BJUI
BJU SUPPLEMENTS
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LDR Brachytherapy: Latest Advances in Prostate Cancer Treatment

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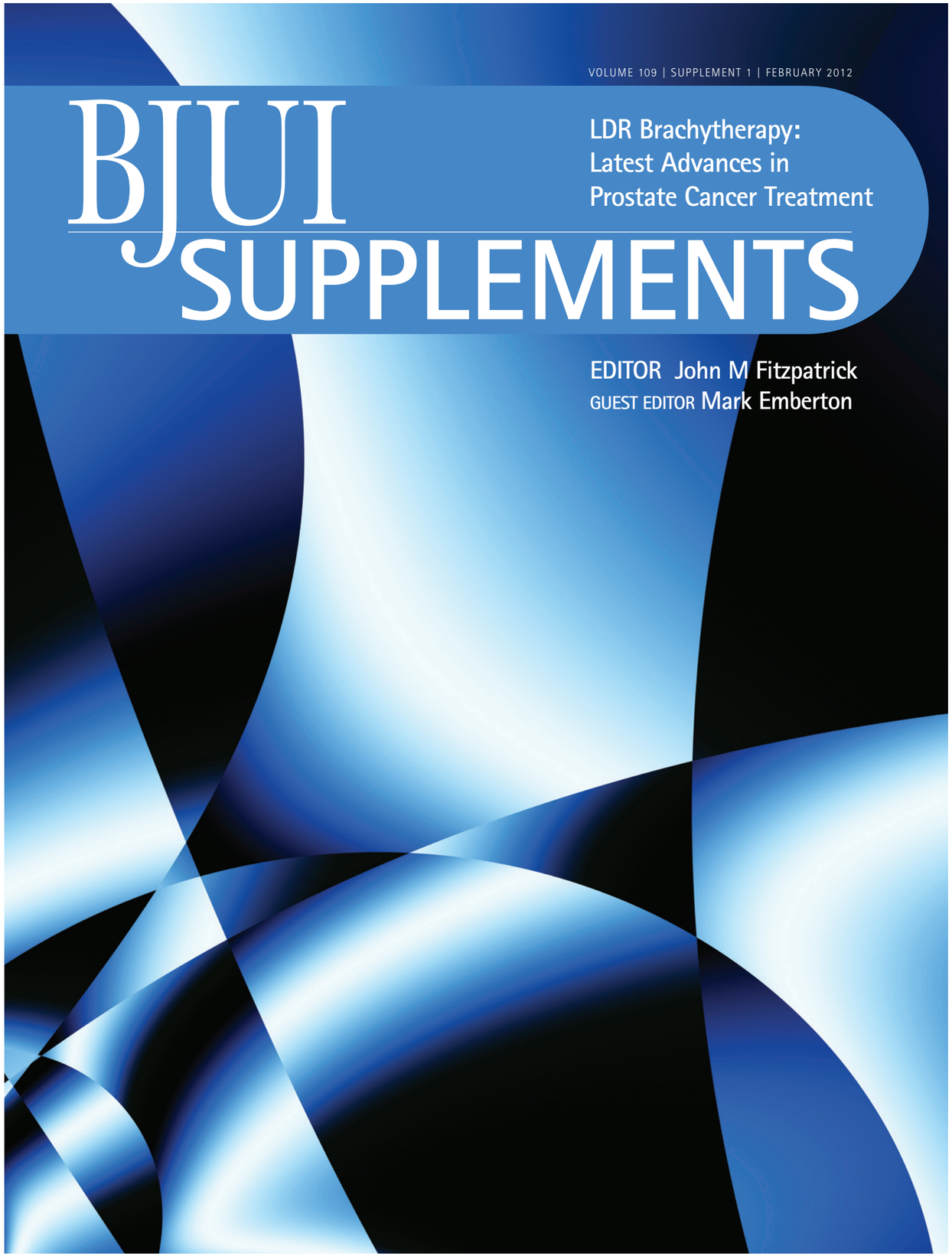

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LDR Brachytherapy: Latest Advances in Prostate Cancer Treatment

GUEST EDITOR
M. Emberton

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Foreword

Mark Emberton

Brachytherapy has been used in the treatment of prostate cancer since the 1970s. Contemporary practice, however, bears little resemblance to those first treated cases. The transforming technology has been transrectal ultrasound, as this has enabled the prostate to be seen with good resolution allowing inputs into planning (volume) and real-time execution of the plan (the placement of the seeds). Gradual but steady increments have been achieved as a result of the refinements in the software traditionally used to plan treatments but now capable of informing real-time implants. This supplement is for both the clinicans performing brachytherapy as well as the interested but dislocated observer who offers his or her patients brachytherapy as part of the therapeutic options, but does not actually perform it. It hopes to signpost the areas in which both development and innovation are active. In this sense, it will serve as a refresher by updating the reader on how brachytherapy is currently applied in the best centres.

This is nicely illustrated in the paper by Langley and Laing in which a novel, one-stage real-time brachytherapy implant technique, termed 4D Brachytherapy, is described involving the deployment of both stranded and loose seeds. The technique is based on an algorithm derived from over 1000 prior procedures and provides the operator with a predictive model to assist the conduct of the implant. The outputs include improved dosimetry, reduced operating time and improved short-term morbidity.

As well as these valuable updates I would like to draw your attention to something new. I have great personal pleasure in highlighting a novel paper – the first of its type I believe – summarizing a consensus meeting that was recently convened to see whether brachytherapy implants could be planned and executed in a tumour-selective manner. The consensus findings provide guidance on patient selection for focal brachytherapy as well as recommendations for conducting therapy and patient follow-up. The consensus meeting also addressed the difficult question of how best to approach the design of a phase II/III study on focal brachytherapy.

One of the main reasons why patients choose therapies other than radiotherapy is that they worry about the salvage opportunities should the radiation treatment fail. The prevailing view is that salvage treatment for radio-recurrent disease is usually difficult to perform and is associated with poor oncological and functional outcomes. In this issue, Veiga and colleagues reconsider the situation by reviewing the role of salvage brachytherapy for patients who have failed after their primary radiotherapy. They introduce the notion of using a precise form of brachytherapy in patients with proven recurrence after radiation failure. The results reported in the few series that exist suggest that this is an area worthy of scrutiny, citing favourable biochemical disease free survival rates compared with other salvage methods. The intriguing area of managing failure after radical surgery is also addressed. In this situation, the standard of care remains external beam radiation therapy. The authors explore a recent initiative led by a Spanish consortium in which brachytherapy is used as a salvage therapy in the setting of biochemical failure after surgery. The low toxicity profile and good early oncological results suggest that this is also an area that warrants further scrutiny.

The final objective of this supplement is to provide updated results for us to share with our patients. Techniques evolve with time and results improve. Informed consent demands that we share the most recent data associated with an intervention as well the results achieved within the institution in which the patient is considering being treated. The report from the Prostate Cancer Results Study Group does this for us. It summarizes the literature published from 2000 to 2010 on studies describing the 5-year outcome of therapy in men with prostate cancer. It provides, in my view, a very useful and timely summary that will allow us to provide information on contemporary outcomes of care and, moreover, apply them in a risk-stratified manner.

I do hope that you enjoy reading this issue and that, more importantly, it will give you insights into the future as well as providing information on the exact place of brachytherapy as we approach 2012.

CONFLICT OF INTEREST

Mark Emberton receives funding from USHIFU, GSK and Advanced Medical Diagnostics for clinical trials. He is a paid consultant to Steba Biotech and has received funding from USHIFU/Focused Surgery/Misonix Inc./UKHIFU (manufacturers and distributors of the Sonablate500 HIFU device) for medical consultancy and travel to conferences.

