BJUI SUPPLEMENTS

4D Brachytherapy, a novel real-time prostate brachytherapy technique using stranded and loose seeds

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This paper reviews the development of a new one-stage prostate brachytherapy technique (4D Brachytherapy) using a combination of stranded and loose seeds. This novel technique utilizes a nomogram constructed from over 1000 procedures to calculate the seed requirement in advance of the implant. This allows stranded seeds to be pre-ordered and loaded prior to the procedure rather than per-operatively, resulting in a more efficient use of operating room time. The use of both stranded and loose seeds may reduce the risk of migration from peripherally placed seeds via the venous plexus, whilst maintaining the flexibility to optimize the dose within the prostate and especially at the apex of the gland. Prospectively collected data show significantly improved dosimetry: median D_{90} 143 and 153 Gy ($P < 0.005$) and median V_{100} 88% and 93% ($P < 0.005$) for the Seattle technique and 4D Brachytherapy implant technique, respectively. Also there was a reduced short-term urinary morbidity as assessed by the change in International Prostate Symptom Score (IPSS) at 3 months and 1 year compared with the Seattle technique. Mean (SD) change in IPSS from baseline at 1 year was 2.73 (5.92) and 0.97 (5.10) for the Seattle and 4D Brachytherapy series, respectively ($P < 0.049$).

What's known on the subject? and What does the study add?
There are a number of techniques used successfully to perform brachytherapy, including 2-stage procedures and realtime techniques using loose seeds.

This study demonstrates a one-stage realtime brachytherapy technique using stranded seeds with improved time efficiency and clinical outcome: 4D Brachytherapy.

KEYWORDS

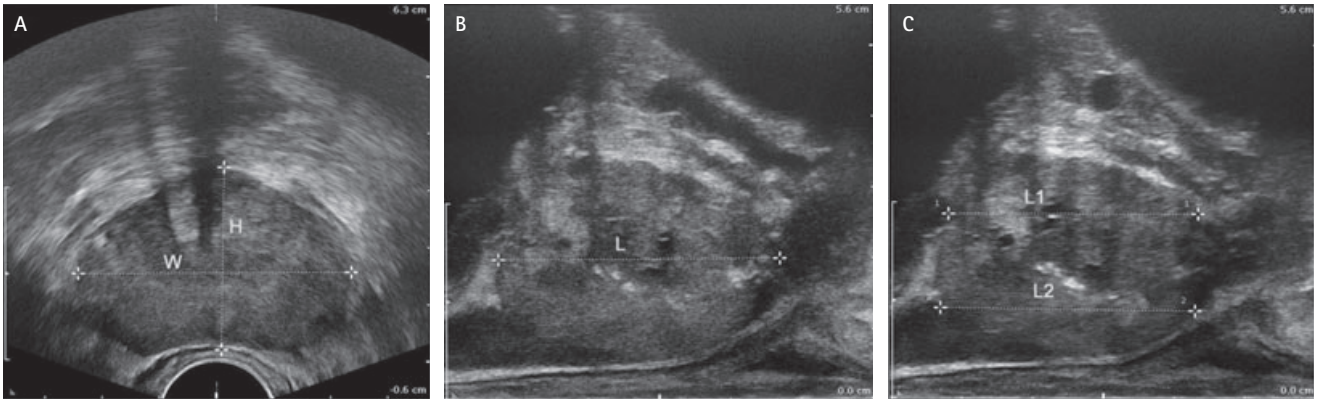
brachytherapy, prostate cancer, 4D Brachytherapy, realtime planning

INTRODUCTION

The use of low dose rate prostate brachytherapy was initiated in the 1970s using a freehand technique to insert radioactive pellets into an open prostate; the amount of radioactivity was calculated using a volume-based nomogram [1]. However, the early results were poor due to the random placement of the seeds. The use of transrectal ultrasound (TRUS) for precise placement of transperineal radioactive seeds was first reported by Holm *et al.* in 1983 [2]. Further developments were made by Blasko, Grimm, Ragde and co-workers [3,4] resulting in the two-step procedure with a TRUS pre-plan taking place usually 2–4 weeks prior to seed implantation. The aim of pre-planning is that 99% of the prostate should be covered with the prescription isodose. The measurement of prostate volume involves recording a series of transverse images 5 mm apart from the base to the apex of the prostate. The pictures are then digitized to produce a 3D model of the prostate on the planning computer and the number and positioning of the seeds can subsequently be calculated. A modified uniform distribution of seeds is typically used with a loading pattern that has reduced density around the urethra and increased seed density on the periphery. The planning target volume extends approximately 5 mm beyond the prostate in the cranial, caudal and anterior directions and 3–5 mm laterally; there is no margin extension at the rectal surface for toxicity reasons. Generally, in this approach, preloaded needles are used containing loose or stranded seeds. Loose seeds can also be placed using a Mick applicator (Mick TP 200, Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA).

