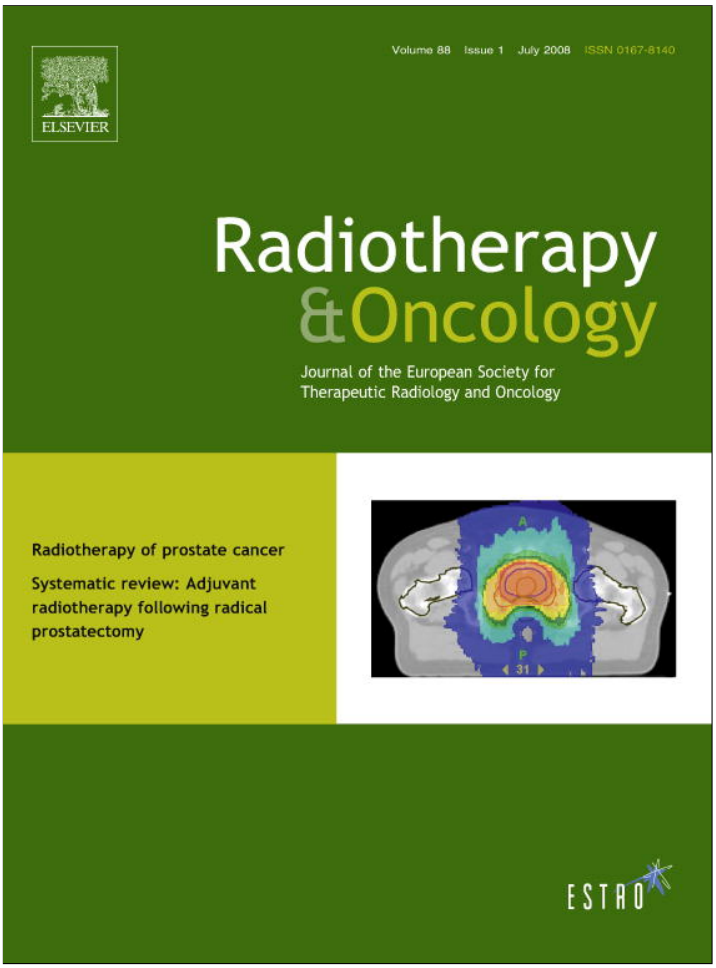

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Prostate brachytherapy

Novel prostate brachytherapy technique: Improved dosimetric and clinical outcome

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Abstract

***Purpose*: Erectile dysfunction following prostate brachytherapy is reported to be related to dose received by the penile bulb. To minimise this, whilst preserving prostate dosimetry, we have developed a technique for I-125 seed brachytherapy using both stranded seeds and loose seeds delivered with a Mick applicator, and implanted via the sagittal plane on trans-rectal ultrasound.**

***Materials and methods*: Post-implant dosimetry and potency rates were compared in 120 potent patients. In Group 1, 60 patients were treated using a conventional technique of seeds implanted in a modified-uniform distribution. From January 2005, a novel technique was developed using stranded seeds peripherally and centrally distributed loose seeds implanted via a Mick applicator (Group 2). The latter technique allows greater flexibility when implanting the seeds at the apex. Each patient was prescribed a minimum peripheral dose of 145 Gy. No patients received external beam radiotherapy or hormone treatment. There was no significant difference in age or pre-implant potency score (mean IIEF-5 score 22.4 vs. 22.6, $p = 0.074$) between the two groups.**

***Results*: The new technique delivers lower penile bulb doses (D_{25} as %mPD — Group 1: 61.2 ± 35.7, Group 2: 29.7 ± 16.0, $p < 0.0001$; D_{50} as %mPD — Group 1: 45.8 ± 26.9, Group 2: 21.4 ± 11.7, $p < 0.0001$) whilst improving prostate dosimetry (D_{90} — Group 1: 147 Gy ± 21.1, Group 2: 155 Gy ± 16.7, $p = 0.03$). At 2 years, the potency rate was also improved: Group 1: 61.7%; Group 2: 83.3% ($p = 0.008$).**

***Conclusions*: In this study, the novel brachytherapy technique using both peripheral stranded seeds and central loose seeds delivered via a Mick applicator results in a lower penile bulb dose whilst improving prostate dosimetry, and may achieve higher potency rates.**

Keywords: Prostate brachytherapy; Erectile dysfunction; Penile bulb; Implant technique

Prostate brachytherapy continues to be used as a curative treatment option for localised prostate cancer. Biochemical control rates are reported to be excellent and equivalent to those for radical prostatectomy and conformal external beam radiotherapy (EBRT) [1—3]. Thus, when discussing treatment options with the patient, issues such as post-treatment quality of life and sexual function become increasingly important [4—7]. Consequently, the selection of a treatment modality by the patient is often preceded by an extensive evaluation of treatment-related morbidity [8].

