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Original Article

Comparative Analysis of Clinical Outcomes and Procedural Costs between the Conventional Two-stage Technique and 4D Brachytherapy for Early Prostate Cancer

S.E.M. Langley, J. Uribe, S. Uribe-Lewis, J. Money-Kyrle, C. Perna, S. Khaksar, R. Soares, R. Laing

St Luke's Cancer Centre, Guildford, UK

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Abstract

Aims: To assess long-term outcomes and resource use of 4D Brachytherapy, a one-stage real-time implant for the treatment of prostate cancer that uses stranded and loose iodine-125 seeds, and to compare with the conventional two-stage (2S) technique.

Materials and methods: Prospectively collected data of men who underwent 2S and 4D low dose rate brachytherapy in a single institution were analysed. Survival estimates were analysed using the Kaplan–Meier method and Log-rank test. Treatment failure rates were further compared by Cox proportional hazards (Coxph) regression or by a surrogate prostate-specific antigen value cut-off of 0.4 ng/ml 48 months post-implant. Treatment toxicity outcomes were also evaluated. Comparative costs were based on published English National Health Service data.

Results: We compared outcomes of 690 men treated with 2S and 1031 men with 4D brachytherapy. Median follow-up times were 10.4 and 5.2 years ($P < 0.001$) for 2S and 4D cases, respectively. Day 0 post-implant dosimetry was improved in 4D brachytherapy patients. Five years post-implant ≥98% of cases were alive and ≥95% were free from disease relapse irrespective of technique. Coxph regression showed the risk of relapse after 4D brachytherapy was similar to the 2S technique (hazard ratio 0.67, 95% confidence interval 0.44–1.03, $P = 0.065$). Forty-eight months post-implant there was a significantly greater proportion of 4D brachytherapy cases with a prostate-specific antigen below 0.4 ng/ml relative to the 2S technique. Urinary and bowel symptom scores showed reduced toxicity after 4D implants and potency conservation was similar to the 2S technique. The reduction in time and resource use decreased the cost of 4D brachytherapy by 40% compared with the 2S technique.

Conclusion: Two-stage and 4D brachytherapy are both highly effective for the control of localised prostate cancer. However, relative to the 2S technique, the 4D technique was associated with improved dosimetry, reduced treatment-related toxicity and reduced cost. Further follow-up will assess disease control superiority of 4D brachytherapy beyond 5 years post-implant.

Key words: Brachytherapy; cost; 4D brachytherapy; prostate cancer; real-time planning

Introduction

Beginning in March 1999, patients with localised prostate cancer have been treated in our institution with iodine-125 seeds, either as monotherapy or in combination with androgen deprivation therapy (ADT) and/or external beam radiation therapy (EBRT). From the outset, a prospective customised web-based data registry was implemented to comprehensively collect data on treatment parameters, medical outcomes, patient-reported symptom scores and quality of life questionnaires. Patients are followed up for a minimum of 10 years after treatment.

By an adaptive process we gradually developed the conventional 2S (Seattle) technique [1,2] into a real-time intraoperative dose planning solution and delivery technique denominated 4D Brachytherapy [3]. We sought to combine the advantages of interactive real-time planning [2] and the use of patient-specific sterile kits comprised of needles preloaded with strands of regularly spaced seeds, together with loose seeds in Mick applicator compatible cartridges. The aim was to avoid seed migration in the

Author for correspondence: S.E.M. Langley, St. Luke's Cancer Centre, Royal Surrey Hospital, Guildford GU2 7XX, UK. Tel: +44-1483-575511; Fax: +44-1483-540455.

E-mail address: semlangley@gmail.com (S.E.M. Langley).

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periphery of the gland using stranded seeds while retaining the flexibility that loose seeds provide in order to optimise dosimetry. This combination was made possible by the development of a web-based computerised nomogram, derived from over 1000 dosimetric plans, that can predict the required number of preloaded stranded and loose seeds as well as their positions in the prostate. Although these efforts were directed towards improving treatment outcomes, an additional aim was to meet an institutional challenge of cutting waiting lists, increasing efficiency and reducing costs.