An alternative to the two-stage system is intraoperative planning, whereby planning and seed placement is conducted in a single step [5]. Before the implant, the prostate volume is determined using TRUS and a nomogram is used to calculate approximately how many seeds are required. The planning dosimetry calculations are then performed per-operatively. Loose seeds are usually used for the implant although some techniques utilize stranded seeds that require loading into needles whilst the patient remains under anaesthetic in the operating room (OR) before implantation. One advantage of this technique is that the patient position remains the same and that there is no change in prostate volume between the planning and insertion stages. However, the use of loose seeds in the periphery of the gland risks seed migration and techniques using stranded seeds are often lengthy to perform.

FIG. 1. The five prostate measurements required to generate the seed order for 4D Brachytherapy: ***A****, maximum height and width;* ***B****, maximum length;* ***C****, two para-sagittal lengths L1 and L2, situated approximately one-quarter of the height medially from the anterior and posterior border of the prostate.*



NOVEL ONE-STAGE PROCEDURE: 4D BRACHYTHERAPY

A new one-stage real-time procedure has been developed to utilize a combination of stranded and loose seeds. The aim was to use the benefits of stranded seeds in the periphery of the gland to optimize the dosimetry whilst retaining the flexibility that loose seeds provide in the centre of the prostate. This whole procedure can be performed in a one-stage technique using real-time dosimetry in the same time as the second part of a standard two-stage technique, i.e. approximately 45 min. The technique termed 4D Brachytherapy is described below.

ASSESSMENT SCAN

The procedure starts with a standard outpatient assessment prior to surgery to determine prostate size and shape using TRUS in the left lateral position without the need for stirrups. Five measurements are taken (prostate height, width, length and two para-sagittal lengths) (Fig. 1).

SEED ORDER

A web-based nomogram has been developed by analysing data from over 1000 implants performed by the Guildford group. Using the five prostatic measurements, the nomogram calculates how many stranded and loose seeds will be required, which can then be ordered online; additional loose seeds are also ordered to ensure flexibility. The stranded seeds are delivered in preloaded needles numbered in the correct order for implantation. The loose seeds are preloaded into Mick cartridges, reducing the time required for needle preparation and seed loading.

IMPLANT

A two-person team works closely together in the OR to insert the seeds and monitor the process. Initially, an intraoperative planning scan is conducted using a biplanar ultrasound and a computer with planning software (Variseed, Varian Inc. version 8.0). The planning computer builds up a 3D picture from the images generated and this will be used in the intraoperative dosimetry calculations. An alignment of the seed order, preloaded into the planning computer as determined by the nomogram, is then performed to the actual shape of the prostate. To do this, the ultrasound probe is moved to reveal the maximum diameter of the gland in the transverse view. The strand-carrying needle positions are moved on the planning computer to be evenly spaced around the periphery of the gland, approximately 1 cm apart. These needle positions are transferred to the ultrasound screen and indicate where the needles need to be inserted in the transverse (x, y) plane. While these needles are being inserted, the planning computer operator outlines the urethra and rectum on the transverse images to allow dosimetric assessment. Once complete, planning of the number and position of loose seeds commences. When all the anterior and lateral strand-carrying needles have been inserted in the transverse plane, the two clinicians work together to insert the stranded seeds. Switching to the longitudinal (z) plane, each needle is separately identified by rotating the probe in the cradle of the stepping unit. Initally the anterior strands are implanted and then, alternating left to right, the lateral strands are implanted. The needles are all advanced to the base of the prostate as seen on the ultrasound with the seeds being inserted as far cranially as possible; retraction planes are not used.

Following this a similar process is undertaken to insert the posterior needles and strands, with care being taken to ensure alignment between the actual prostate position and the virtual prostate on the planning computer. When all the peripheral stranded seeds are inserted, dosimetry data from the computer are generated intraoperatively in real time to determine the placement of the loose seeds and a plan is generated. The needle positions are again transferred from the planning computer to the ultrasound to direct the clinician inserting the needles. Empty Mick needles (usually five to seven) are inserted in the transverse view. The Mick applicator containing a cartridge of loose seeds is attached and, in the longitudinal view, each needle is advanced towards the base of the prostate. As each seed is inserted at the retraction plane determined by the planning software, its position is loaded onto the planning computer. A 3D image of implanted seeds is shown in Fig. 2.