Erectile dysfunction (ED) is a common complication of all potentially curative therapies for early prostate cancer [9], and is reported to occur in 6—53% of cases after permanent prostate brachytherapy alone [10—13]. The aetiology of this is not completely understood, but is likely to be related to multiple factors, including issues such as local neurogenic and vascular compromise, as well as psychogenic causes [14]. The structures of the proximal penis, namely the penile bulb and proximal crura, have been implicated as being site-specific structures implicated in the development of ED after brachytherapy [15—17]. Two studies have shown no discernible relationship between radiation dose to the neurovascular bundles and post-treatment loss of erectile function [13,18].

In this study, we have investigated the effect of a novel brachytherapy implant technique, which aims to minimise the radiation dose delivered to the penile bulb. This technique was designed to implant stranded seeds in the peripheral prostate gland, and loose seeds centrally via the Mick applicator. Seeds are implanted under direct visualisation in the sagittal trans-rectal ultrasound plane, which allows for greater precision of seed placement, particularly at the prostatic apex. We have evaluated the effect of this

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technique in terms of radiation dosimetry to the penile bulb and prostate, as well as post-implant potency preservation.

Materials and methods

At our centre, the I-125 prostate brachytherapy programme began in March 1999. After an initial learning curve [19,20], a total of 120 patients with pre-implant potent erectile function underwent I-125 permanent prostate brachytherapy for clinical stage T1c–T2c prostate cancer (2002 American Joint Committee on Cancer) [21]. Potency was defined using the International Index of Erectile Function-5 (IIEF-5) survey score of $\geqslant$11/25 [22,23].

All the patients underwent a trans-rectal ultrasound-guided two-stage implant. Treatment plans were generated prior to the implant date using Variseed 7.1 planning software (Varian Medical Systems, Inc., Palo Alto, CA, USA), without the subsequent use of intra-operative real-time planning. Patients in Group 1 (n = 60) were treated (non-consecutively) between September 2001 and January 2004 using the classical modified-uniform implant technique, as developed in Seattle [24]. From February 2005, the novel technique was instituted, and 60 patients who underwent this technique were analysed as Group 2. For this technique, stranded seeds (RapidStrand™, Oncura, Plymouth Meeting, PA, USA) were implanted into the peripheral prostate. Following this, loose seeds were implanted more centrally using the Mick applicator through between 4 and 6 needles. All the seeds were delivered under direct vision in the sagittal trans-rectal ultrasound plane to ensure conformity to the prostate gland, particularly at the apex. Fig. 1 demonstrates pre-plan images from the mid-gland and apex, showing needle geometry and isodoses for each implant technique.

No patients received supplemental EBRT or androgen deprivation therapy. All were prescribed a minimal peripheral dose (mPD) of 145 Gy. The mean pre-treatment PSA, Gleason score, clinical stage, prostate volume, age and IIEF-5 scores were similar between the two groups, as shown in Table 1. The median Gleason score was 6 in both group (Group 1: range 3–7; Group 2: range 5–7). In terms of clinical stage, no patients were documented to have clinical or radiological extracapsular disease.

Post-implant CT imaging for dosimetric assessment was performed on day 1 [25,26], with the penile bulb contoured at 5 mm intervals on the CT images. At present, MR imaging is not available as standard practice at our centre for this purpose. The penile bulb was contoured by the authors SJK, MAH and JPN, as trained by an independent Uro-Radiologist. The physicians who contoured the penile bulb were not blinded as to which implant technique the patient underwent. Prostate and penile bulb dosimetry was recorded. Erectile function was evaluated at baseline, 12 and 24 months following treatment using the IIEF-5 score. Phosphodiesterase-5 inhibitor use, which is encouraged in the first year after implantation as part of the overall treatment protocol, was also recorded [27].

Unpaired t tests were used to make statistical comparisons between the demographic, dosimetric and clinical parameters in the two groups. Non-parametric tests were used to assess non-linear data. For all the tests, $p \leqslant 0.05$ was considered statistically significant. Statistical analysis was performed with Minitab version 14.