The 4D technique is based on five preoperative transrectal ultrasound (TRUS) measurements, taken in an outpatient clinic setting, to calculate the seed and needle requirements in advance of the implant. Alternatively, TRUS measurements obtained during the initial biopsy session may be used. Subsequently, the implant is carried out as a one-stage technique, using real-time dosimetry, that can be executed in about 45 min. The 4D technique eliminates a planning session in theatre, the first stage of the 2S method. The sterile preloaded kit eliminates preoperative needle loading. In-house seed activity verification of the kit is conducted according to American Association of Physicists in Medicine recommendations [4]. At present, four patients can readily be treated in a 4 h theatre session [5].

Herewith we present the clinical outcomes from our cohort of patients treated with the 4D brachytherapy technique since 2009 and compare them with the clinical outcomes of our patients treated with the earlier 2S technique. We also present comparative time-based activity costs between the 2S and 4D brachytherapy techniques within the framework of the English National Health Service (NHS).

Materials and Methods

Patient Selection and Stratification

The database was accessed on 9 December 2016. From 3445 cases enrolled up to that date we selected for cases with at least 3 years post-implant from the data download date, a minimum of four prostate-specific antigen (PSA) measurements (the initial pre-treatment PSA [iPSA] and three post-implant values), documented pre-treatment clinical staging, Gleason score and day 0 post-implant dosimetry. These selection steps (illustrated in Figure 1) resulted in 1721 consecutive cases available for analyses, of whom 690 were treated with the 2S technique and 1031 with 4D brachytherapy.

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. The PSA at 48 months consisted of the nearest PSA value to 48 months between 42 and 54 months post-implant.

Initially patients classified as having low-risk disease received brachytherapy alone. Those with intermediate-risk disease had 3 months of ADT and brachytherapy; those with high-risk disease had a combination of ADT, EBRT and brachytherapy. Starting in 2007, our regimen was modified. Patients with intermediate-risk disease and Gleason 3+4 had brachytherapy monotherapy instead of combination therapy [6]. Twenty per cent of patients were documented as having required ADT for prostate volume reduction. Patients were prescribed tamsulosin 400 mg daily for the first 3–6 months post-implant. They were encouraged to take a phosphodiesterase type 5 inhibitor if erectile function was suboptimal and as a preventative approach [7] once or twice per week to maintain nocturnal and early morning erections.

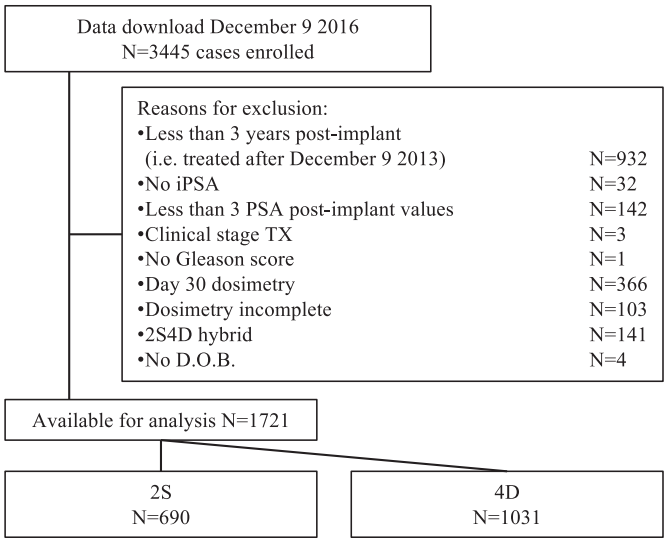


Fig 1. CONSORT diagram for study case selection. The database was accessed on 9 December 2016 when 3445 cases had been enrolled. After exclusion steps, 1721 cases were available for the final analysis, of whom 690 had been treated with the 2S technique and 1031 with 4D brachytherapy.

Dosimetry

Our dosimetric parameters are consistent with 2007 Groupe Européen de Curiethérapie (GEC) and the European SocieTy for Radiotherapy & Oncology (ESTRO) recommendations for prostate (D90, V100, V150) and the recommended dose constraints for urethra and rectum [8]. A day 0 post-implant computed tomography scan provided quality assurance and early dosimetric feedback.