The final stage of the procedure is to check dosimetry parameters. The target doses with 4D Brachytherapy are as follows: V_{100} >

FIG. 2. ***A****, Position of the stranded seeds around the periphery of the prostate (red); the anterior rectal wall (blue) and urethra (green) are also shown.* ***B****, Sleeve of radiation created by these stranded seeds.* ***C****, The completed radiation dose cloud (145 Gy) achieved by subsequently implanting the centre of the prostate with loose seeds.*

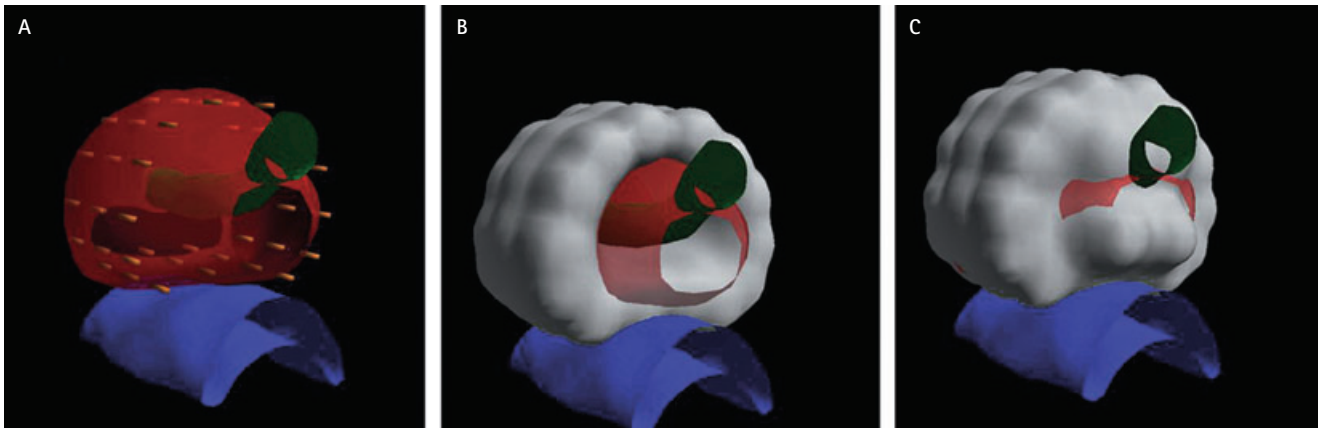


TABLE 1 Patient characteristics

	Two-stage Seattle (n = 100)		Two-stage Guildford hybrid (n = 100)			Two-stage real-time optimized (n = 53)			4D Brachytherapy (n = 100)		
Parameter	Median (range)	Mean ± SD	Median (range)	Mean ± SD	P (t test)	Median (range)	Mean ± SD	P (t test)	Median (range)	Mean ± SD	P (t test)
Age (years)	63 (51–78)	63 ± 6	63 (49–77)	63 ± 6	0.83	62 (50–76)	63 ± 6	0.45	65 (49–79)	64 ± 7	0.31
Follow-up (months)	96 (3–120)	81 ± 32	48 (3–64)	45 ± 12	< 0.005	36 (3–48)	33 ± 10	< 0.005	30 (25–33)	30 ± 2	< 0.005
PSA (ng/mL)	8 (1–26)	9 ± 4	6 (2–26)	7 ± 3	< 0.005	7 (3–17)	7 ± 3	0.02	8 (2–21)	8 ± 3	0.4
% Core involvement	21 (2–43)	21 ± 18	20 (5–60)	31 ± 21	0.37	21 (3– 43)	22 ± 15	0.93	20 (1–55)	23 ± 16	0.78
Gleason grade	6 (2–10)	6 ± 1	6 (6–8)	6 ± 0	< 0.005	6 (6–7)	6 ± 0	0.01	6 (5–9)	6 ± 1	< 0.005
TRUS volume (mL)	41 (19–63)	41 ± 10	37 (18–67)	38 ± 10	0.08	35 (14–66)	38 ± 12	0.16	38 (15–70)	38 ± 13	0.13

PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

95%; V_{150} 50–65%; D_{90} 155–185 Gy; U_{150} < 7%; and rectal value R_{100} < 1 mL. A post-implant computed tomography scan is conducted for quality assurance. At Guildford, the practice is to perform this within 24 h so that early dosimetric feedback is obtained [6]. A more detailed description of 4D Brachytherapy including an instructional video can be found on the website www.4Dbrachytherapy.com.