Results

Table 2 summarises the penile bulb post-implant dosimetry recorded for each implant technique using day 1 CT-based analysis. All dosimetric parameters were statistically lower using the novel technique. In particular, the D_{25} and D_{50} comply with previously recommended constraints of <60% and <40%mPD, respectively (Group 1 vs. Group 2: 61% vs. 30%; 46% vs. 21%, $p < 0.0001$) [16].

Prostate dosimetry also differed between the groups (Table 3). Prostate implant quality was significantly improved in Group 2 (D_{90} 147 Gy vs. 155 Gy, $p = 0.03$), with a trend to increased dosimetric coverage (V_{100} 90.7% vs. 91.7%, $p = 0.29$). However, this did not result in a simultaneous unfavourable increase in prostate V_{150} (55% vs. 53%, $p = 0.27$).

All the patients completed an IIEF-5 score at baseline and at 12 and 24 months, with a score of $\geqslant$11/25 defining potency. The distribution of IIEF-5 scores pre- and 24 months post-implant is demonstrated in Fig. 2 for both implant techniques. Table 4 illustrates potency preservation post-brachytherapy. There is a significant improvement in potency preservation using the novel technique at 2 years (61.7% vs. 83.3%, $p = 0.008$), with a greater documented use of phosphodiesterase-5 inhibitors in Group 1 (53.3% vs. 31.7%, $p = 0.016$) at this time point. Mean IIEF-5 scorer were higher in Group 2 at 12 months (14.1 vs. 18.0, $p = 0.006$) and at 24 months (12.9 vs. 17.9, $p = 0.001$). The average change in IIEF-5 score between baseline and 24 months post-implant was also significantly lower in Group 2 (−9.5 vs. −4.7, $p = 0.001$). Interestingly, there was little reduction in IIEF-5 score after 1 year (−1.2 vs. −0.07, $p = 0.37$), with 12-month potency rates being similar to those a year later (65% vs. 85%, $p = 0.011$).

Discussion

Erectile dysfunction is a common sequela of curative therapies for early prostate cancer, and can have an adverse effect on quality of life [9,28]. Although it has been claimed that preservation of erectile function is more likely after brachytherapy, the incidence of brachytherapy-induced ED is actually greater than initially described [29,30]. ED has been demonstrated in subgroup analyses in 6–90% of patients undergoing brachytherapy alone or with additional therapies such as external beam radiotherapy or androgen deprivation therapy [10–13,17,22,30,31]. The wide ranges of reported ED are likely to reflect the use of retrospective analyses, unclear definitions of potency, use of non-validated instruments to assess potency, and studies where a single question regarding erectile function was asked [32]. The rate of ED following prostate brachytherapy will also vary with age, co-morbidities, pre-potency and phosphodiesterase-5 inhibitor use of the study population. There is increasing evidence that brachytherapy-induced ED may also be technique-related and so potentially minimised by precise attention to seed placement [33].

The radiation dose to the prostate gland and its surrounding structures has been studied in order to identify an association with the development of post-implant ED. The largest body of evidence supports the penile bulb and prox-