Toxicity Outcomes

As previously described [9], urinary and bowel toxicity scores were obtained using the International Prostate Symptom Score (IPSS) questionnaire (including the urinary quality of life domain) and the bowel function subscale of the European Organization for Research and Treatment of Cancer (EORTC) QOL PR25 questionnaire. The International Index of Erectile Function (IIEF-5) questionnaire was used to assess erectile function. Cases with complete scores documented at baseline and follow-up visits were included in the analysis. The number of cases for each quality of life assessment is shown in Supplementary Table S1.

Statistics

Statistical analyses were carried out within the R statistical environment [10]. The 'survival' package was used for overall mortality, prostate cancer-specific mortality, relapse-free survival (RFS) estimates, Kaplan–Meier plots, log-rank tests and Cox proportional hazards (Coxph) regression (proportional hazards confirmed with the coxzph test). Categorical data (proportions) were analysed using Fisher's exact test. Unpaired two-tailed *t*-tests were used for continuous data or the Wilcoxon signed-rank test when a normal distribution could not be assumed.

Cost Analysis

Using time-based activity costing for the 2S technique with reference to published NHS costs [11, appendix 13] we compared the procedural elements and resource use between 2S and 4D brachytherapy delivered as monotherapy. The comparison covered pre-treatment consultation, treatment planning, treatment delivery, post-implant dosimetry and implant quality assessment. Based on a micro-costing exercise, the costs of brachytherapy in Ramsay *et al.* [11] were estimated from a treatment pathway and associated resource inputs in an NHS hospital in the north of England. Personnel and hospital costs reported are NHS reference costs for the period 2011–2012. The 2S technique described by Ramsay *et al.* [11] comprises the individual procedural steps formerly used in our hospital for our 2S patients. This enables a fair comparison in the time-based activity components and their associated cost between the 2S technique reported in Ramsay *et al.* [11] and 4D brachytherapy. Capital costs, equipment maintenance costs and quality assurance were assumed to be equal for both techniques. The cost of iodine-125 seeds was not included in the analysis.

Results

We report on 690 men treated with the 2S technique and 1031 men treated with the 4D brachytherapy technique (Table 1). The 4D brachytherapy cases were older at treatment, had a shorter follow-up time and a higher iPSA. Most

Table 1
Patient characteristics

	2S brachytherapy	4D brachytherapy	
Treatment era	January 2004 to December 2008	January 2009 to December 2013	
Number of cases	690	1031	
	Median (range)		*t*-test *P*
Age at implant (years)	63 (47–80)	66 (47–82)	<0.001
Follow-up time* (years)	10.4 (0.6–13.0)	5.2 (0.7–7.9)	<0.001
PSA follow-up time† (years)	8.2 (0.6–12.7)	4.1 (0.6–7.9)	<0.001
iPSA (ng/ml)	6.8 (1–33)	7.4 (0.4–50)	<0.001
iPSA (ng/ml)	***Number (%) of cases***		Fisher's *P*
iPSA < 10	556 (81)	784 (76)	0.436
iPSA 10–20	125 (18)	228 (22)	0.106
iPSA > 20	9 (1)	19 (2)	0.442
Clinical stage	***Number (%) of cases***		Fisher's *P*
T1a–T2a	529 (77)	744 (72)	0.43
T2b	103 (15)	213 (21)	0.012
T2c–T3b	58 (8)	74 (7)	0.408
Gleason	***Number (%) of cases***		Fisher's *P*
Gleason < 7	464 (67)	530 (51)	0.001
Gleason = 7	206 (30)	468 (45)	<0.001
Gleason > 7	20 (3)	33 (3)	0.777
Risk	***Number (%) of cases***		Fisher's *P*
Low	316 (46)	331 (32)	<0.001
Intermediate	295 (43)	587 (57)	0.001
High	79 (11)	113 (11)	0.816
Treatment type	***Number (%) of cases***		Fisher's *P*
BXT monotherapy	525 (76)	707 (69)	0.172
BXT + ADT	102 (15)	158 (15)	0.839
BXT + EBRT	16 (2)	21 (2)	0.736
BXT + ADT + EBRT	47 (7)	143 (14)	<0.001

PSA, prostate-specific antigen; iPSA, initial (pre-treatment) PSA; BXT, brachytherapy; ADT, androgen deprivation therapy; EBRT, external beam radiation therapy.