THE GUILDFORD SERIES

In order to avoid learning curve effects, data were collated from consecutive patients with prostate cancer treated with brachytherapy following our initial 300 implants. One of four methods was assessed: (i) two-stage pre-planned technique with stranded seeds (Seattle technique); (ii) two-stage pre-planned technique with peripheral stranded seeds and centrally placed loose seeds (Guildford hybrid technique); (iii) two-stage technique with stranded seeds placed peripherally, loose seeds placed centrally and real-time dosimetry optimization (real-time optimized technique); and (iv) the new 4D Brachytherapy procedure with stranded and loose seeds using the nomogram for seed ordering and real-time planning. Target dosimetric parameters for all of the implants were the same with a prescription of 145 Gy and 110 Gy for patients treated by monotherapy and in combination with external beam radiotherapy (EBRT), respectively.

A comparison was made of patient characteristics, dosimetry and clinical outcomes (International Prostate Symptom Score [IPSS], and its quality of life domain and biochemical outcome) with the different techniques. Statistical analysis of the data was conducted using Student's t test and Fischer's exact test. The reference point for comparisons was the original brachytherapy procedure (Seattle) to which each of the other techniques was compared.

Patient characteristics and the number of patients treated with each procedure are shown in Table 1. There was no significant difference between the cohorts with regard to patient age, percentage biopsy core involvement or TRUS prostate volume. As expected, the duration of follow-up was significantly shorter in the later series of patients ($P < 0.005$) compared with the two-stage Seattle series of patients. Prostate-specific antigen (PSA) level prior to treatment was also significantly lower for the Guildford hybrid ($P < 0.005$) and real-time optimized ($P = 0.02$) procedures compared with the Seattle series but not for the 4D Brachytherapy technique. Significant

TABLE 2 Disease stage prior to treatment and use of hormone therapy or external beam radiotherapy (EBRT) prior to brachytherapy

	Two-stage Seattle ($n = 100$)	Two-stage Guildford hybrid ($n = 100$)		Two-stage real-time optimized ($n = 53$)		4D Brachytherapy ($n = 100$)	
Parameter	*n* (%)	*n* (%)	*P* (Fisher's exact)	*n* (%)	*P* (Fisher's exact)	*n* (%)	*P* (Fisher's exact)
Stage T1c–T2b	74 (74)	92 (92)	< 0.005	47 (89)	< 0.005	92 (92)	< 0.005
Stage T2b–T3b	26 (26)	8 (8)		5 (9)		8 (8)	
Hormones	66 (66)	19 (19)	< 0.005	8 (15)	< 0.005	35 (35)	< 0.005
EBRT	20 (20)	5 (5)	< 0.005	4 (8)	0.024	10 (10)	0.073

TABLE 3 Brachytherapy radiation dosages

	Two-stage Seattle ($n = 100$)		Two-stage Guildford hybrid ($n = 100$)			Two-stage real-time optimized ($n = 53$)			4D Brachytherapy ($n = 100$)		
Variable	Median (range)	Mean ± SD	Median (range)	Mean ± SD	*P* (*t* test)	Median (range)	Mean ± SD	*P* (*t* test)	Median (range)	Mean ± SD	*P* (*t* test)
$\%D_{90}$	98 (63–132)	97 ± 13	109 (84–135)	109 ± 10	< 0.005	103 (81–124)	105 ± 9	< 0.005	106 (91–133)	107 ± 8	< 0.005
D_{90} (Gy) (monotherapy only)	143 (105–192)	143 ± 18	157 (122–193)	157 ± 14	< 0.005	150 (117–178)	151 ± 13	0.01	153 (132–193)	154 ± 11	< 0.005
V_{100}	88 (65–99)	87 ± 8	94 (18–99)	93 ± 9	< 0.005	93 (70–99)	91 ± 6	< 0.005	93 (82–99)	93 ± 4	< 0.005
V_{150}	44 (19–78)	44 ± 12	55 (34–84)	56 ± 12	< 0.005	44 (12–67)	44 ± 11	0.97	44 (23–78)	45 ± 10	0.54

differences in median (range) Gleason score were also observed for the three techniques ($P < 0.005$ to $P = 0.01$). With regard to stage of disease prior to treatment, significantly more patients treated with the modified brachytherapy techniques had earlier stage disease (T1c–T2b) than the Seattle series ($P < 0.005$) (Table 2). Also, significantly fewer patients received hormone therapy or EBRT prior to brachytherapy in the Guildford hybrid ($P < 0.005$) or the real-time optimized groups ($P = 0.024$) than in the Seattle group; no difference was observed for the 4D Brachytherapy group.