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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

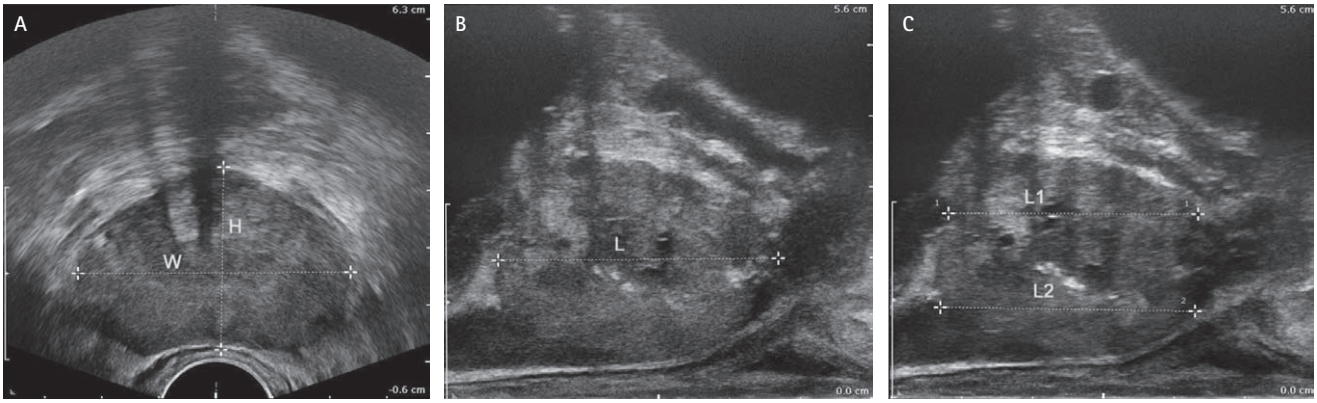
brachytherapy, prostate cancer, 4D Brachytherapy, realtime planning

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.*

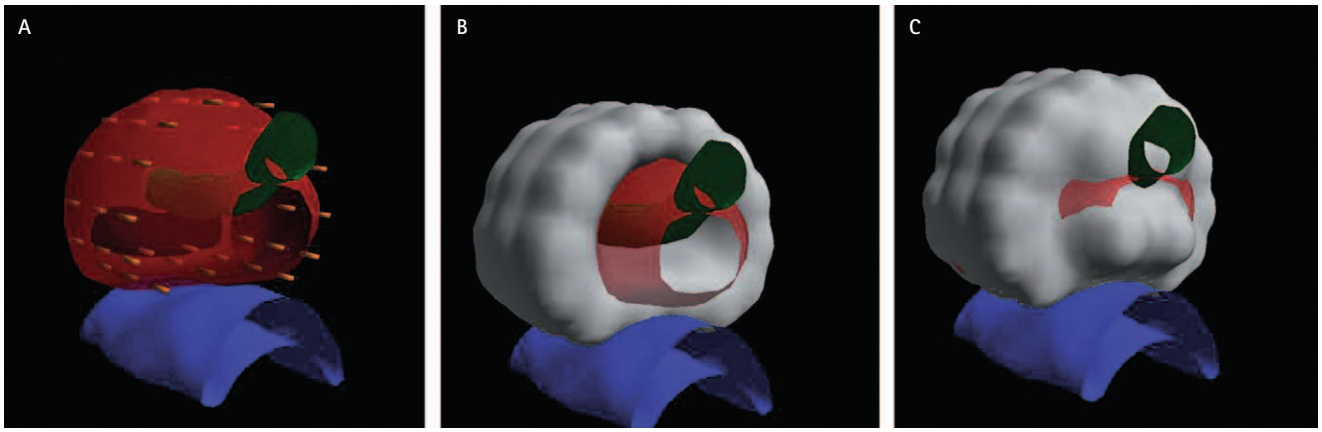


TABLE 1 Patient characteristics

	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.

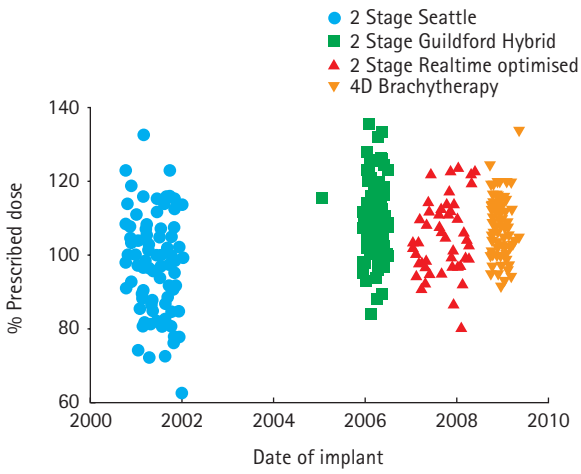


FIG. 3.
Dosimetry according to the brachytherapy technique.

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 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

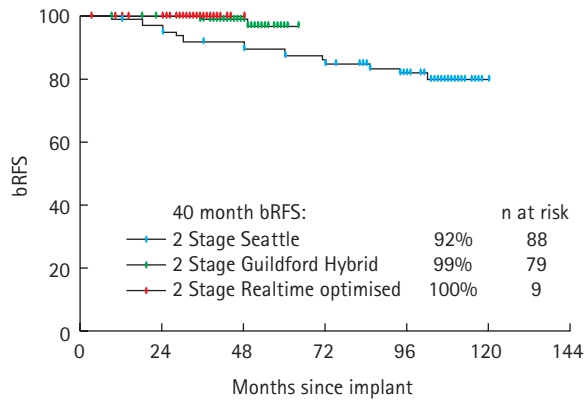


FIG. 4. Biochemical relapse free survival (bRFS) following brachytherapy.

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.

BJUI SUPPLEMENTS

Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer

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Low dose rate prostate brachytherapy is an effective treatment for localized prostate cancer. Recently, it has been considered for use in a focused manner whereby treatment is targeted only to areas of prostate cancer. The objective of focal brachytherapy is to provide effective cancer control for low-risk disease but with reduced genitourinary and rectal side-effects in a cost-effective way. We report on the outputs of a consensus meeting of international experts in brachytherapy and focal therapy convened to consider the feasibility and potential development of focal brachytherapy. A number of factors were considered for focal brachytherapy including optimal patient selection, disease characterization and localization, treatment protocols and outcome measures. The consensus meeting also addressed the design of a clinical trial that would assess the oncological outcomes and side-effect profiles resulting from focal brachytherapy.

What's known on the subject? and What does the study add?
Whole gland brachytherapy has been used to successfully treat prostate cancer but the protocol for focal therapy has not previously been established.

The consensus findings provide guidance on patient selection for focal brachytherapy as well as recommendations for conducting therapy and patient follow-up.

KEYWORDS

prostate cancer, brachytherapy, focal therapy, patient selection, outcome

INTRODUCTION

Low dose rate (LDR) brachytherapy is a recognized treatment option for localized prostate cancer [1], with good functional and oncological outcomes reported to 15 years [2]. Currently, brachytherapy encompasses the whole gland, in common with other treatment options such as radical prostatectomy, external beam radiotherapy, cryotherapy and high intensity focused ultrasound (HIFU). Whole gland treatment may be associated with side-effects such as erectile dysfunction, incontinence and rectal toxicity due to the effects on the surrounding structures (neurovascular bundles, sphincter, bladder neck, rectal wall). As early detection becomes more widespread, prostate cancer is being diagnosed at an earlier stage with an associated lower disease burden [3]. With improved imaging techniques [4] coupled with better sampling of the prostate [5] it is possible to identify men with low- to intermediate-risk prostate cancer who have low volume focal disease and who may be suitable for tissue preservation strategies. Depending on risk categories selected and the focal ablative strategy employed, it has been estimated that between one-half [6] and two-thirds [7] of men with prostate cancer may be amenable to some form of focal therapy.

Until quite recently, focal therapy was limited to the ablation technologies that tend to exploit extremes of temperature in order to achieve the targeted cell kill, such as cryotherapy and HIFU [8]. It might seem more logical to consider whether a therapy might be suitable for focal application after it has been demonstrated to be effective as a whole gland treatment. However, the radiotherapy community has been relatively slow in applying their techniques to the challenges of defining a therapeutic target around the cancer focus or foci rather than the organ that contains it. Signs are that this is changing [9]. This report describes the output of a recently convened international consensus meeting that was constituted to provide a clear development pathway for the focal application of LDR brachytherapy seeds. It was, we believe, the first expert panel of its type to address the issue of focal brachytherapy and comprised individuals with a wide range of expertise in the field.

