based data registry was designed and implemented to comprehensively collect data on treatment parameters, medical outcomes, patient-reported symptom scores, and quality-of-life (QoL) questionnaires. Patients are followed-up for a minimum of 10 years after treatment. At the time of analysis we had treated 3262 patients with LDR brachytherapy using ^{125}I seeds, of whom 597 were aged ≤60 years at time of treatment.

In the present study, we report oncological outcomes together with acute and long-term genitourinary, gastrointestinal, and erectile function outcomes of patients aged ≤60 years at time of treatment.

Patients and Methods

Our database was accessed on the 7 July 2016. The patient population consisted of patients who were aged ≤60 years at the time of treatment with ≥3 years post-implantation follow-up and a minimum of four PSA level measurements, including an initial pre-treatment PSA level (iPSA) and three post-implantation values. This resulted in 597 patients for analysis. Disease risk stratification followed the guidelines issued by the National Institute for Health Care and Excellence (NICE) [6], where low-risk is defined by clinical stage T1–T2a AND a Gleason score of ≤6 AND PSA level of <10 ng/mL; intermediate-risk is T2b OR Gleason score 7 OR PSA level of 10–20 ng/mL; high-risk is ≥T2c OR Gleason score 8–10 OR PSA level of >20 ng/mL. Biochemical failure was defined by a PSA nadir plus 2 ng/mL (nadir + 2) without a return to levels below the nadir + 2 value (i.e. not a bounce). Treatment failure consisted of a biochemical failure and/or documented clinical failure. Our initial implantation technique was a conventional Seattle two-stage technique [8], which we modified in 2009 to a one-stage real-time 4D Brachytherapy technique [9].

Initially, patients classified as having low-risk disease received brachytherapy alone. Those with intermediate-risk disease were given androgen-deprivation therapy for 3 months before and 3 months after their brachytherapy implants. Patients with high-risk disease received a combination of 3 months of neoadjuvant androgen deprivation (NAAD), EBRT, and brachytherapy boost. HT was continued for 3 months after implantation. Less than 5% of the patients received androgen deprivation for 12 months, representing those with the highest risk cancer. Starting in 2007, our regimen was modified and patients with low-risk intermediate disease (Gleason 3+4) had brachytherapy as monotherapy [10]. Patients also received NAAD for prostate volume reduction if their gland was >60 mL. Patients were prescribed Tamsulosin 0.4 mg/day 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, once or twice per week, to maintain nocturnal and early morning erections. Patients were followed up at 6, 12 and 26 weeks for the first year, six monthly until 5 years, and annually thereafter.

Dosimetry

Our dosimetric parameters are consistent with 2007 Groupe Européen de Curiethérapie (GEC) European SocieTy for Radiotherapy and Oncology (ESTRO) recommendations for prostate [D90, the dose (reported as percentage of the prescription dose) received by 90% of the prostate; V100, V150, percentage of the prostate volume receiving 100%, 150% of the prescription dose, respectively] together with the recommended dose constraints for urethra and rectum [11]. At day 0 after implantation CT is used for quality assurance, thus enabling early dosimetric feedback.

Toxicity Outcomes

Physician-reported toxicity was assessed by the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) grading system [12]. Patient-reported symptom scores for erectile function were obtained using the five-item version of the International Index of Erectile Function (IIEF-5) questionnaire, for urinary toxicity using the IPSS questionnaire [including the urinary QoL (QoLU) domain], and for bowel toxicity using the bowel function subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire prostate specific 25-item (EORTC QLQ PR25) questionnaire. Patients with at least two score measurements including the baseline and follow-up visit (s) were used in the analysis.

Statistics

All statistical analyses were performed within R statistical environment [13]. The 'survival' package was used for overall survival, prostate cancer-specific survival, relapse-free survival, Kaplan–Meier plots, and log-rank tests. Survival objects were right censored using the data download date. Categorical data were analysed using Fisher's exact tests and continuous data with two-tailed *t*-tests.