Dosimetry data for each of the patient groups is shown in Table 3. D_{90}, $\%D_{90}$ (D_{90} as a percentage of the prescribed dose) and V_{100} were all significantly higher for the three modifications to the procedure compared with the original Seattle series ($P < 0.005$ to $P = 0.01$) indicating improved delivery of radiation to the prostate. The $\%V_{150}$ was significantly greater for the Guildford hybrid series ($P < 0.005$) but not for the subsequent modifications (real-time optimized or 4D Brachytherapy) indicating that safety in the form of urethral exposure was not compromised by improved prostate dosing. The plot of individual $\%D_{90}$ values for each of the patients is shown in Fig. 3

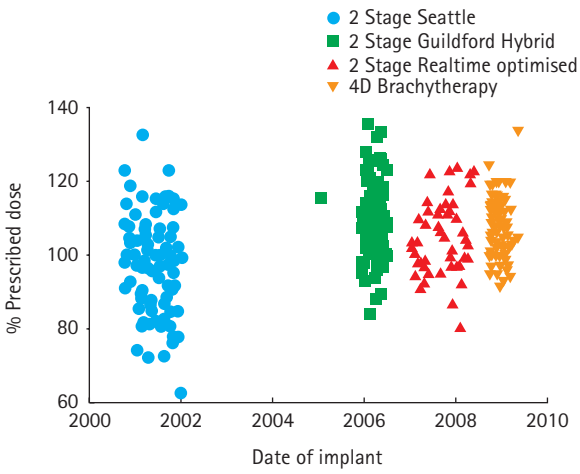


FIG. 3.
Dosimetry according to the brachytherapy technique.

and reveals a reduction in variance of dose with values concentrated around 100% for 4D Brachytherapy compared with the other techniques.

There was no significant difference between the mean change in IPSS between techniques except for 4D Brachytherapy at 3 months ($P = 0.037$) and 1 year ($P = 0.049$), where the increase in score was significantly less than the Seattle series (Table 4) suggesting reduced short-term urinary morbidity. At 2 years the IPSS evened out with no differences observed between techniques, each providing comparable benefits. A similar finding was observed with the quality of life scores. Previous studies reported from Guildford have demonstrated beneficial improvements in potency with a combination of stranded and loose seeds. There was a significant improvement in potency preservation as recorded using the International Index of Erectile Function at 2 years with the stranded/loose seed

TABLE 4 Change in International Prostate Symptom Score (IPSS) and quality of life score following brachytherapy

	Two-stage Seattle ($n = 100$)	Two-stage Guildford hybrid ($n = 100$)	P (t test)	Two-stage real-time optimized ($n = 53$)	P (t test)	4D Brachytherapy ($n = 100$)	P (t test)
Mean (SD) change in IPSS from baseline							
3 months	5.92 (6.82)	4.56 (5.11)	0.12	5.50 (5.77)	0.71	4.0 (5.70)	0.037
1 year	2.73 (5.92)	3.12 (5.71)	0.67	3.31 (5.72)	0.6	0.97 (5.10)	0.049
2 years	1.50 (5.29)	1.72 (4.34)	0.79	3.67 (3.67)	0.047	1.50 (5.80)	0.99
Mean (SD) change in quality of life from baseline							
3 months	1.30 (1.8)	1.0 (1.5)	0.24	1.2 (1.6)	0.63	0.68 (1.3)	0.0044
1 year	0.73 (1.5)	0.81 (1.5)	0.76	0.65 (1.3)	0.77	0.27 (1.5)	0.06
2 years	0.32 (1.4)	0.41 (1.0)	0.67	0.63 (1.4)	0.29	0.03 (1.3)	0.27