CONSENSUS PROCESS

The consensus meeting involved a multidisciplinary board of international contributors that represented a wide range of expertise and competences pertinent to

the primary objective of the meeting. Together the group have experience in performing over 10 000 prostate cancer brachytherapy procedures over the past 25 years and can be considered experts in this field (Table 1). The primary objective of the meeting was to seek consensus on defining (i) the appropriate patient population; (ii) the manner of evaluation; and (iii) the conduct of treatment for focal brachytherapy. A secondary objective was to design, in outline, the structure of a phase II trial evaluating this novel approach. The meeting, which was co-chaired by Professor Stephen Langley (Guildford, UK) and Professor Mark Emberton (London, UK), conformed to the three generally accepted stages of a consensus process [10]. Items for discussion were preselected and individual members of the board were tasked with reviewing the published evidence relating to the topic. The findings were then presented to the other members at the meeting with this used as the basis for a moderated discussion (Level 1). Within this section of the meeting issues relating to the topic were resolved (Level 2). A consensus was established, noting any individuals who were not in agreement with the general view on specific items (Level 3).

TABLE 1
Attributes of the consensus panel

Name	Speciality	Country
H. Ahmed	Academic urologist	UK
B. Al-Qaisieh	Radiation physicist	UK
D. Bostwick	Pathologist	USA
L. Dickinson	Academic urologist	UK
M. Emberton	Urologist	UK
F. Gomez Veiga	Urologist	Spain
P. Grimm	Radiation oncologist	USA
S. Langley	Urologist	UK
S. Machtens	Urologist	Germany
F. Guedea	Academic radiation oncologist	Spain

TABLE 2 Disease classification [56]

Disease status	Characteristics
Clinically insignificant disease	Gleason 3 + 3 and maximum lesion length ≤ 3 mm equivalent to a maximum cancer volume $V = (4/3)\pi r^3 = 0.014$ mL
Indeterminate disease	Gleason 3 + 4 and/or maximum lesion length 4–5 mm equivalent to a maximum cancer volume of 0.065 mL
Clinically significant disease	Gleason ≥4 + 3 and/or maximum lesion length ≥ 6 mm equivalent to a maximum cancer volume of 0.113 mL

CONSENSUS FINDINGS

PATIENT SELECTION

Patient selection was discussed in terms of imaging and biopsy protocols required to accurately identify and localize disease that may be amenable to a focal approach.

Imaging

A number of imaging techniques are being evaluated for the localization of prostate cancer including B-mode ultrasound, colour Doppler imaging, contrast enhanced ultrasound, elastography and sonohistology. These imaging techniques capitalize on the difference in vascularity and tissue density of the tumour compared with normal prostate tissue. A number of studies have evaluated the effectiveness of localizing cancer in the prostate with colour Doppler ultrasound [11,12] or contrast enhanced ultrasound [13,14]. Inconsistent outcomes suggest that further research is required. Colour Doppler ultrasound directed biopsies have been used in one study prior to men undergoing focal cryotherapy [15].

Elastography imaging is based on the premise that significant differences exist between the elastic properties of normal and cancerous prostate tissue [16] and it may play a role in identifying large tumours. HistoScanning™ is a tool for differentiation, visualization and quantification of changes in solid organ tissue using an ultrasound image and computer program to identify suspicious areas. It has shown some promise in a small series of patients, with positive predictive values (PPV) for tumours sized ≥0.2 mL and ≥0.5 mL of 95% and 100%, respectively [17]. The PPV values at the larger size range can be attributed to the fact that several of the tumours detected were considerably larger than 0.5 mL. In common amongst studies using novel ultrasound imaging techniques is a lack of rigour in the methodology and the absence of a robust reference standard. In particular, because of the lack of sound-wave penetration leading to incomplete gland assessment, ultrasound may be particularly limited to those men with smaller glands without significant areas of calcification. The majority of studies have not set thresholds for identifying clinically significant cancer and further research is needed.

Magnetic resonance imaging (MRI) in the form of multi-parametric (mp) MRI [18] has been proposed as an improved imaging technique for the identification of prostate tumours when functional sequences (diffusion-weighting, dynamic contrast enhancement, MR spectroscopy) are combined with conventional anatomical sequences (T1 and T2 weighting). Villers *et al.* [19] have shown that mpMRI using pre-biopsy pelvic phased array dynamic contrast enhanced imaging is an accurate technique for detecting and quantifying intracapsular transition or peripheral zone tumour foci >0.2 mL. The study also reported that the negative predictive value (NPV) of identifying a tumour sized 0.5 mL was 95% and the PPV was 77%. Sensitivity and specificity for this tumour size were 90% and 88%, respectively. It has been proposed that a distinction can be made between clinically insignificant disease, indeterminate disease and clinically significant disease on the basis of Gleason score and tumour volume (Table 2) [20]. MRI was reported as identifying indeterminate and clinically significant disease with 88% and 97% NPV, respectively, but was less accurate for the clinically insignificant disease (NPV 60%) [21]. Good sensitivities and specificities were reported for both indeterminate (75%, 83%) and clinically significant (84%, 77%) disease. A number of series have now been published showing

TABLE 3 Consensus findings on patient selection for focal therapy

1. Life expectancy >10 years
2. PSA ≤15 ng/mL
3. Multi-parametric (T1W/T2W, diffusion-weighting, dynamic contrast enhancement ± spectroscopy) magnetic resonance imaging prior to biopsy
4. Bilateral template-guided prostate mapping biopsy with 5 mm sampling frame
5. Unilateral disease; lesion size ≤ 0.5 mL (approximately equates to maximum cancer length of 10 mm) with or without clinically insignificant disease on the contralateral side (cancer core length ≤ 3 mm)
6. Gleason score of index lesion 6–7 (3 + 4)
7. Tumour stage ≤ T2b
8. Prostate size ≤ 60 mL

high sensitivities and specificities using MRI-guided targeted biopsy sampling [22–24].

The uptake of mpMRI has been compromised by discordance between outputs in the USA and Europe, the variable conduct and reporting of the technique, and reimbursement issues. Recommendations on the application of MRI as a diagnostic tool have been published as a result of a European consensus meeting that took place in 2010 [4]. One of the recommendations of the meeting was the division of the prostate into 16 sectors in order to facilitate standardized reporting of tumour location.

It was considered by the committee members that the use of mpMRI, ideally prior to biopsy, would result in a more precise risk stratification and rule out the difficulties of imaging interpretation that result from biopsy haemorrhagic artefact. However, a more pragmatic trial design would also allow post-biopsy mpMRI to be performed, but at a minimum period of 6 weeks following biopsy.

Biopsy

Variance in prostate biopsy quality has been reported from the perspective of both the urologist performing the biopsy (e.g. biopsy length and location, number of cores, methodology) and the pathologist analysing the biopsy samples (e.g. number of tissue cuts per specimen, interpretation, processing and cutting skills) [25,26]. Sampling variation has been shown to result in tumour undergrading in over 10% to as many as 30% of cases and in understaging in ≥ 25% of cases [27]. Sensitivity and specificity increased when the number of biopsy cores was increased from six to 12 cores [28], although 12 cores was not considered sufficient for selecting patients for focal therapy. The use of transperineal biopsies, first described in 2004 [5], used in a three-dimensional mapping technique with samples taken using a 5 mm sampling frame has been shown to identify bilateral disease in 39% of cases that were previously negative on transrectal ultrasound (TRUS)-guided biopsy [27].

Biopsy findings have indicated a number of important facts with regard to the use of focal therapy. Overall, in series published since 2000 it was shown that between 13% [29] and 35% [30] of prostate cancers were unifocal and that, in low-risk disease, only 1% of unifocal lesions showed extracapsular extension [31]. In multifocal disease, 97% of index lesions had the same Gleason grade as the overall cancer [32]. More recently, Svennson *et al.* [33] showed intra-tumoral heterogeneity for E26 transformation-specific gene rearrangements in 7% of tumours [33].

Metastatic deposits appear to originate from a single focus of cancer [34]. What has been questioned is whether this focus is always the index lesion [35], although more recent studies by Guo *et al.* [36] suggest that this is indeed the case. Ohori *et al.* [31] reported that 92% of extracapsular extension came from the index lesion. It has also been suggested that non-index lesions have little or no immediate clinical significance [37–39]. The consensus findings on patient selection for focal therapy are summarized in Table 3.