Results

After identification of patients with >3-years post-implantation follow-up, at least four PSA measurements (including the iPSA), and who were aged ≤60 years at therapy, we obtained data on 597 men for analysis. The median age was 57 years, median follow-up was 8.9 years, median PSA follow-up was 5.9 years, and median iPSA was

6.3 ng/mL (Table 1). At the time of treatment 53%, 37% and 10% of the patients were classified as having low-, intermediate-, and high-risk disease, respectively (Table 1). In all, 72% of the patients were treated with monotherapy, and 13%, 3% and 12% with NAAD, EBRT, or a combination of all three modalities, respectively (Table 1).

In all, 13 patients died, six specifically from prostate cancer. Patients with progressive metastatic disease were recorded as death from prostate cancer. The median (range) time to death was 5.8 (2.2–12.3) years with Kaplan–Meier overall survival (OS) estimates at 5 and 10 years after implantation of ≥93% across disease risk categories (Fig. 1, top left). Prostate cancer-specific survival (PCSS) was ≥95% at 5 and 10 years after implantation, irrespective of disease risk (Fig. 1, top right). In all, 44 patients had disease relapse using the nadir + 2 definition for biochemical failure, with a median (range) time to treatment failure of 5.5 (1.5–12.3) years. Treatment failure occurred in 4% (n = 13), 10% (n = 21) and 16% (n = 10) of low-, intermediate-, and high-risk patients, respectively. Kaplan–Meier RFS estimates were 98%, 96%, and 92% at 5 years and 95%, 90%, and 87% at 10 years, for low-, intermediate-, and high-risk disease, respectively; survival estimates were statistically significantly greater for low-risk relative to intermediate- and high-risk disease (log rank P = 0.006). However, there was no statistically significant difference in RFS estimates between treatment types (Fig. 1, bottom right).

Table 1 Demographics of the patients aged ≤60 years at time of brachytherapy.

Variable	Value
Number of patients	597
Median (range)	
Age, years	57 (44–60)
Follow-up*, years	8.9 (1.5–17.2)
PSA follow-up†, years	5.9 (0.8–15)
iPSA level, ng/mL	6.3 (1–33)
N (%)	
iPSA level, ng/mL	
<10	485 (81)
10–20	102 (17)
>20	10 (2)
Stage	
T1a–T2a	469 (79)
T2b	80 (13)
T2c–T3b	48 (8)
Gleason score	
≤6	434 (73)
=7	154 (26)
≥8	9 (1)
Risk category	
Low	316 (53)
Intermediate	220 (37)
High	61 (10)
Treatment type	
BXT monotherapy	430 (72)
BXT + HT	80 (13)
BXT + EBRT	18 (3)
BXT + HT + EBRT	69 (12)

*BXT, LDR brachytherapy. *Time from brachytherapy to data download date; †Time from brachytherapy to the last PSA level date.*

The median (range) of the total dose delivered (defined by the percentage of the D90 from the prescription dose of 145 Gy for brachytherapy alone and 110 Gy for brachytherapy combined with EBRT) was 106.4 (64.1–147.3)%. There was sub-optimal dosimetry (<90% of total dose) in 36 patients (6%); however, on review none of these patients required additional EBRT or further seed implantation. Of these, three patients (0.5% of 597) had biochemical relapse, representing 7% of treatment failures (P = 0.741 for the association between failure and suboptimal dosimetry).

Toxicity Outcomes

For genitourinary toxicity, urinary stricture/stenosis was the most common adverse event, which occurred in 19 patients (3.2%, not shown). Of these, six presented Grade 1, 12 presented Grade 2, and one presented Grade 3 using the CTCAE v3.0 criteria.

ICS continence scores (not shown) were recorded from 2008. All patients (n = 207) had a score of 0 (no leakage) at baseline. Grade 0 and 1 (absent or mild - no pads required) were recorded in 99% of assessed patients at 3 months, 97% at 12 months and 100% at 5 years. Grade 2 urinary incontinence was observed at only one time point (between 3 months and 3 years) in seven patients (<0.5%) over a 5-year follow-up period.

In our 597 patients, who were followed-up for a median of 8.9 years, 22 patients (3.7%) used intermittent self-catheterisation (ISC). This was either performed in patients presenting with urinary retention or after a urethral dilatation for a urethral stricture to prevent recurrence.