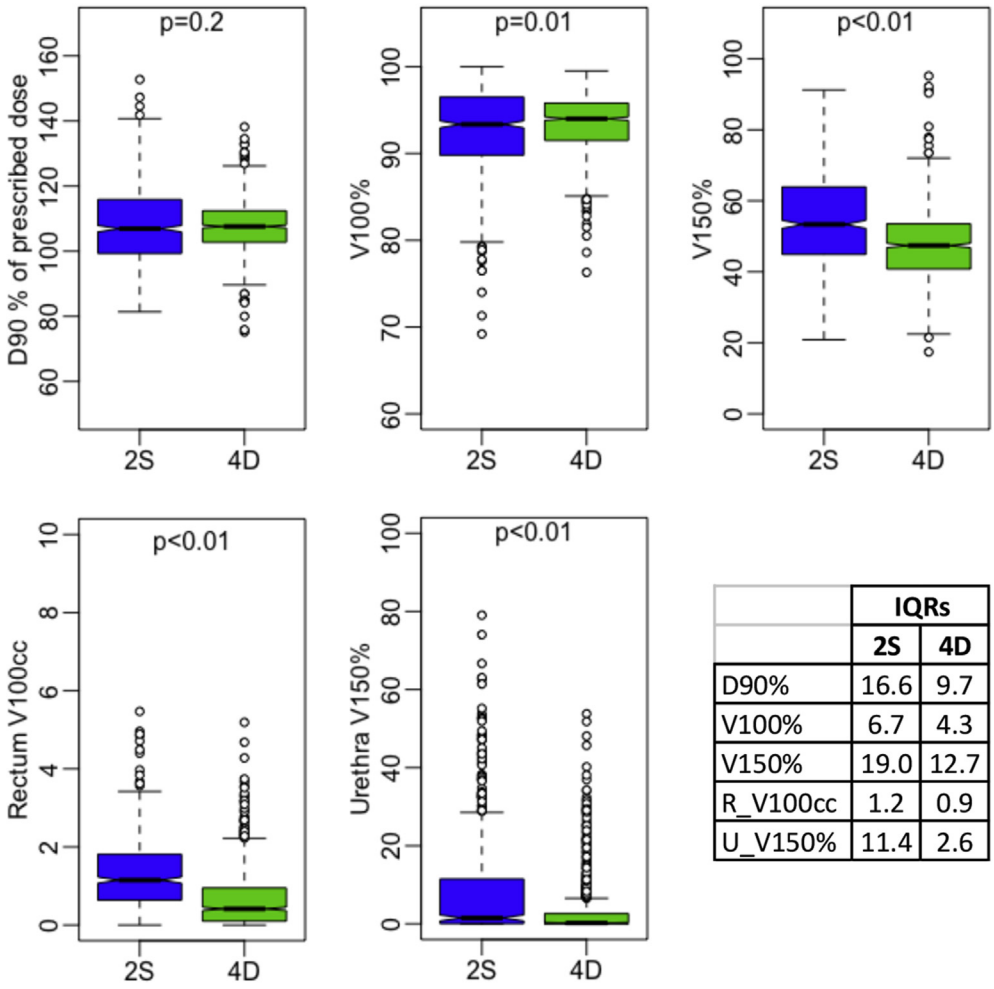
* Time from implant date to data download date.

† Time from iPSA value date to the last documented PSA value follow-up date.

of the 4D brachytherapy cases were intermediate risk (57%), whereas those treated with the 2S technique were low risk (46%). The proportion of 4D brachytherapy cases treated with monotherapy or in combination with ADT or EBRT was not significantly different to that for 2S cases. Brachytherapy with ADT and EBRT was used in a small percentage of cases but more frequently in 4D brachytherapy relative to the 2S technique (Table 1). Target dosimetric parameters were the same for all of the implants, with a prescription dose of 145 Gy and 110 Gy, respectively, for monotherapy or combined with EBRT. Postoperative day 0 computed tomography scan dosimetry showed that prescribed doses were achieved with improved consistency (reduced variation) in doses delivered by 4D brachytherapy (Figure 2).