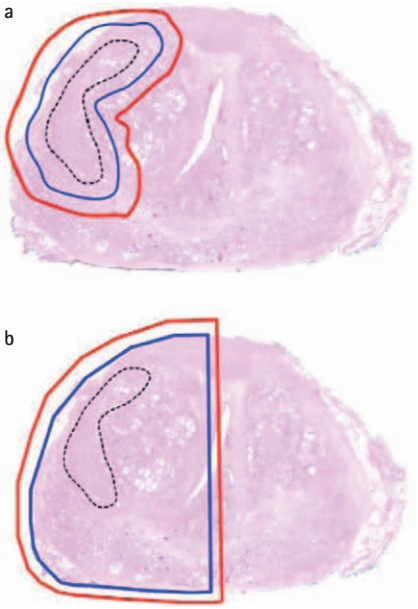
TECHNICAL CONSIDERATIONS FOR FOCAL BRACHYTHERAPY

It was considered by the consensus panel that, in focal brachytherapy, a pre-planned approach [40] would initially be sensible, ideally involving an image fusion of TRUS with mpMRI. The ability to monitor the procedure with intraoperative dose planning software would also be desirable [40]. The technical limitation of the difference between patient positioning on MRI and during seed placement is currently being investigated using treatment planning systems to match and fuse the magnetic resonance image to the ultrasound image [41]. However, such image fusion technologies are currently not in widespread clinical use.

The initial use of a two-step brachytherapy procedure (pre-plan approach) would allow more time to develop an implant strategy utilizing all the imaging and biopsy results available. When reviewing the characteristics of the different permanent seed isotopes available (^{125}I, ^{103}Pd and ^{131}Cs) it was noted that ^{125}I had the most favourable characteristics. The combination of a relatively shorter half-life of isotopes such as ^{103}Pd and ^{131}Cs together with oedema, induced by needle insertion and radiation, could lead to a geographical miss and under-dosing around the periphery of the target volume, in particular with ^{131}Cs with the shortest half-life [42,43]. In addition, with ^{131}Cs the implant geometry is less flexible because of the relatively higher seed energy, dose rate constant and the recommended use of source strength according to the Bice *et al.* protocol [44]. This makes it more difficult to place seeds closer to the urethra with ^{131}Cs, which would be an important consideration in focal brachytherapy.

With regard to seed type used, it was considered preferable to use stranded or linked seeds at the periphery of the prostate in order to overcome the issue of seed migration, which would be more critical in focal brachytherapy. However, the greater flexibility afforded by loose seeds may be important for implanting the central portion of the prostate as in a hemi-gland implant. Here the irregular course of the prostatic urethra can be difficult to avoid with connected seeds. With regard to seed activity, lower activity seeds seem preferable

FIG. 1. Target definition for focal brachytherapy: (a) ultra-focal approach; (b) hemi-focal approach. The red line represents F-PTV, the blue line F-CTV and the dotted line F-GTV.

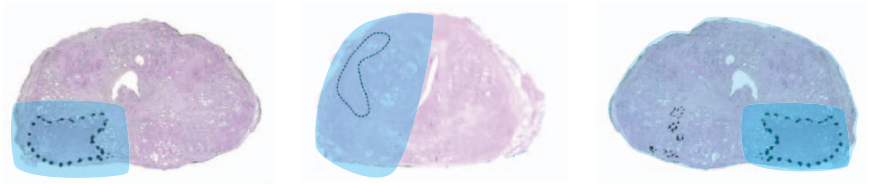


as they can be spaced closer together, which may prove beneficial in conforming the prescription dose to the target volume.

Currently, the clinical target volume (CTV) for prostate brachytherapy is the whole prostate gland plus a 3 mm margin [45]. New terminology was suggested for focal brachytherapy including F-GTV, the gross visible or clinically demonstrable location and extent of the targeted cancer; F-CTV, F-GTV plus clinically insignificant disease; and F-PTV, F-CTV plus a margin to compensate for uncertainties in image registration and treatment delivery, such as movement (Fig. 1). F-PTV contours would be restricted to organs at risk contours such as urethra and rectum. The actual margin size was undetermined at the present time.

A number of treatment scenarios were considered in the focal brachytherapy setting (Fig. 2). In patients with unilateral disease, an *ultra-focal* or focal (hemi-gland) protocol could be considered delivering 145 Gy. For the patient with a unilateral index lesion but with a degree of clinically insignificant disease on the contralateral side a *focused therapy* option might be considered with 145 Gy given to the side of the prostate with the index lesion plus a lower dose applied to the contralateral side.

FIG. 2. Focal brachytherapy options.



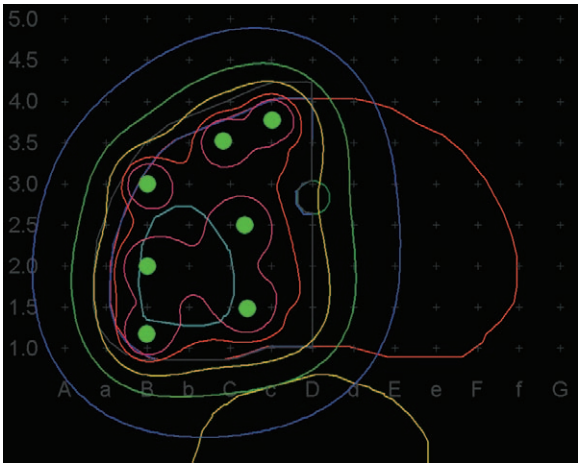


FIG. 3. Dosimetry for a hemi-ablation brachytherapy approach using 145 Gy.

Prescription dose	Source strength	No. needles	No seeds	
145 Gy	0.5 U	14	44	
DVH parameters				
	Prostate	F-GTV	F-CTV	F-PTV
Volume (cc)	35.7	3.2	16.3	19.4
V200 (%)	16.1	65.32	35.1	31.5
V150 (%)	34.6	99.3	76.0	69.1
V100 (%)	48.6	100	98.5	98.1
D100 (Gy)	14.4	204.4	94.8	94.25
D90 (Gy)	31.4	256.4	184.5	175.0
Urethra				
Volume (cc)	0.5			
V150 (cc)	0.0			
D30 (%)	103.2			
D10 (%)	113.6			
Rectal Wall				
D2cc (Gy)	66.8			
D0.1cc (Gy)	117.5			

For the ultra-focal protocol, loose seeds might be preferable. Dosimetric calculations for the hemi-ablation approach involving 145 Gy are shown in Fig. 3. It may be feasible that treatment of one side of the prostate might result in a radiation dose being received on the contralateral side with beneficial results. Careful consideration

TABLE 4 Consensus findings on technical considerations for focal brachytherapy

1. Pre-planning method should be used initially; implement interactive/dynamic technique during treatment
2. ^{125}I linked seeds with low activity ~ 0.5 U
3. Target definitions to be used: F-GTV, F-CTV and F-PTV
4. Shape of the prostatic urethra to be considered and organs at risk identified
5. Consideration to be given to the organs at risk: urethra, rectum, penile bulb, contralateral neurovascular bundle at apex
6. Further modelling is required for prescription dose recommendations. Options discussed were
   - hemi-gland brachytherapy to the target lesion side of the gland (145 Gy) + low dose to whole gland in men with unilateral disease + clinically insignificant disease on the contralateral side
   - hemi-gland brachytherapy to the target lesion side of the gland (145 Gy) in men with unilateral disease
7. Post-implant dosimetry conducted within 24 h or at 4 weeks

should be given to the rectal and urethral dose and should follow the current guidelines for whole gland brachytherapy [45].

Post-implant dosimetry was recommended either within 24 h of the procedure or at 4 weeks following implant to assess the quality of the procedure. The consensus findings on technical considerations for focal brachytherapy are summarized in Table 4.

POTENTIAL MEASUREMENTS OF OUTCOME FOLLOWING FOCAL THERAPY

Tissue biomarkers

The majority of papers on focal therapy published to date have used the kinetics of prostate-specific antigen (PSA) as the basis for their outcome variables and the threshold for biopsy. Newer biomarkers that are actively being studied include transmembrane protease serine 2 (*TMPRSS2*)–*ERG* gene fusion, the phosphatase and tensin homologue (*PTEN*) gene and prostate cancer gene 3 (*PCA3*). The *TRMPRSS2*–*ERG* gene fusion is specific to prostate cancer and has been identified in 41% of cases of moderately to poorly differentiated prostate cancers [46]. Urinary engrailed-2 (*EN2*) is a promising new biomarker that has been shown to have 66% sensitivity and 90% specificity in prostate cancer detection [47].