Patient-reported toxicity outcomes at baseline are presented in Table 2. The IPSS questionnaire showed a median score at baseline of 4 (Table 2) and a mean change of +2 points at 5 years after implantation irrespective of treatment type (Fig. 2).

Erectile function assessed with the IIEF-5 questionnaire showed that most patients were potent at baseline (median score of 23; Table 2) and that 70–80% of brachytherapy monotherapy patients had preserved potency (defined by an IIEF-5 score >11) from 3 months to 5 years after implantation (Fig. 2). We detected no reduction in long-term potency with the use of HT. Actuarial analysis (not shown) confirmed 72% probability of potency preservation 5 years after implantation and no significant difference between treatment types (log rank P = 0.64).

Fig. 1 Survival analyses. Top panels: Kaplan–Meier curves for overall survival (OS) and prostate cancer-specific survival (PCSS) by disease risk. Bottom panels: Kaplan–Meier curves for RFS by disease risk and by treatment type (Tx). Percentage survival estimates (*n* at risk) at 5 and 10 years after implantation by disease risk categories are indicated. Int., intermediate; BXT, brachytherapy; Mono, brachytherapy monotherapy.

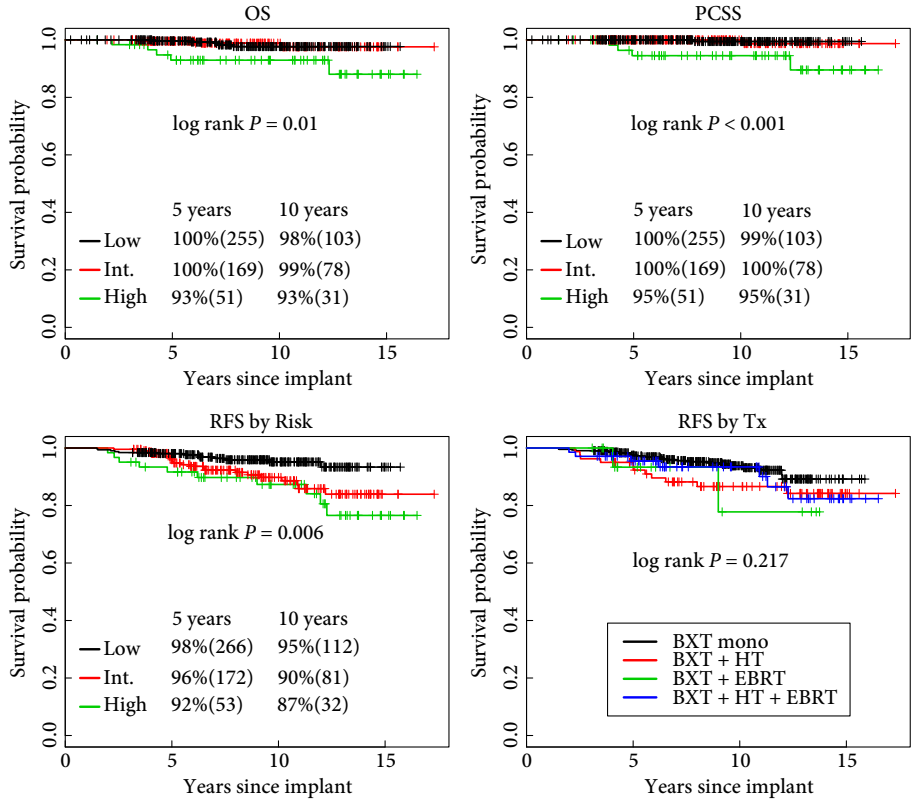


Table 2 Toxicity scores at baseline.

Score at baseline	Median (range) [*n*]
IPSS	4 (0–21) [541]
QoLU	1 (0–5) [520]
QoLB	4 (4–4) [189]
IIEF-5	23 (1–25) [464]

An additional finding was the development of Peyronie's disease in six patients (not shown).