Thirty-five patients died, three specifically due to prostate cancer, resulting in overall and prostate cancer-specific survival of 98% and 99% 5 years post-implant after 2S and 4D brachytherapy, respectively (not shown).

RFS was similar between the two techniques with 5 year post-implant estimates of 95% and 96% RFS for 2S and 4D brachytherapy, respectively (Figure 3A). Survival estimates assessed by multivariable Coxph regression also showed the risk of failure was similar between the two techniques (hazard ratio 0.67, 95% confidence interval 0.44–1.03, $P = 0.065$; Supplementary Table S2). Because of the significant difference in follow-up lengths between the 2S and 4D brachytherapy techniques (10.4 and 5.2 years, respectively, $P < 0.001$) that might influence survival estimates, treatment failure rates were further assessed by stratifying with a 0.4 ng/ml cut-off in PSA values 48 months post-implant. This cut-off has previously been described as a useful early surrogate marker for treatment failure [12]. From 1126 cases with an available PSA value at this time point, the analysis showed a significantly greater proportion of 4D brachytherapy cases with a PSA < 0.4 ng/ml 48 months post-implant relative to cases treated with the 2S technique (odds ratio 0.6, 95% confidence interval 0.45–0.83, $P < 0.001$; Figure 3B), indicating that 4D brachytherapy implants are associated with improved disease control 4 years after brachytherapy.



	IQRs	
	2S	4D
D90%	16.6	9.7
V100%	6.7	4.3
V150%	19.0	12.7
R_V100cc	1.2	0.9
U_V150%	11.4	2.6

Fig 2. Day 0 computed tomography post-implant dosimetry. Boxplots for measures of post-implant dosimetry after 2S (blue boxes) and 4D (green boxes) brachytherapy implants show the first quartile (lower box edge), median (at the notch), third quartile (upper box edge) and whiskers extending to 1.5 times the interquartile range (IQR). The first to third IQRs for 2S and 4D measures are summarised in the lower right hand table. R, rectum; U, urethra.

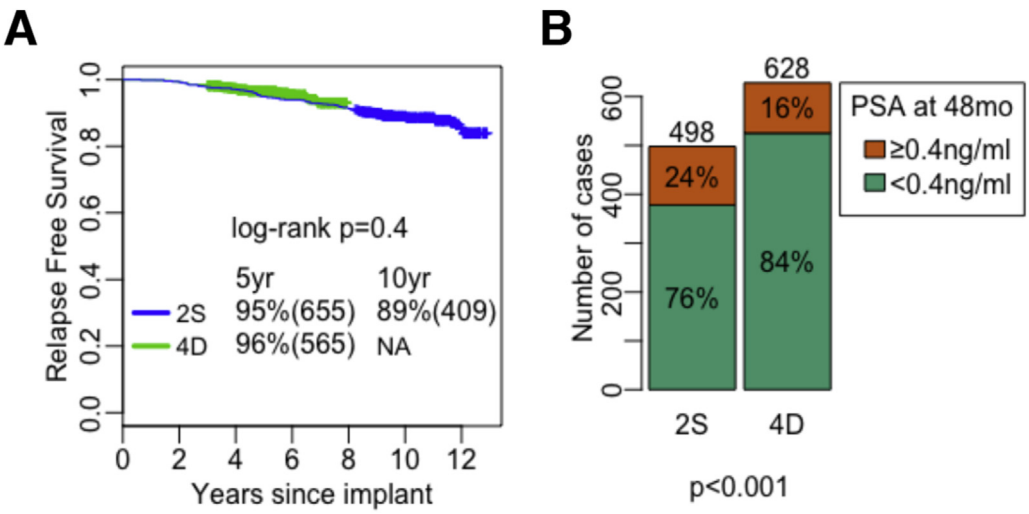


Fig 3. Treatment failure rates in 2S and 4D brachytherapy. (A) Kaplan–Meier plot for relapse-free survival estimates (*n* at risk) 5 and 10 years after 2S or 4D brachytherapy implants. NA, not applicable. (B) Bar plot for the proportions of cases with a prostate-specific antigen (PSA) cut-off of 0.4 ng/ml 48 months post-implant.