Imaging biomarkers

As in the setting of pretreatment localization, post focal brachytherapy imaging using mpMRI may have a role in determining recurrent or residual disease [48]. Early studies show promise in this regard but require validation in focal brachytherapy studies [49,50].

Biopsy

Prospective trials evaluating focal therapy in other ablative therapies have incorporated histological outcomes as the primary determinant to verify cancer control [51]. Following brachytherapy, histological outcomes require at least 2–3 years to demonstrate absence of cancer and can be difficult to interpret. However, in expert histopathology hands it was agreed that biopsies at 2 years would give clinically meaningful outcomes on cancer control.

SALVAGE THERAPY POST-FOCAL BRACHYTHERAPY

Regarding treatment recurrence following focal brachytherapy, patients should be offered an appropriate treatment option. For recurrence on the treated side, surgery, cryotherapy or HIFU can be considered. However, whole gland salvage HIFU for brachytherapy failures has been associated with a recto-urethral fistula rate of 60% (3/5 patients) [52], and about 2% for whole gland salvage for failed external beam radiotherapy; the rate for focal HIFU after failed external beam radiotherapy is 2.5% [53,54]. Limited data exist on salvage cryotherapy for brachytherapy failure with the absence of prospective clinical trials (although it is likely that similar rates of rectal toxicity are probable). Equally, outcomes from a focal salvage approach for failed brachytherapy are uncertain and caution should be taken in salvage ablative therapy after brachytherapy. For recurrence on the contralateral side, a focal therapy (brachytherapy, cryotherapy, HIFU, intensity-modulated radiotherapy) protocol could be considered in patients seeking curative treatment. Watchful waiting or delayed hormonal therapy are also options for patients not wanting additional treatment.

FOCAL BRACHYTHERAPY CLINICAL TRIAL PROTOCOL PROPOSAL

A number of focal therapy trials are ongoing involving HIFU, cryotherapy and thermal laser techniques including those shown in Table 5. Two focal brachytherapy studies have been initiated, one involving hemi-gland brachytherapy [9] and the other an ultra-focal protocol [55]. The majority of studies involve low grade disease (Gleason 6 only) and TRUS or template biopsy with or without mpMRI for disease localization. The most common primary outcome parameter due to the short follow-up time is adverse events. A discussion took place on the protocol for a clinical trial on focal brachytherapy that could be undertaken by the present group. The proposal was for a 3-year randomized phase II study involving focal (hemi-gland implants), focused and whole gland arms. The concept of ultra-focal treatment was not considered at this stage due to the inherent difficulty of subsequently re-biopsying the treated position of the gland 2 years later.

The process of selecting patients for the focal brachytherapy clinical trial is shown in Fig. 4. Men would undergo template prostate mapping using a 5 mm sampling frame as the primary determinant for entry into the trial, with disease risk stratified according to recent validation studies [56]. Patients identified as having unilateral disease and patients with bilateral disease with the non-index microscopic lesion on the contralateral side up to Gleason score 6 and ≤3 mm in size would be randomized to focused, focal (hemi-ablation) or standard brachytherapy. It was considered important to include a whole gland treatment arm in order to allow the identification of potential improvements in safety and quality of life outcome measures with focal brachytherapy over standard treatment. It was noted that at some centres it might be difficult to randomize patients to whole gland therapy

TABLE 5 Examples of current recruiting clinical trial protocols involving focal therapy for prostate cancer

	Study phase	Treatment	No. of patients	Gleason grade	Inclusion tests	Primary	Secondary	Follow-up (months)
Guazzoni *et al.* Italy	I	Cryotherapy (hemi-ablation)	100	≤ 6	TPM (≥12 cores)	• Safety, feasibility, tolerability • Oncological	Changes in QoL	60
Eggener *et al.* USA	I	MRI-targeted laser-based thermotherapy (Visualase; ultra-focal)	20	≤ 7	TRUS + MRI	Adverse events	–	6
Trachtenberg *et al.* Canada	I	MRI-targeted interstitial laser thermal therapy (ultra-focal)	15	Any grade	TRUS + MRI	Oncological	–	4
Zelefsky *et al.* USA	II	Brachytherapy (hemi-gland)	80	≤ 6	TRUS	Adverse events	• Oncological • Changes in QoL • Correlation of postoperative endorectal coil MRI with histology	24
Emberton *et al.* UK	II	HIFU (quadrant or hemi-ablation)	140	≤ 7	TPM + MRI	Oncological	• Functional outcomes • Short-term oncological outcomes • Changes in QoL • Health economic analysis • Correlation of imaging with histology (TRUS at 12 months and TPM at 3 years)	38
Cosset *et al.* France	I	Ultrafocal brachytherapy	10	4 or 5	Biopsy + MRI	Adverse events	–	

TPM, template biopsy; QoL, quality of life; MRI, magnetic resonance imaging; TRUS, transrectal ultrasound; HIFU, high intensity focused ultrasound.

when their preference might be for a more focal approach. One trial design that could be considered was a preference based study in which men are offered a choice of two treatments and are then randomized to either treatment. This type of preference based randomization is a recognized study format [57]. Physician opinion would also be involved in the randomization process.

Outcomes of the study would be classified into cancer-related, functional and health economics aspects. Biopsy at 2 years after focal brachytherapy should follow the same protocol as used for study entry, i.e. 5 mm template prostate mapping. Clinicians would be permitted to perform 'for-cause' biopsies if PSA levels increased to pretreatment levels. The occurrence of any disease on the treated side would be classed as a failure, while the occurrence of microscopic disease on the contralateral side would not be classed as a failure in focal (hemi-gland) implants as this may have been present in the initial presentation due to sampling errors that are inherent even in 5 mm template mapping. PSA and other biomarkers should be measured at 3 monthly intervals for the first year and 6 monthly thereafter. Biochemical failure for brachytherapy is currently based on the Phoenix definition (nadir + 2) [58], and in the absence of a specific definition for focal brachytherapy this was considered to be one of the definitions that could be applied. Other options included PSA doubling time and free:total PSA ratio, although the study design allowed a focal brachytherapy-specific definition to be derived and validated.

mpMRI should be conducted prior to any biopsy as this would help target the correct areas for biopsy. Functional outcomes would be assessed using a number of patient questionnaires including International Prostate Symptom Score, Expanded P rostate Cancer Index Composite, Short Form 36, International Index of Erectile Function 15, European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30, EORTC QLQ Pr25, Euro QOL, pain score and urinary diaries. A generic patient consent form would be instituted to collect urine, blood and tissue samples for future translational studies for biomarker discovery

FIG. 4. Consensus findings on a focal brachytherapy study protocol.