Health-related QoL

The QoLU domain of the IPSS questionnaire showed that the large majority of patients were 'pleased' with their urinary symptoms at base (median score of 1, Table 2). An increase of 1 point in the QoLU score meant patients were 'mostly satisfied' at 3–6 months after treatment and returned to 'pleased' with their urinary condition 5 years after implantation (QoLU, Fig. 2). Bowel function (QoLB, Fig. 2) was normal at baseline (score of 4, Table 2), with an overall mean increase in score of 1 point (2 points at most) indicating changes to bowel function were 'mild' (defined by scores from 5 to 8) with a return to baseline levels 5 years after implantation.

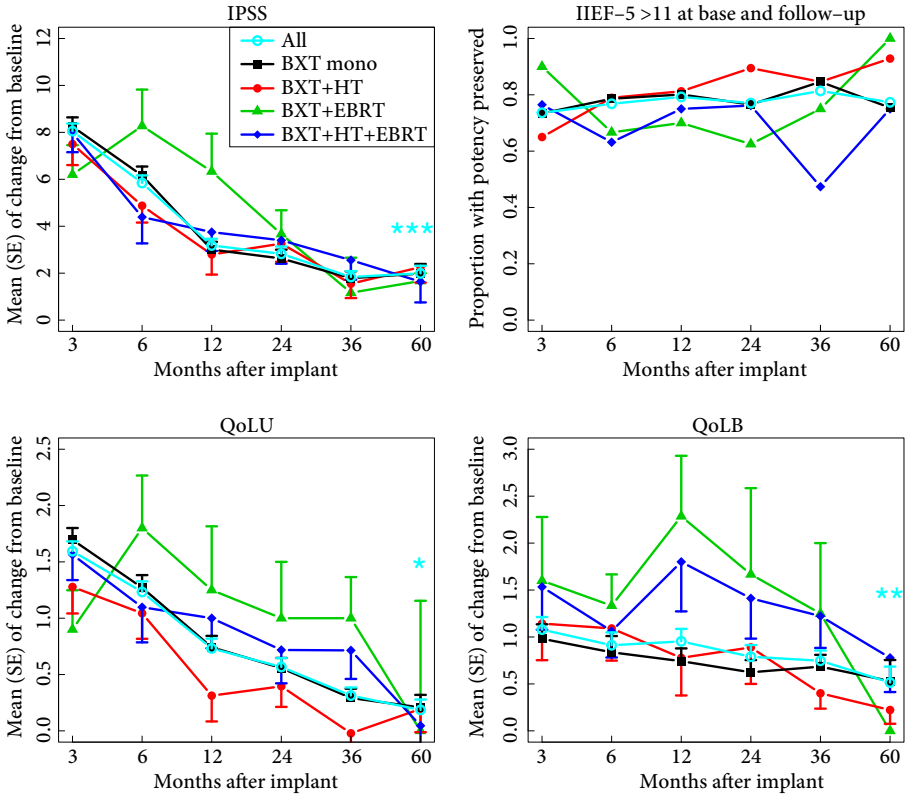
Second Primary Cancers (SPCs)

We assessed the occurrence of SPCs in this cohort of patients at ≥5 years after brachytherapy. Three patients with SPCs were identified with cancer of the rectum, urethra, and leukaemia occurring 7, 11 and 7 years after brachytherapy, respectively.

Salvage Therapy

In all, 28 patients (seven with low-, 15 with intermediate-, and six with high-risk disease) of the 44 documented with treatment failure underwent salvage therapy. Treatments included RPs in 12 patients (four with low- and eight with intermediate-risk disease), HT in eight (three with low-, three with intermediate-, and two with high-risk disease), cryotherapy in one intermediate-risk patient and androgen deprivation combined with chemotherapy and radiotherapy to pelvic lymph nodes in seven patients (three with intermediate- and four with high-risk disease). Two patients died, both from prostate cancer with high-risk disease, and 16

Fig. 2 Patient-reported toxicity outcomes. The mean and standard error (SE) of the change in scores after pre-treatment baseline in the IPSS, QoLU and QoLB. For erectile function, the proportions of patients with preserved potency at follow-up are shown, i.e. patients with an IIEF-5 score >11 at baseline and at follow-up. There were no statistically significant differences at any of the time points shown between treatment types relative to brachytherapy (BXT) monotherapy (*t*-test for continuous data and Fisher's exact test for categorical data). Asterisks summarise *P* values for *t*-tests that compared scores in baseline (not shown) and 60 months after implantation for all treatments; the absolute mean of the differences between baseline and 60 months (not shown) were 1.9, 0.2 and 0.5 for IPSS, QoLU and QoLB, respectively. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; mono, monotherapy.



patients were lost to follow-up. The remainder are being followed-up for survival.