Health-related quality of life outcomes are shown in Figure 4. The mean change in IPSS and urinary quality of life scores from baseline showed the expected acute increase in toxicity after brachytherapy, followed by a gradual reduction and a return to baseline. Throughout follow-up, the mean change in urinary scores for 4D brachytherapy were equal to or below those observed for the 2S technique, with significantly reduced urinary symptoms 4 and 5 years post-implant (Figure 4). Bowel symptom scores also showed improved outcomes for 4D brachytherapy relative to the 2S technique. Erectile function analysis showed that the proportion of patients potent post-implant, by an IIEF-5 score > 11 and relative to the number of potent cases at baseline, was considerable and similar between 2S and 4D brachytherapy, where 71% of the cases were potent 5 years after brachytherapy (Figure 4).

The 4D technique reduced time and resource use and, therefore, the cost of the procedure by 40% relative to the 2S technique in several ways (see Table 2). Dispensing with a TRUS planimetry theatre session reduced the cost by £639.90. The use of the online nomogram to generate the dosimetric plan based on the outpatient clinic measurements reduced the cost of 4D brachytherapy by a further £50.00 compared with manually creating a 2S plan. During the implant session proper, the 4D method reduced personnel and theatre time, generating savings of £704.90. The use of a sterile patient-specific implant kit eliminated the cost of needle loading.

Discussion

The 2S technique has stood the test of time, as seen by the excellent long-term survival outcomes reported here and elsewhere [13]. However, technology and planning software improvements have evolved, allowing real-time interactive planning and dynamic dosimetry to achieve greater accuracy of seed placement. The relative merits and technical details are beyond the scope of this report and can be found in a review by Polo *et al.* [14]. The 4D technique takes this trend a step further by incorporating preloaded stranded seeds into the real-time interactive approach, providing improvements in work flow and cost saving.

Tapen *et al.* [15] first showed the minimal seed migration associated with stranding seeds. Seeds may migrate to other anatomical sites or voided. Seed migration may affect the dosimetry of the implant and risk leaving a 'cold' spot. Other authors have described the absence of lung migration in 400 patients [16] and improved dosimetry [17,18] using stranded seeds. A further advantage of stranded seeds is that the clinical target volume can include tissue outside the prostatic capsule without fear of migration, thus extending the dose to mitigate the risk posed by extra-prostatic extension [19].

Intraoperative real-time planning using loose seeds within the centre of the gland allows seed placement to be readily adjusted in theatre based on real-time needle and seed ultrasound feedback. It also facilitates variable inter-seed spacing.

4D brachytherapy achieves the best of both worlds. Stranded seeds from a patient-specific customised preloaded kit are placed around the periphery of the prostate assuring seed fixity. The use of loose seeds in the peri-urethral tissue affords flexible optimisation of the dose plan, particularly at the prostatic apex and penile bulb. Here we showed improved IPSS, urinary and bowel quality of life scores compared with the 2S conventional technique together with comparable proportions of potency preservation.

The commissioning of a low dose rate brachytherapy service involves a modest capital outlay and regulatory infrastructure. Currently the set-up cost of equipment in the UK is about £160 000 (personal communication with suppliers, March 2017). The cost of the treatment episode including the cost of iodine-125 seeds was £6407 per