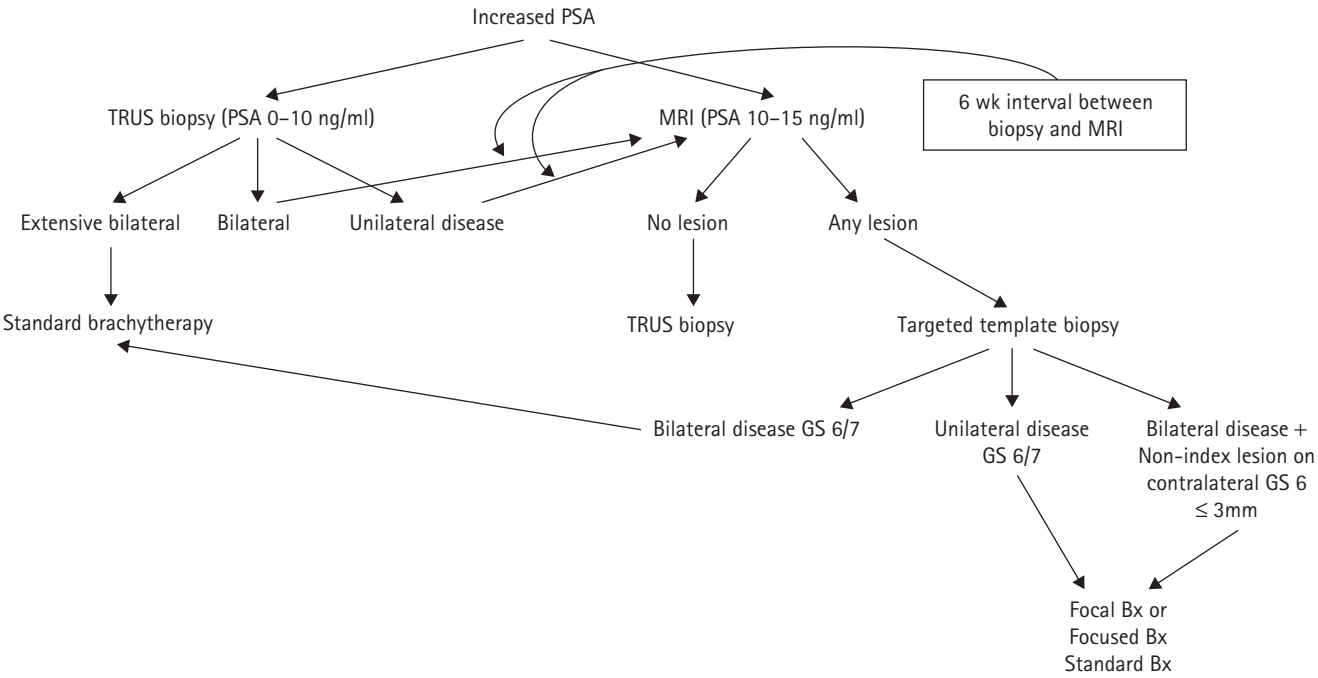


TABLE 6 Consensus findings on a focal brachytherapy clinical trial protocol: follow-up

1. Template prostate mapping biopsy (5 mm sampling frame) of treated and untreated tissue
2. PSA monitoring at 3-month intervals in year 1 and then 6 monthly
3. Biochemical progression free survival: options include Phoenix definition (nadir + 2), PSA doubling time, percentage free/total PSA
4. mpMRI prior to biopsy
5. Functional outcomes to be assessed using patient urinary diaries and patient questionnaires: IPSS, EPIC, SF-36, IIEF-15, EORTC QLQ C30, EORTC QLQ Pr25, Euro QOL, pain score
6. Health economics

IPSS, International Prostate Symptom Score; EPIC, Expanded P rostate Cancer Index Composite; SF-36, Short Form 36; IIEF-15, International Index of Erectile Function 15; QOL, quality of life; PSA, prostate-specific antigen; mpMRI, multi-parametric magnetic resonance imaging.

and validation. Health economics of focal, focused or whole gland brachytherapy was considered vital and would examine treatment costs (seed costs, operating room time) and overall cost-effectiveness. The consensus findings on patient follow-up are summarized in Table 6.

DISCUSSION

The consensus meeting achieved Level 3 consensus in the key areas that were predetermined: defining the population suitable for focal brachytherapy and establishing how LDR focal brachytherapy should be conducted and followed up. In addition, there was fairly good agreement on the disposition of a phase II study on focal brachytherapy. This indicates that we have navigated through both professional and technical barriers to entry, and as a result it should be possible to offer men focal brachytherapy within a trial context in the relatively near future. Before considering the implications of the consensus process, some methodological issues need to be considered. First, our chosen process was not formal in the sense that no objective scoring of opinion was sought. This was considered by the co-chairs but dismissed as unfeasible given time and financial constraints. The bias that this can introduce is that opinions are open and individuals may be more amenable to persuasion compared with a process that allows private voting. Nevertheless, we believe our outputs to be representative of the group as the meeting was conducted in an open and fair manner so that all participants had a voice. Second, it is normally good practice to have lay representation at such meetings. Once again it was decided by the chairs that, as the meeting was of such a technical nature, it would not be possible to incorporate lay views in the time permitted. Despite these limitations we feel that the outcome of the process should prove useful to the many brachytherapists who are considering embarking on a focal programme. We are aware of two trials that are currently recruiting, one in New York [9] and one in France [55]. We hope that as a result of the deliberations that took place within the meeting more studies will result from our consensus recommendations. In the immediate follow-up to the meeting, it was decided to undertake a dosimetry simulation study in order to determine the optimal dosing for the phase II study.

CONCLUSIONS

It is anticipated that these consensus findings will provide teams currently conducting prostate brachytherapy with guidance on patient selection for focal brachytherapy and recommendations for how the technique should be conducted. Future papers from this international committee will provide more specific recommendations on dosimetry and plan a roadmap forward to conduct the phase II randomized comparative study in a timely manner that would derive early results in order to benefit men with prostate cancer.

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CONFLICT OF INTEREST

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Abbreviations: **LDR**, low dose rate; **HIFU**, high intensity focused ultrasound; **PPV**, positive predictive values; **mpMRI**, multi-parametric magnetic resonance imaging; **NPV**, negative predictive value; **CTV**, clinical target volume; **EORTC**, European Organisation for Research and Treatment of Cancer; **PSA**, prostate-specific antigen.

BJUI SUPPLEMENTS

Brachytherapy for the treatment of recurrent prostate cancer after radiotherapy or radical prostatectomy

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Salvage therapeutic options following radical prostatectomy or radiotherapy for patients with local relapse of prostate cancer include radical prostatectomy, radiotherapy, brachytherapy or cryotherapy. Salvage radical prostatectomy following radiotherapy failure is associated with a 5-year PSA relapse-free rate of 30–40%. Biochemical relapse-free survival rates after salvage radiotherapy following radical prostatectomy failure range from 10% to 77% after a follow-up of 22–60 months. A number of studies have evaluated salvage brachytherapy for radiotherapy failure and 5-year biochemical disease-free survival (bDFS) rate results reported are of the order of 20–87%; one study reported a 10-year bDFS rate of 54%. Fewer studies in small numbers of patients and with shorter follow-up have been conducted on brachytherapy for radical prostatectomy failure and bDFS rates reported include 25.8% at a median of 29 months to 70% at a median of 20 months. The side-effects were as expected for brachytherapy. A newer initiative conducted in Spain in a larger series of 42 patients with failure following radical prostatectomy involves brachytherapy with RAPID Strand^{TM} ^{125}I seeds and real-time placement. The 5-year bDFS rate was 88.6% and cancer-specific survival was 97%; complication rates were low. Optimization of salvage brachytherapy is under way and involves accurate placement of seeds, dose optimization and optimal patient selection.

What's known on the subject? and What does the study add?
The curative treatment of prostate cancer includes surgery, external beam radiation or interstitial radiation. However, a high percentage of patients may develop recurrent disease, which is often localised. The possibilities of treatment in these cases, including surgery or adjuvant radiotherapy, are not well defined.

Brachytherapy is a well established first-line treatment option. We review and update the use of brachytherapy in the treatment of recurrences post-radiotherapy, brachytherapy or radical prostatectomy as an alternative to surgery and radiotherapy, with a focus on functional and oncological outcomes.

KEYWORDS

salvage therapy, radical prostatectomy, radiotherapy, brachytherapy, prostate cancer

INTRODUCTION

The two established therapies for localized prostate cancer are radiation therapy and radical prostatectomy [1]. Radiation therapy has proved successful for patients in different risk groups and reported 5-year prostate-specific antigen (PSA) relapse-free rates for low-risk patients are 75–85%, for intermediate-risk patients 58–65% and for high-risk patients 35–38% [2–4]. For radical prostatectomy 5-year PSA progression-free rates range from 69% to 84% and again vary according to specific risk group characteristics such as Gleason score, pathological stage and surgical margin status [5–9]. Salvage therapy options following failure of radiation therapy include radical prostatectomy, brachytherapy, high intensity focused ultrasound (HIFU) and cryotherapy. The European Association of Urology (EAU) guidelines recommend that, in general, salvage radical prostatectomy be considered only in patients with a low comorbidity, organ-confined prostate cancer <T2, Gleason grade <7 and pre-surgical PSA <10 ng/mL [1]. Interstitial brachytherapy and cryosurgery are options for patients who are not suitable for surgery while HIFU remains an experimental procedure. For patients with presumed systemic relapse, androgen deprivation therapy (ADT) is an option. A number of salvage radical prostatectomy series for radio-recurrent disease report an overall 5-year PSA relapse-free rate of 30–40% [3,10–12].

The EAU guidelines propose salvage radical prostatectomy, radiotherapy, cryotherapy or brachytherapy for local failures and ADT for systemic failure following radical prostatectomy [1]. Biochemical relapse-free survival rates following salvage radiotherapy range from 10% to 77% after a follow-up of 22–60 months [13].