Discussion

The present study is the largest prospectively collected series from a single institution on long-term oncological outcomes in patients treated with LDR prostate brachytherapy when aged ≤60 years. Our present results support previous reports that focused on this patient population but with smaller patient numbers [14,15] and mirrors studies on long-term outcomes with large patient numbers of all ages [16,17].

Buckstein et al. [14] reported outcomes in 131 patients who received brachytherapy with or without EBRT and/or HT when aged ≤60 years; biochemical recurrence using the Phoenix (nadir + 2) definition occurred in 13 patients (9.9%) with a median interval to recurrence of 3.7 years and only one biochemical failure after 10 years. After 10 years, only one death was related to prostate cancer and there were three deaths from other causes. Our present cohort of 597 patients had 7.4% of treatment failures, with a median interval to recurrence of 5.5 years. Six patients died from prostate cancer at a median of 6.4 years after implantation and seven died from other causes after a median of 5.9 years from treatment.

Results published by Kollmeier et al. [15] describe outcomes on 236 patients who were aged ≤60 years at LDR brachytherapy or high-dose-rate brachytherapy (11% received high-dose-rate brachytherapy which we do not use). The 8-year OS, PCSS and PSA RFS rates of 96%, 99% and 96%, respectively, were reported by Kollmeier et al., whereas in our present study they were 98%, 99% and 94%, respectively at this time point (not shown). For patients with low- and intermediate-risk disease, the 8-year RFS rates were 97% and 94% ($P = 0.34$), respectively, in the Kollmeier et al. study; and 96% and 92% ($P = 0.01$), respectively, in our present study (not shown). Kollmeier et al. did not assess patients with high-risk disease. There was no statistically significant difference in PSA RFS between brachytherapy alone and combined therapy in the Kollmeier et al. study, which concurs with our present study.

Ashamalla et al. [18] recently reported on ~16 000 men in the Surveillance, Epidemiology and End Results (SEER) database who were aged ≤60 years at the time of LDR brachytherapy (with or without EBRT) or EBRT alone. The 8-year overall prostate cancer-specific mortality was 1.9% and was significantly lower for patients who were treated with LDR brachytherapy relative to those treated with EBRT alone (1.1% vs 2.8% respectively, $P < 0.001$). These results agree with 8-year PCSS of 99% reported by the present study and by Kollmeier et al. [15].

Toxicity Outcomes

Urinary stenosis/stricture was the most common Grade 2 adverse event, occurring in 19 (3.2%) patients. The site of stricture was normally at the membranous urethra, which typically occurred 18 months after implantation, with the patient characteristically presenting with penile tip dysuria. Treatment comprised urethral dilatation followed by ISC on a weekly basis for 1 year to prevent recurrence. Only one patient had a Grade 3 treatment-related urinary stricture. The development of Peyronie's disease in six patients of the 597 aged <60 years at treatment was unexpected. Only two additional patients are documented in the rest of our database.

There was a mean change in IPSS of +2 points relative to baseline at 60 months after implantation. This is similar to data reported by Gómez-Iturriaga Piña et al. [19], who analysed brachytherapy monotherapy in patients aged ≤55 years, where +2 points in the IPSS was reported 60 months after treatment relative to the baseline. They reported a peak of 13 in the IPSS at 1–3 months after implantation from a median baseline of 6, whereas we had a peak of 8 at 3 months from a baseline of 4. These data show an acute 'moderate' effect, defined by an IPSS from 8 to 19, of brachytherapy on urinary function with a consistent return towards baseline levels soon after treatment.

Our present results on potency preservation are comparable to previous studies by Cesaretti et al. [20], where patients aged 50–59 years at implantation had a potency rate of 64% for an IIEF-5 score of ≥16 at a follow-up of ≥7 years; and Buckstein et al. [14], where 69% were potent 10 years after treatment. Similarly, Keyes et al. [21] reported potency preservation at 5 years to be 82% in men aged <55 years and 73% in patients aged 55–59 years at time of treatment.