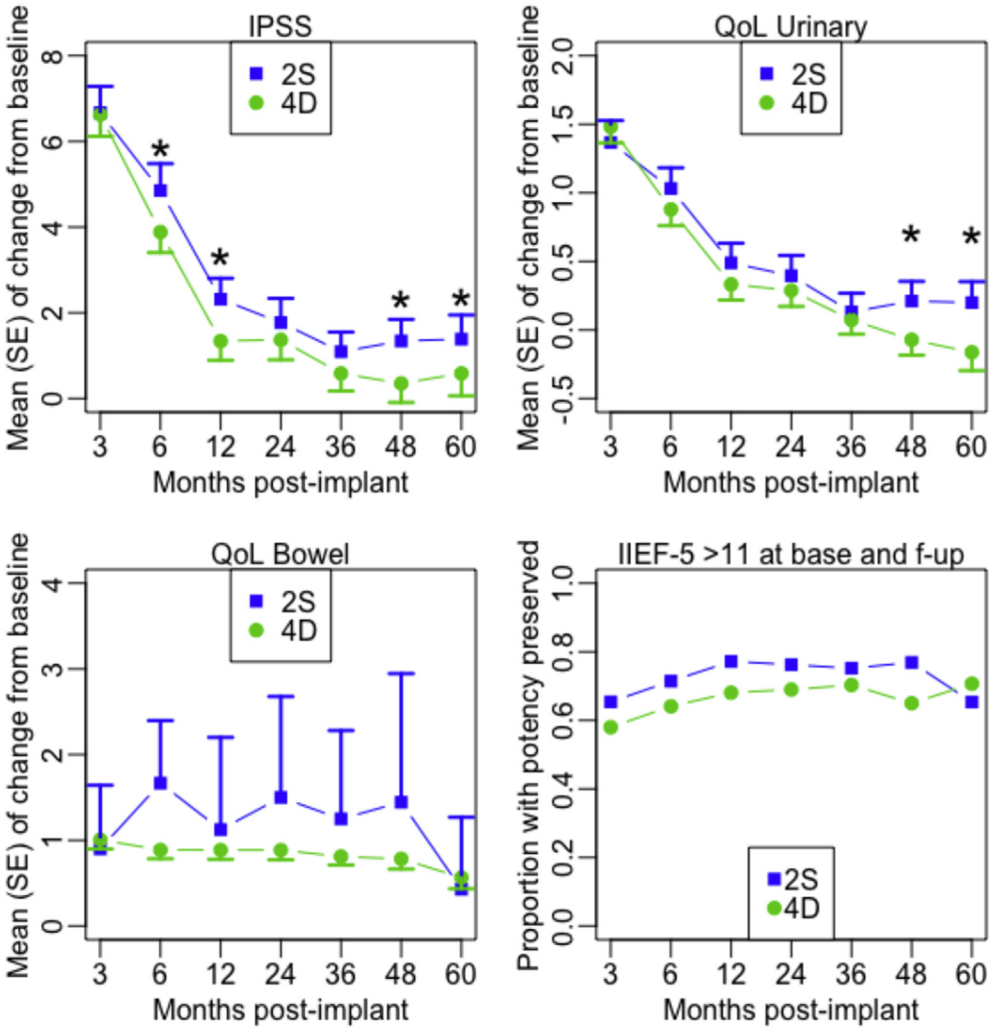


Fig 4. Urinary, bowel and erectile function toxicity outcomes. International Prostate Symptom Score (IPSS), urinary and bowel quality of life (QoL) assessments show the mean and standard error (SE) of the change in scores at the follow-up visits relative to the baseline. For erectile function the plot shows the proportion of potent cases (IIEF-5 score >11) at follow-up relative to the number of potent cases at baseline. Time points with a *P* value < 0.05 are indicated by an asterisk (Student's *t*-test in IPSS, urinary QoL and bowel QoL plots and by Fisher's test in the IIEF-5 plot).

patient in 2015 [11]. Compared with the activity-based costing in Ramsay *et al.* [11] we have reduced resource use in a number of the procedural steps. In the 4D approach an intraoperative planning session is unnecessary given that prostate volume measurements are calculated in the initial outpatient visit by means of TRUS. At that time, a patient-specific preoperative plan is generated by the 4D online nomogram and ordering system. During the procedure proper, Ramsay *et al.* [11] calculated that the urologist and oncologist are both in theatre for 2 h as opposed to the 45 min we take to carry out the 4D procedure. Furthermore, the preloaded kit precludes the need to load needles in theatre, affording savings in theatre and personnel time.