SALVAGE BRACHYTHERAPY AFTER RADICAL PROSTATECTOMY

EFFICACY

There are very few reported series of patients undergoing salvage brachytherapy after radical prostatectomy and those that have been published involve small numbers of patients. Losa *et al.* [14] evaluated the use of brachytherapy following local relapse after radical prostatectomy in a series of 10 patients between October 1999 and March 2002. Eight of the patients also underwent external beam radiotherapy (EBRT) prior to brachytherapy, five patients for biochemical progression during follow-up and three immediately after surgery due to poor histological findings. The median interval (range) between surgery and brachytherapy was 60.2 (11–125) months and seed implants involved ^{103}Pd ($n = 2$) and/or ^{125}I ($n = 8$). Relapse was based on histological findings and was well defined on magnetic resonance imaging (MRI) and endorectal ultrasonography. PSA values were 1.1–6.1 ng/mL and one of the patients had metastatic disease. Seeds were implanted under ultrasound guidance using pre-planned dosimetry and a peripheral loading algorithm and with a planned target volume of 5–26.7 mL; the number of seeds implanted was 22–53. Post-implant dosimetry evaluation revealed a V_{100} of 84.5–95.9% and a D_{90} of 85.08–129.43%. The radiation dose received by the organs at risk was a D_1 of 44.54–261.17% for the urethra and a D_1 of 50.91–138.81% and a V_{100} of 0–0.23 mL for the rectum. At a median (range) follow-up of 20.6 (11–38) months one patient had died of disease progression at 25 months, one patient had biochemical progression at 24 months, and one patient had clinical and biochemical progression at 13 months. The remaining seven patients had progressively decreasing ($n = 3$) or stable ($n = 4$) PSA levels.

Niehoff *et al.* [15] employed a combination of intensity modulated brachytherapy (IMBT) and EBRT in 35 patients with transrectal ultrasound (TRUS)-visible local recurrence following radical prostatectomy [15]. All patients had a minimum of 5 mm between the tumour and anterior rectal wall and no infiltration of the bladder or the bladder neck. Mean (range) pre-radiotherapy PSA level was 5.02 (0.14–20.6) ng/mL and mean (range) time to PSA increase after surgery was 42 (6–103) months. The applied dose of IMBT was 15 Gy given as two doses at 2-week intervals using TRUS-guided pretreatment planning plus 30 Gy EBRT to the small pelvis at 1 day after the seed implant. Fourteen of the patients also received in addition two fractions of 5 Gy IMBT plus 40 Gy EBRT. The mean (range) follow-up for patients receiving the lower radiation dose was 29 (5–70) months at which time 5/21 (23.8%) patients were PSA progression free. In the remaining 16 patients, mean time (range) to PSA progression was 16 (6–42) months. In patients at the higher radiation dose, the mean (range) follow-up was 26 (5–44) months at which time PSA progression-free survival was shown in 6/14 (42.9%) patients. One patient had a PSA increase immediately after salvage therapy. The mean time to PSA increase in the remaining patients was 10 (6–24) months. The difference in PSA progression-free rates between the two doses was not significant.

The third published study on salvage brachytherapy was reported by Traudt and associates [16] and involved five patients with recurrence following radical prostatectomy as documented by digital rectal examination, ultrasonography and computed tomography. Recurrence was anterior to the rectum and did not involve the bladder. The median interval since radical prostatectomy was 8 years, the median PSA level with recurrent disease was 4.73 ng/mL and mean Gleason score was 7. The D_{90} was 118–20 Gy and the rectal V_{100} was 0–0.1 mL. A 144 Gy dose was delivered to a rectal volume of <1 mL. The PSA nadir after brachytherapy was <0.03–1.05 ng/mL and the time interval to PSA nadir was 7–44 months. At a median follow-up of 13 months the PSA level was <0.03–1.41 ng/mL. PSA doubling times were 0 in three patients and 8.8 and 33 months in the other two.

SAFETY

In the Losa study [14] of 10 patients, the complications reported were as expected for brachytherapy. Median International Prostate Symptom Score increased from a median (range) of 8.3 (3–17) to 10.5 (3–17) at 1 month and fell back to 8.7 (4–18) at 12 months [14]. The most common side-effects during the first month were frequency, urgency and urethral burning, but these were transitory and easily managed with non-steroidal anti-inflammatory drugs. There was a slight impact on one patient who used one pad per day before brachytherapy but this was transient. No rectal complications were reported.

In the Niehoff study [15], six patients developed Grade I/II dysuria and six Grade

TABLE 1 Salvage brachytherapy for radiotherapy failure: efficacy outcome

Study	No. of patients	Median follow-up (months)	% bDFS (timepoint)	Dosage
Wallner *et al.* [17]	13	36	51 (5 years)	170 Gy ^{125}I
Loening and Turner [18]	31	23	67 (5 years)	100–200 Gy ^{198}Au
Grado *et al.* [19]	49	64	34 (5 years)	160 Gy ^{125}I or 170 Gy ^{103}Pd (median)
Beyer [20]	17	62	53 (5 years)	120 Gy ^{125}I or 90 Gy ^{103}Pd
Koutrouvelis *et al.* [21]	31	30	87 (5 years)	144 Gy ^{125}I or 120 Gy ^{103}Pd
Wong *et al.* [22]	17	44	75 (4 years)	120 or 126 Gy ^{125}I or 103.5 or 112.5 Gy ^{103}Pd
Nguyen *et al.* [23]	25	47	70 (4 years)	137 Gy ^{125}I
Lee *et al.* [24]	21	19	89 (2 years)	HDR implants 36 Gy in six fractions
Burri *et al.* [25]	37	86	54 (10 years)	128.8 Gy ^{125}I or ^{103}Pd (median)
Aaronson *et al.* [26]	37	30	88 (3 years)	108–122 Gy ^{125}I or ^{103}Pd
Moman *et al.* [27]	31	108	20 (5 years)	145 Gy ^{125}I

bDFS, biochemical disease-free survival.

TABLE 2 Salvage brachytherapy for radiotherapy failure: safety outcome

Complication	Wallner *et al.* [17]	Grado *et al.* [19]	Beyer [20]	Koutrouvelis *et al.* [21]	Wong *et al.* [22]	Nguyen *et al.* [23]	Lee *et al.* [24]	Burri *et al.* [25]	Aaronson *et al.* [26]	Moman *et al.* [27]
Incontinence (%)	31	6	24	0	6	0	0	NR	2.7	NR
GU toxicity (%)										
Grade 1–2	36	12	NR	6.5 (grade 2 or 3)	53	NR	86	43	2.7	87 (acute phase)
Grade 3–4	NR	14	NR		47	20	14	11	0	3 (acute phase)
GI toxicity (%)										
Grade 1–2	NR	4	NR	6.5 (grade 2 or 3)	65	NR	14	NR	5.4	55 (acute phase)
Grade 3–4	15	2	0	6.5 (grade 4)	6	20	0	NR	2.7	0 (acute phase)
ED (%)	NR	2	NR	NR	NR	NR	95	85	NR	NR

GU, genitourinary; GI, gastrointestinal; ED, erectile dysfunction; NR, not reported.

TABLE 3 Patient characteristics prior to brachytherapy

Mean (SD) age (years)	71 (6)
Mean (SD) PSA (ng/mL)	1.5 (1.39)
Gleason score, *n* (%)	
6	9 (25.7)
7	21 (60.0)
8	4 (11.4)
9	1 (2.9)
Tumour stage, *n* (%)	
T0	1 (2.9)
T2a	3 (8.6)
T2b	13 (37.1)
T2c	1 (2.9)
T3a	9 (25.7)
T3b	4 (11.4)
Unknown	4 (11.4)

I/II lower bowel side-effects (proctitis and diarrhoea). No Grade III/IV acute side-effects for lower gastrointestinal (GI) tract or bladder were reported. In the small series of five patients reported by Traudt *et al.* [16], brachytherapy was well tolerated. One patient developed minor urgency but there were no urethral or rectal injuries.