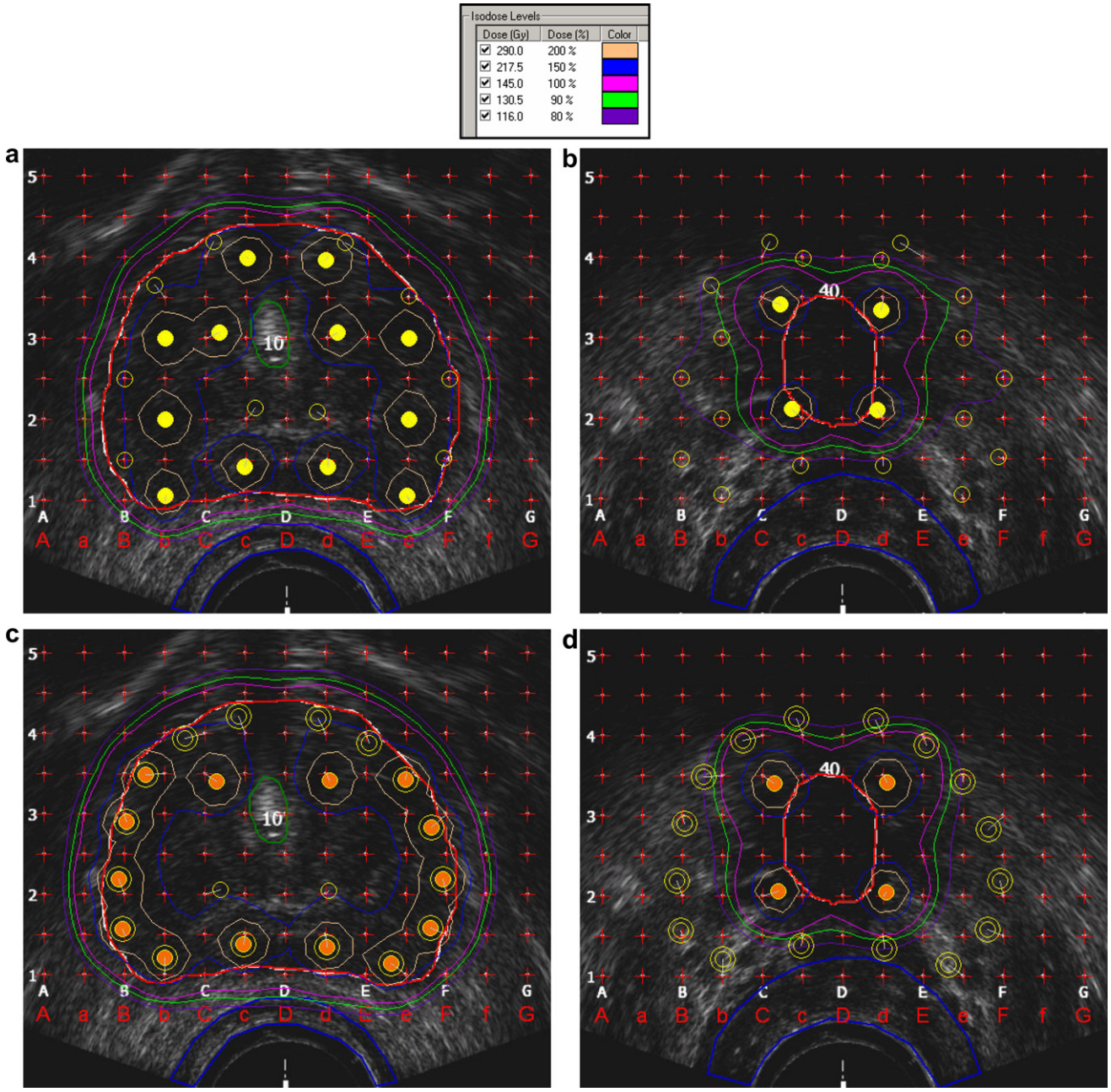

Fig. 1. Mid-gland (a) and apical (b) representation of needle geometry and isodoses for the classical modified-uniform technique and, novel implant technique (c, d) needles carrying stranded seeds are shown as double circles, those with loose seeds as single circles). Contours: prostate, red; urethra, green; rectum, blue.

imal crura, as such sites [15–17]. From these studies investigating the association between radiation dose and post-implant potency, it has been suggested that the penile bulb D_{25} be kept below 60%, and the D_{50} within 40% of the minimum prescribed dose [16].

In terms of the neurovascular bundles as a candidate structure, studies have been unable to find an association between dose received and the development of post-implant ED [13,18]. However, this may reflect the difficulty in structurally identifying the neurovascular bundles on routine post-implant CT imaging. Furthermore, due to the high density of neurovascular tissue in the region of the proximal penis, it may be that the penile bulb represents a surrogate structure for brachytherapy-induced ED, rather than being at risk *per se*.

The use of patient-completed validated sensitive and specific questionnaires such as the International Index of Erectile Function is recognised to be essential for the accurate and reliable collection of sexual quality of life data [29,34]. This requires patients to quantify erectile performance, with a score of $\geqslant 11$ indicating potency in some studies [22,23]. Although various cut-offs for potency have been used with the IIEF score [17,35], for the purpose of this analysis, and consistent with our clinical practice, $\geqslant 11$ is the value employed to define potency. We recognise that changing this va-

Table 1
Patient demographics prior to brachytherapy

Parameter	Group 1, $n = 60$ classical technique Means ± SD	Group 2, $n = 60$ novel technique Means ± SD	p Value
Age (years)	61.2 ± 5.7	62.3 ± 6.4	0.34
Prostate volume (cc)	41.5 ± 11.3	43.1 ± 13.1	0.48
Pre-implant IIEF-5 score[a]	22.4 ± 3.6	22.6 ± 3.2	0.75
Gleason score	5.8 ± 0.8	6.2 ± 0.5	0.001
PSA (ng/ml)	6.0 ± 2.8	7.0 ± 2.7	0.05
Clinical stage (n)			
T1c	34	35	0.86
T2 a–b	21	23	0.71
T2c	5	2	0.24

[a] IIEF-5, International Index of Erectile Function-5.