SPCs

The development of SPC within the radiation field has been recognised as a possible, albeit rare, side-effect of EBRT [22]. The development of a SPC is considered a late radiation effect only if it fits certain predetermined criteria. Radiation-induced SPCs are defined as tumours that develop ≥5 years after radiation therapy from tissue within the irradiated field and have histopathological features different from the primary tumour [23].

In 2006, Moon et al. [24] compared 5-year occurrence of SPCs in >38 000 patients who had radiation-based therapies for prostate cancer and similar numbers who had received RP or neither. The authors showed that, despite the higher doses of radiation delivered, patients who received radioactive implants had the lowest odds of developing SPCs and their risk was similar to patients who received non-radiation-based treatments. These findings were confirmed 10 years later in a systematic review and meta-analysis of studies with large patient cohorts [25], where increased odds for SPCs relative to non-radiation treatment were consistently associated with EBRT but not with brachytherapy.

In the present study, there were three patients with SPCs of the 597 patients who were aged ≤ 60 years at time of treatment. In our entire population of 3262 patients there were 11 SPCs documented (0.3% incidence) over a 17-year period, with a median length of follow-up of 8.9 years. Of these, five were within the radiation field (two bladder, one urethral, and two rectal) and six were outside the radiation field (four haematological, one brain, one stomach). Only one patient (with a bladder SPC) received three-dimensional (3D)-conformal EBRT as an adjuvant to ^{125}I brachytherapy for intermediate-risk prostate cancer. The SPC incidence in our general population may be comparable to that reported for the UK by Musunuru et al. [26], who reported a 10-year cumulative incidence of 14.6%, 1% and 0.84% for any second malignancy, bladder and rectal cancer, respectively, after ^{125}I prostate brachytherapy as monotherapy.

The efficacy of ^{125}I-seed brachytherapy for the treatment of localised prostate cancer has withstood the test of time. In 2000, Ragde et al. [27], were the first to describe a 12-year follow-up in 219 patients with a median age of 70.5 years at treatment between 1987 and 1988. The 10-year disease-free survival for the entire cohort was 70%. Sylvester et al. [28] reported on 15-year biochemical RFS for 215 patients treated with LDR brachytherapy. The median time to biochemical failure was 5.1 years and the 15-year biochemical RFS rate was 85.9%, 79.9%, and 62.2% for low-, intermediate-, and high-risk (D'Amico classification) patients, respectively. The PCSS and OS rates were 84% and 37.1%, respectively, with an average age at treatment of 70 years. Morris et al. [17] found the actuarial rate of recurrent disease after LDR prostate brachytherapy to be ~3% at 5 years and 6% at 10 years. Our present data revealed disease recurrence rates of 3% at 5 years and 6% at 10 years in men aged ≤60 years at treatment. For men aged >60 years disease recurrence rates were 5% at 5 years and 13% at 10 years irrespective of disease risk stratification (log rank $P = 0.012$ for ≤60 vs >60 years; not shown). Although these studies differ in

demographic characteristics and analytical parameters, together they show the efficacy in long-term control of prostate cancer by LDR brachytherapy over the decades.

Critz et al. [29] evaluated long-term outcomes of 3546 patients treated with brachytherapy followed by EBRT, using a 0.2 ng/mL PSA level threshold as an indication of failure after RP. Only 5% of the 313 failures occurred after 10 years. This was similar to disease progression in long-term RP series; 4% treatment failures 10 years after surgery in 1997 men [30], 4.9% biochemical recurrence at 11–15 years after RP in 10 609 men [31], and 9% disease progression 10 years after RP in 553 men in the recently published Prostate Testing for Cancer and Treatment (ProtecT) trial [32]. The ProtecT and the Prostate Cancer Intervention Versus Observation Trial (PIVOT) randomised clinical trials assessed long-term outcomes between RP and active monitoring, and reported 10-year all-cause mortality rates of 10% and 47% and prostate cancer-specific mortality rates of 1% and 5.8%, respectively. In the present study, the all-cause mortality rate was 2% (i.e. 98% OS) and the prostate cancer-specific mortality rate was 1% (i.e. 99% PCSS), although we selected patients aged ≤60 years at time of LDR brachytherapy. ProtecT and PIVOT also showed that urinary incontinence and erectile dysfunction were significantly more frequent after RP [33,34], and ProtecT showed bowel function was significantly worse after 3D-conformal EBRT relative to RP or active monitoring [33]. Patient-reported outcome instruments differ from those used in our present study impeding a direct comparison. However, the Expanded Prostate cancer Index Composite (EPIC) instrument used in the ProtecT has previously shown LDR brachytherapy scored better in sexual and urinary domains relative to RP [35], and in the bowel domain relative to EBRT [36].