The cost of seeds was not included in our analysis. First, the objective of the comparison between the 2S and 4D techniques was to show the time-saving elements afforded by the latter and the effect on published NHS costs. Second, the price of seeds varies depending on presentation, regulatory and importation costs and commercial arrangements. Ramsay *et al.* [11] quoted seeds at £3088 per patient. The cost of the implant needles was reported separately. The kit used in 4D brachytherapy includes the stranded seeds in preloaded peripheral needles and loose seeds in Mick cartridges. The needles for the Mick applicator are acquired separately (Table 2). For fair comparison we have used the same cost of needles as the 2S method described by Ramsay *et al.* [11]. The procedural modifications associated with the 4D technique reduce the cost of the procedure carried out in our hospital by about 40% compared with the 2S technique without taking into account the specific cost of the seeds in either case. We treat on average 300 patients per year, so the optimisation of resources in the current climate of cost containment is considerable. NHS unit costs for personnel are published on a yearly basis [20]. However, other costs may be NHS Trust specific and as such the Health Technology Assessment

Table 2
Time activity based costs for 2S and 4D brachytherapy

Step	2S brachytherapy [11]				4D brachytherapy			
	Resource	h	Rate (£)	Cost per patient (£)	Resource	h	Rate (£)	Cost per patient (£)
Pre-treatment	Outpatient clinic			159.00	Outpatient clinic			159.00
	Urodynamics and TRUS			104.00	Urodynamics and TRUS			104.00
Subtotal				***263.00***				***263.00***
Planning session formal theatre volume case study	Theatre session			258.00	Volume data obtained in outpatient clinic			0.00
	Urologist	1.0	172.00	172.00				
	Oncologist	1.0	157.00	157.00				
	Physicist	2.0	26.40	52.90				
Subtotal				***639.90***				***0.00***
Prostate brachytherapy plan created	Consultant urologist	0.3	172.00	43.00	Physicist – generates plan with 4D software online, orders preloaded kit after approval by oncologist	0.5	26.40	13.20
	Physicist	0.3	26.40	6.60				
	Physicist	2.0	26.40	52.90	Oncologist	0.3	157.00	39.30
Subtotal				***102.50***				***52.50***
Implantation procedure	2× brachytherapy physicist technicians	2.0	22.20	44.30	NA			0.00
	Seeds			0.00	Implant kit includes seeds preloaded in peripheral needles and loose seeds for Mick applicator			0.00
	Needles: 28 per patient			225.00	Mick needles: 6 per patient			225.00
					Physics quality assurance of implant kit	0.3	26.40	6.60
	Disposables			144.30	Disposables			144.30
	Theatre session	2× 258.00		516.00	Theatre session	1× 258.00		258.00
	Urologist	2.0	172.00	344.00	Urologist	1.0	172.00	172.00
	Oncologist	2.0	157.00	314.00	Oncologist	1.0	157.00	157.00
	2× medical physicist brachytherapy technicians	4.0	22.20	88.70	Physicist	2.0	26.40	52.90
	Radiographer	2.0	22.20	44.30	Radiographer		NA	0.00
Subtotal				***1720.70***				***1015.80***
Post-implant MRI and CT scan	1 night length of stay*			321.00	1 night length of stay*			321.00
	CT scan			92.00	CT scan			92.00
	Radiographer	0.5	18.50	9.20	Radiographer	0.5	18.50	9.20
	MRI scan			199.00	MRI scan			199.00
	Radiographer	0.5	18.50	9.20	Radiographer	0.5	18.50	9.20
Subtotal				***630.50***				***630.50***
Post-implant quality assurance				81.50				81.50
Subtotal				***81.50***				***81.50***
Total without seeds				£3438.10				£2043.30

TRUS, transrectal ultrasound; MRI, magnetic resonance imaging; CT, computed tomography; h, hours.
* When indicated.

evaluation published by the NHS National Institute for Health Research [11] was used as a benchmark for time and resource use to provide a fair comparison between the 2S and 4D techniques.

In conclusion, 4D brachytherapy is as efficacious as the 2S method for disease control of localised prostate cancer with reduced treatment-related toxicity and reduced cost. Further follow-up will assess disease

control superiority of 4D brachytherapy beyond 5 years post-implant.

Conflicts of Interest

SEML and RL report personal fees, non-financial support and other from BXTAccelyon, outside the submitted work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clon.2017.09.006.

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