Table 2
Penile bulb post-implant dosimetry for each implant technique

Parameter	Group 1, $n = 60$ classical technique % Minimal peripheral dose means ± SD	Group 2, $n = 60$ novel technique	p Value
D_{10}	79 ± 50	37 ± 20	<0.0001
D_{25}	61 ± 36	30 ± 16	<0.0001
D_{50}	46 ± 27	21 ± 12	<0.0001
D_{90}	29 ± 15	13 ± 8	<0.0001

Table 3
Prostate post-implant dosimetry for each implant technique

Parameter	Group 1, $n = 60$ classical technique Means ± SD	Group 2, $n = 60$ novel technique	p Value
D_{90}	147 Gy ± 21	155 Gy ± 17	0.03
V_{100}	90.7% ± 6.0	91.7% ± 5.2	0.29
V_{150}	55.2% ± 10.3	52.8% ± 13.4	0.27

lue would obviously alter the data reported, but we hope that future work, involving larger patient cohorts, can examine the clinical significance of which value is used.

One limitation of the IIEF score is that, in order to achieve a 'potent' score, the patient is required to have been sexually active over the preceding month, rather than recording the potential to have intercourse. Nevertheless, it is to date the most widely endorsed system of evaluating erectile function, and documentation of the sequelae of prostate brachytherapy in this manner will help to further determine the aetiology of ED. Ultimately, this will lead to modifications in implant technique with consequent improved potency preservation and overall quality of life. Fortunately, most patients with brachytherapy-induced ED respond to the early use of phosphodiesterase-5 inhibitors [27,36].

The classical prostate brachytherapy implant technique employs stranded seeds implanted in a modified-uniform distribution throughout the prostate gland [24]. When these preloaded needles are implanted towards the central gland, the lack of flexibility of individual seed placement at the apex has implications for radiation dose to the penile bulb. Should the more centrally positioned strands or pre-loaded loose seeds inadvertently be placed more caudally than planned (when deposited within the prostate), they will then lie in proximity to the proximal penis. This will lead to an increased radiation dose to the penile bulb, with consequent deleterious effect on post-implant erectile function.

This study investigates the effect of a novel implant technique, in terms of radiation dose to the penile bulb and incidence of post-implant erectile dysfunction at 24 months.

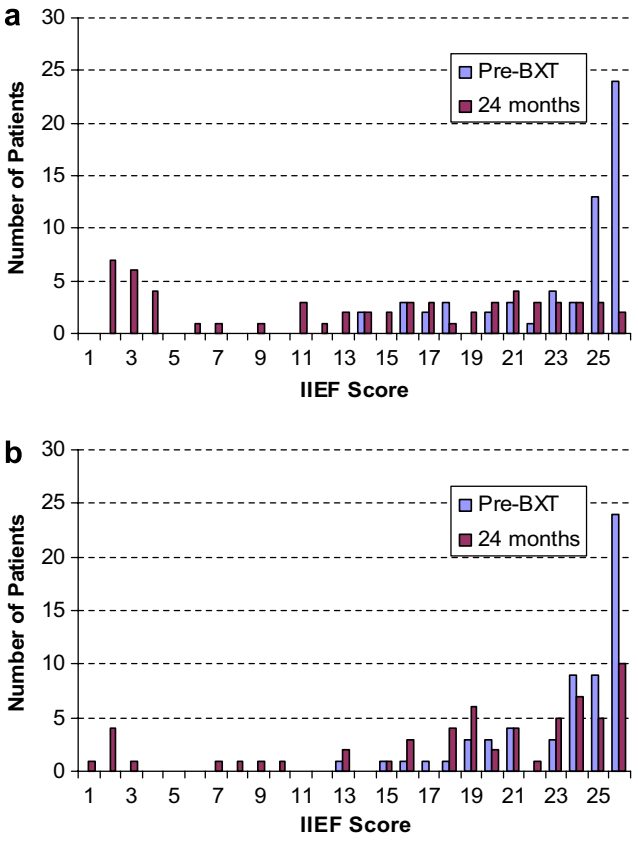

Fig. 2. Histograms of International Index of Erectile Function-5 (IIEF-5) score distributions before and 24 months after prostate brachytherapy (BXT). (a) Classical technique scores. (b) Novel technique scores.