Our present study has limitations due to its retrospective nature. Although a median follow-up of nearly 9 years provides a robust estimation of long-term cancer control and toxicity, further follow-up is required to estimate the risks of secondary malignancy, albeit our present results are unlikely to differ substantially from that observed for the UK general population. Different treatment strategies were used for intermediate-risk cancer during the analysis period; there was no rigid study protocol but clinicians were using the best available evidence to decide upon individual patients' treatment.

Conclusions

LDR brachytherapy is an effective treatment, with long-term control of prostate cancer in men aged ≤60 years at time of treatment. It was associated with low rates of treatment-related toxicity and can be considered as a first-line treatment for prostate cancer in this age population. A longer follow-up is required to better estimate the risk of SPCs.

Conflicts of Interest

Stephen E.M. Langley and Robert Laing report personal fees, non-financial support and other from BXTAccelyon, outside the submitted work.

Ricardo Soares, Jennifer Uribe, Santiago Uribe-Lewis, Julian Money-Kyrle, Carla Perna and Sara Khaksar have nothing to disclose.

References

1 **Cancer Research UK.** *Prostate Cancer Statistics*, 2014. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed July 2017.

2 **Office for National Statistics.** *National Life Tables, United Kingdom: 2012–2014*. Available at; http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2015-09-23. Accessed July 2017.

3 **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

4 **National Comprehensive Cancer Network.** *NCCN Clinical Practice Guidelines in Oncology*, 2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 2017.

5 **Mottet N, Bellmut J, Briers E et al.** *EAU-ESTRO-SIOG Guidelines on Prostate Cancer*, 2016. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf. Accessed July 2017.

6 **National Institute for Health and Care Excellence.** *Prostate Cancer: Diagnosis and Management*. Clinical guideline [CG175], 2014. Available at: https://www.nice.org.uk/guidance/cg175. Accessed July 2017.

7 **Davis BJ, Horwitz EM, Lee WR et al.** American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012; 11: 6–19

8 **Grimm P, Sylvester J.** Advances in brachytherapy. *Rev Urol* 2004; 6 (Suppl. 4): S37–48

9 **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

10 **Rodrigues G, Warde P, Pickles T et al.** Pre-treatment risk stratification of prostate cancer patients: A critical review. *Can Urol Assoc J* 2012; 6: 121–7

11 **Salembier C, Lavagnini P, Nickers P et al.** Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. *Radiother Oncol* 2007; 83: 3–10

12 **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 July 2017.

13 **R Core Team.** *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2015. Available at: http://www.r-project.org/. Accessed July 2017.

14 **Buckstein M, Carpenter TJ, Stone NN, Stock RG.** Long-term outcomes and toxicity in patients treated with brachytherapy for prostate adenocarcinoma younger than 60 years of age at treatment with minimum 10 years of follow-up. *Urology* 2013; 81: 364–8

15 **Kollmeier MA, Fidaleo A, Pei X et al.** Favourable long-term outcomes with brachytherapy-based regimens in men ≤60 years with clinically localized prostate cancer. *BJU Int* 2013; 111: 1231–6