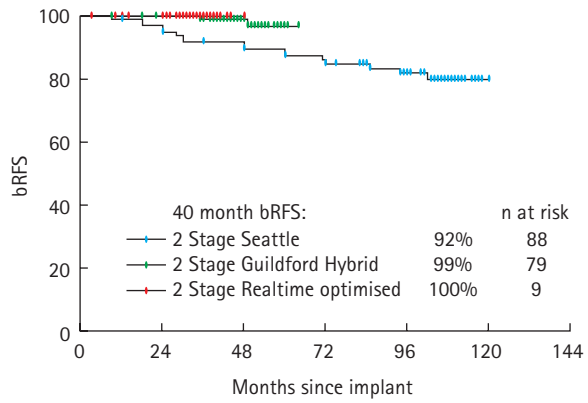


FIG. 4. Biochemical relapse free survival (bRFS) following brachytherapy.

combination technique compared with the Seattle technique (83.3% vs 61.7%, $P = 0.008$) [7].

Biochemical relapse free survival (bRFS) data up to 10 years are shown in Fig. 4 (Phoenix definition). A comparison can only be made between the first of the three techniques detailed (the Seattle, the Guildford hybrid and the real-time optimization) as there is insufficient follow-up time for the 4D Brachytherapy patients. Clearly these data are not randomized; however, the bRFS of patients treated by these techniques is excellent.

COMPARATIVE STUDIES: PRE-PLANNING VS INTRAOPERATIVE

A comparative series was reported by Wilkinson *et al.* [8] and involved 61 patients in the pre-planning group and 52 patients in a one-step group. Statistically significant differences were shown for mean $\%V_{100}$ and D_{90} doses, which were 76.2% and 120.5 Gy for the pre-planned technique and 84.9% and 136.5 Gy for the real-time technique. More recently, Matzkin and co-workers [9] showed that the length of physicist time and OR team time was more than double in a pre-planned group of 142 patients compared with 214 men treated with intraoperative planning (205 vs 100 min). There were also benefits with regard to dosimetry. Mean V_{90}, V_{100} and V_{150} were 67.5%, 58.35% and 21.5%, respectively, for the pre-planned group and 97.9%, 95.2% and 45%, respectively, for the intraoperative planning group. Comparative mean D_{90} values were 53% and 114% for the pre-planned and intraoperative groups, respectively.

Benefits have also been reported for biochemical control and clinical disease free survival when an intraoperative planning protocol was used. In a series of 135 patients treated between 1996 and 2001, 42 patients underwent pre-planning and 93 patients intraoperative planning [10]. Four-year biochemical control rates based on the American Society for Therapeutic Radiology and Oncology guidelines were 80% and 94% for pre-planning and intraoperative groups, respectively, and the equivalent values for 4-year clinical disease free survival rate were 87% and 99%, respectively. In addition, a recent review by Polo *et al.* [11] concludes that, with the evolution of imaging technology and planning software, interactive planning in the OR can achieve greater accuracy of seed placement.

CONCLUSIONS

4D Brachytherapy is a quick procedure that can generally be performed in ≤45 min compared with the 2–3 h frequently taken with other one-stage procedures, especially when stranded seeds are used. The technique affords a shorter anaesthetic time for the patient and a more efficient use of OR and clinician time. The technique is intuitive to learn using visual feedback about where to insert the stranded seeds rather than relying on coordinates and retraction planes. Due to the use of loose seeds, 4D Brachytherapy is flexible and allows easy accommodation of asymmetrically shaped glands. The use of stranded seeds also offers the ability to implant some seeds just outside the capsule of the prostate so optimizing the delivered dose whilst minimizing the risk of seed migration, which occurs mainly through the venous system via the dorsal venous plexus. The most common final destination of these seeds is the lung. Migration can occur in 10–20% of implants when only loose seeds

are used [12]. Dosimetry data with 4D Brachytherapy reported by our team show improvements over other brachytherapy treatment protocols. Optimizing the radiation dose delivered at the apex of the gland/penile bulb has been shown to correlate with erectile function [7,13]. The combination of the stranded seeds with the placement of loose seeds centrally in the 4D Brachytherapy procedure allows the apex of the prostate to be carefully implanted, minimizing the dose to the membranous urethra and the penile bulb and thereby reducing the risk of urethral stricture rate and optimizing erectile function.

CONFLICT OF INTEREST

Stephen Langley and Robert Laing receive funding from Oncura Ltd for medical consultancy and to attend medical conferences.

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Abbreviations: **OR**, operating room; **EBRT**, external beam radiotherapy; **IPSS**, International Prostate Symptom Score; **bRFS**, biochemical relapse free survival.