Table 4
Post-implant potency data at 12 and 24 months

Parameter	Time post-implant (months)	Group 1, $n = 60$ classical technique	Group 2, $n = 60$ novel technique	p Value
IIEF-5 score $\geqslant$ 11/25	12	65%	85%	0.011
	24	61.7%	83.3%	0.008
Mean IIEF-5 score ± SD	12	14.1 ± 8.4	18.0 ± 6.9	0.006
	24	12.9 ± 8.3	17.9 ± 7.4	0.001
Mean change in IIEF-5 score ± SD	0–24	−9.5 ± 8.1	−4.7 ± 7.7	0.001
	12–24	−1.2 ± 8.3	−0.07 ± 5.1	0.37
PDE-5[a] inhibitor	24	53.3%	31.7%	0.016

[a] PDE-5, phosphodiesterase-5.

The use of stranded seeds (RapidStrand™) implanted in the peripheral gland is known to reduce the rate of seed migration, and consequently improve prostate coverage [37–39]. Using this technique, we have demonstrated a significant improvement in all penile bulb dosimetric parameters, as measured by day 1 CT-based dosimetry. Furthermore, the quality and coverage of the prostate dosimetry was improved, without an unwanted increase in the prostate V_{150}. At 24 months post-implant, the group of patients who underwent the modified implant technique had a higher rate of potency preservation, with a significantly reduced rate of phosphodiesterase-5 inhibitor use. This was determined using the patient-completed validated IIEF-5 score, as previously discussed.

Post-implant dosimetry at our centre is routinely acquired on day 1, and with the use of CT imaging. We acknowledge that T2-weighted magnetic resonance imaging is superior over 5 mm CT slices particularly when defining the prostatic apex and extracapsular sites such as the penile bulb and neurovascular bundles [40]. We have reported results derived from standard practice at our centre, which as yet does not involve the use of MRI; however, we anticipate the future use of this technology, which will hopefully enhance the accuracy of reported apical and bulb dosimetry. Imaging is performed on day 1 in order to receive rapid dosimetric feedback, which can have implications for technique and timely correction of areas of underdosage if necessary; this timing also allows for urethral dose to be calculated whilst the patient is still catheterised [26]. Steggerda et al. have used a combined TRUS-CT scan to assess patients on day 1, 1 month and $3\frac{1}{2}$ months after seed implantation [25]. V_{100} and D_{90} were not influenced by geometrical changes and were independent of scan date. However, we recognise that geometrical changes over time and the possibility of seed migration are arguments for the use of imaging on day 30 [41].

The quality of the data presented is limited by small numbers, being non-randomised and by the use of historical cohorts. The fact that the physicians who contoured the penile bulb were not blind to treatment technique is another potential source of bias. Nevertheless, a 24-month potency rate of 83.3% compares favourably with previous published reports of brachytherapy-induced ED, and with sexual function outcomes for radical prostatectomy and conformal EBRT [5,11,42,43]. All the patients underwent treatment at least 2 years after the prostate brachytherapy programme began in our centre, and so differences between patients in the two groups cannot be attributed to the effect of a learning curve [19,20].

Since brachytherapy-induced ED has previously been reported to be 50% at 3 years post-treatment [17], we recognise that it is important to re-evaluate our data at future time points. The patients whose data were used in this study will continue annual follow-up as per standard treatment guidelines. This will facilitate longer-term data to be eventually recorded, providing consistency with published literature, and allowing further information regarding the natural history of post-treatment potency deterioration and the effect of technique modifications on this process.

In this study, data regarding co-morbidities and lifestyle factors (such as cardiovascular disease, diabetes mellitus and smoking status) which could negatively impact erectile function were not collected [44]. Such conditions could account for differences in potency rates, especially with small group numbers. Further studies using larger, randomised patient cohorts, with analysis of the impact of other pre-existing risk factors for ED will continue to add to and improve this clinical data. It is anticipated that the consequent improvement in prostate dosimetry may also have an advantage in terms of biochemical control rates, but this will be borne out by results of future studies.

Conclusions

Using a novel prostate brachytherapy implant technique, potency was preserved in 83.3% of patients at 2 years following treatment. This was associated with improvement in penile bulb and prostate dosimetry. The results of this study confirm that technique modifications can translate into dosimetric benefit and may improve long-term potency.

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