16 **Potters L, Morgenstern C, Calugaru E et al.** 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005; 173: 1562–6
17 **Morris WJ, Keyes M, Spadinger I et al.** Population-based 10-year oncologic outcomes after low-dose-rate brachytherapy for low-risk and intermediate-risk prostate cancer. *Cancer* 2013; 119: 1537–46
18 **Ashamalla H, Guirguis A, McCool K et al.** Brachytherapy improves outcomes in young men (≤60 years) with prostate cancer: a SEER analysis. *Brachytherapy* 2017; 16: 323–9
19 **Gómez-Iturriaga Piña A, Crook J, Borg J, Lockwood G, Fleshner N.** Median 5 year follow-up of 125iodine brachytherapy as monotherapy in men aged<or=55 years with favorable prostate cancer. *Urology* 2010; 75: 1412–16
20 **Cesaretti JA, Kao J, Stone NN, Stock RG.** Effect of low dose-rate prostate brachytherapy on the sexual health of men with optimal sexual function before treatment: analysis at > or = 7 years of follow-up. *BJU Int* 2007; 100: 362–7
21 **Keyes M, Pickles T, Crook J et al.** Effect of aging and long-term erectile function after iodine-125 prostate brachytherapy. *Brachytherapy* 2015; 14: 334–41
22 **Brenner DJ, Curtis RE, Hall EJ, Ron E.** Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000; 88: 398–406
23 **Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J.** ESTRO PgoG. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. *Radiother Oncol* 2014; 110: 213–28
24 **Moon K, Stukenborg GJ, Keim J, Theodorescu D.** Cancer incidence after localized therapy for prostate cancer. *Cancer* 2006; 107: 991–8
25 **Wallis CJ, Mahar AL, Choo R et al.** Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ* 2016; 352: i851
26 **Musunuru H, Mason M, Murray L et al.** Second primary cancers occurring after I-125 brachytherapy as monotherapy for early prostate cancer. *Clin Oncol (R Coll Radiol)* 2014; 26: 210–15
27 **Ragde H, Korb LJ, Elgamal AA, Grado GL, Nadir BS.** Modern prostate brachytherapy. Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000; 89: 135–41
28 **Sylvester JE, Grimm PD, Wong J, Galbreath RW, Merrick G, Blasko JC.** Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: seattle experience. *Int J Radiat Oncol Biol Phys* 2011; 81: 376–81
29 **Critz FA, Benton JB, Shrake P, Merlin ML.** 25-Year disease-free survival rate after irradiation for prostate cancer calculated with the prostate specific antigen definition of recurrence used for radical prostatectomy. *J Urol* 2013; 189: 878–83
30 **Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC.** Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591–7
31 **Loeb S, Feng Z, Ross A, Trock BJ, Humphreys EB, Walsh PC.** Can we stop prostate specific antigen testing 10 years after radical prostatectomy? *J Urol* 2011; 186: 500–5
32 **Hamdy FC, Donovan JL, Lane JA et al.** 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016; 375: 1415–24
33 **Donovan JL, Hamdy FC, Lane JA et al.** Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016; 375: 1425–37
34 **Wilt TJ, Brawer MK, Jones KM et al.** Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; 367: 203–13
35 **Crook JM, Gomez-Iturriaga A, Wallace K et al.** Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. *J Clin Oncol* 2011; 29: 362–8
36 **Ferrer M, Guedea F, Suarez JF et al.** Quality of life impact of treatments for localized prostate cancer: cohort study with a 5 year follow-up. *Radiother Oncol* 2013; 108: 306–13

Correspondence: Stephen E. M. Langley, St. Luke's Cancer Centre, Royal Surrey Hospital, Guildford, Surrey GU2 7XX, UK.

e-mail: semlangley@gmail.com

Abbreviations: 3D, three-dimensional; CTCAE v3.0, Common Terminology Criteria for Adverse Events, version 3.0; EBRT, external beam radiation therapy; HT, hormone therapy; IIEF-5, five-item version of the International Index of Erectile Function; iPSA, initial pre-treatment PSA level; ISC, intermittent self-catheterisation; LDR, low dose rate; OS, overall survival; PCSS, prostate cancer-specific survival; PIVOT, Prostate cancer Intervention Versus Observation Trial; QoLB, bowel function domain of the IPSS questionnaire; QoL, quality of life; QoLU, urinary QoL domain of the IPSS questionnaire; RP, radical prostatectomy; SPC, second primary cancer.