SALVAGE BRACHYTHERAPY AFTER RADIOTHERAPY

EFFICACY

There are a number of reports on salvage brachytherapy for radiotherapy failures, with patient numbers varying from 13 to 49 [17–27]. A summary of the efficacy outcomes from these studies is shown in Table 1. Varying definitions of failure were used in the studies including the American Society for Radiation Oncology, Phoenix, PSA level >10 ng/mL and two increases above nadir, which could account for the variability in outcome. Four-year biochemical disease-free survival (bDFS) rates reported were 70% and 75% while 5-year bDFS rates ranged from 20% to 87%. Of note, in the study with the highest 5-year bDFS of 87%, 97% of patients received 3 months of neoadjuvant androgen ablation [21]. However, adjuvant hormonal therapy was used in 47% of patients in another study reporting a 5-year bDFS of 53% [20]. The radioactive dose delivered either as ^{125}I or ^{103}Pd varied between 108–170 Gy and 90–170 Gy, respectively, and did not appear to be related to outcome.

SAFETY

A summary of the complications reported in the studies under review is shown in Table 2. GI or genitourinary (GU) complications were the most common types reported. The incidence of Grade 1–2 gastrointestinal complications ranged from 5.4% to 65% and for Grade 3–4 2.7% to 20%. The incidence of genitourinary complications was 23–87% and 3–47% for Grades 1–2 and 3–4, respectively. Erectile dysfunction rates were high with salvage brachytherapy in two studies at 85% [25] and 95% [24] but low in another at 2% [19].

SPANISH EXPERIENCE: SALVAGE BRACHYTHERAPY FOR RADICAL PROSTATECTOMY FAILURES

A series of 42 patients with failure following radical prostatectomy were treated with brachytherapy at a single centre in Spain during April 2004 and July 2009. Initial treatment failure was based on a PSA level of ≥0.4 ng/mL and biopsy-proven local recurrence. Patients were treated with TRUS Stepper Guided RAPID Strand™ ^{125}I seeds involving VariSeed™ 7.1 software and real-time placement. The prescribed dose was 145 Gy.

Outcome at 6 months is available for 35 patients and baseline characteristics are shown in Table 3. Dosimetry data include the following mean (SD) values: D_{90} target 179.10 (23.16) Gy, V_{100} target 8.4 (5.4) Gy and a D_{90} urethra 123.3 (26.28) Gy. Biochemical freedom from failure was defined as PSA nadir + 2 ng/mL and median (range) follow-up was 29.5 (6–60.5) months. Median time (range) to biochemical recurrence was 26 (6–95) months; four patients had progressed and three patients had died, two of non-cancer-related causes. Five-year bDFS survival was 88.6% and cancer-specific survival was 97%. From a mean PSA prior to implant of 1.5 (1.39) ng/mL, during follow-up PSA levels of 0.98 (1.01), 1.12 (1.02), 1.32 (1.27) and 1.19 (1.40) ng/mL were recorded at 6, 12, 24 and 36 months follow-up, respectively.

In terms of complications, no major perioperative complications were reported and all patients were discharged without a urethral catheter. The rates of acute GI complications Grades 1 and 2 were two (5.7%) and one (2.9%), respectively, and for acute GU complications Grades 1 and 2 14 (40%) and three (8.6%), respectively. Mild previous incontinence improved in three patients (8.6%). The rates of late GI

complications Grades 1 or 2 were three (8.8%) and one (2.9%), respectively, and the equivalent values for GU complications were three (8.6%) and one (2.9%), respectively.

CONCLUSIONS

Salvage brachytherapy for patients with disease progression after radical prostatectomy or radiotherapy is a viable option. Aspects of treatment that are still under development include appropriate patient selection and the optimal dose of radiation that should be applied. Real-time techniques now allow us to adjust doses, and optimal placement of the seeds has been facilitated using stranded seeds in contrast to the past or external radiation therapy techniques. Important features of salvage brachytherapy also include an accurate location of the site of recurrence of the disease through biopsy.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **HIFU**, high intensity focused ultrasound; **EAU**, European Association of Urology; **ADT**, androgen deprivation therapy; **bDFS**, biochemical disease-free survival; **EBRT**, external beam radiotherapy; **IMBT**, intensity modulated brachytherapy.

BJUI SUPPLEMENTS

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

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A large number of studies have been conducted on the primary therapy of prostate cancer but very few randomized controlled trials have been conducted. The comparison of outcomes from individual studies involving surgery (radical prostatectomy or robotic radical prostatectomy), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy, cryotherapy or high intensity focused ultrasound remains problematic due to the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. The Prostate Cancer Results Study Group was formed to evaluate the comparative effectiveness of prostate cancer treatments. This international group conducted a comprehensive literature review to identify all studies involving treatment of localized prostate cancer published during 2000–2010. Over 18 000 papers were identified and a further selection was made based on the following key criteria: minimum/median follow-up of 5 years; stratification into low-, intermediate- and high-risk groups; clinical

What's known on the subject? and What does the study add?

Very few comparative studies to date evaluate the results of treatment options for prostate cancer using the most sensitive measurement tools. PSA has been identified as the most sensitive tool for measuring treatment effectiveness. To date, comprehensive unbiased reviews of all the current literature are limited for prostate cancer.

This is the first large scale comprehensive review of the literature comparing risk stratified patients by treatment option and with long-term follow-up. The results of the studies are weighted, respecting the impact of larger studies on overall results. The study identified a lack of uniformity in reporting results amongst institutions and centres.

and pathological staging; accepted standard definitions for prostate-specific antigen failure; minimum patient number of 100 in each risk group (50 for high-risk group). A statistical analysis (standard deviational ellipse) of the study outcomes suggested that, in terms of biochemical-free progression, brachytherapy provides superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT. It is anticipated that the study will assist physicians and patients in selecting treatment for men with newly diagnosed prostate cancer.

KEYWORDS

prostate cancer, brachytherapy, radical prostatectomy, radiotherapy, cryotherapy, protons, biochemical-free progression

INTRODUCTION

The evaluation of treatment options for low-, intermediate- and high-risk prostate cancer has remained difficult primarily because of the lack of randomized trials. In the absence of such studies, patients and physicians have used individual institution treatment results to evaluate the effectiveness of modern treatments. Despite a relatively large number of these retrospective studies, the comparison of surgery (radical prostatectomy [RP] or robotic RP), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy (low dose rate and high dose rate), cryotherapy or high intensity focused ultrasound is complicated by the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. The Prostate Cancer Results Study Group (PCRSG) was formed to evaluate the comparative effectiveness of prostate cancer treatments using current modern literature results as a basis. The ongoing task of the group is to find comparable studies and present these studies and outcomes in an easily understandable form to interested groups. This initiative is designed to provide physicians, their patients and healthcare providers such as Medicare with comprehensive, evidence-based prostate cancer treatment comparisons in an understandable form. Importantly, uniform *pretreatment* staging criteria are used (rather than the postoperative stage) as this is the information that the patients and clinicians rely on when choosing between the different options. The following is a report of the PCRSG findings.

TABLE 1 Keywords used in the literature searches

Category	Search words
General	prostate cancer, prostate cancer treatment(s), prostate cancer therapy(ies)
Brachytherapy	prostate cancer brachytherapy, brachytherapy prostate cancer, prostate brachytherapy, brachytherapy prostate cancer outcomes, prostate cancer brachytherapy outcomes, HDR brachytherapy, high-dose-rate brachytherapy, prostate brachytherapy biochemical failure, prostate brachytherapy biochemical free survival, prostate cancer, prostate cancer treatment outcomes
Surgery	prostate cancer surgery, prostate cancer surgery outcomes, prostate cancer prostatectomy, prostate cancer radical prostatectomy, prostate cancer radical retropubic prostatectomy, prostatectomy, prostatectomy biochemical failure, prostatectomy biochemical free survival, prostate cancer prostatectomy outcomes
HIFU	prostate cancer HIFU, prostate cancer HIFU outcomes, HIFU prostate cancer treatment outcomes, high intensity focused ultrasound , high intensity focused ultrasound prostate cancer, high intensity focused ultrasound prostate cancer outcomes, HIFU prostate cancer biochemical failure, HIFU prostate cancer biochemical free survival
Proton	proton therapy prostate cancer, prostate cancer proton therapy, prostate cancer proton, prostate cancer proton therapy outcomes, prostate cancer proton therapy biochemical free survival, proton therapy prostate, prostate cancer proton therapy biochemical free survival
EBRT	EBRT, EBRT prostate cancer, EBRT prostate cancer outcomes, EBRT prostate cancer biochemical failure, EBRT prostate cancer biochemical free survival, radiation therapy prostate cancer, prostate cancer radiation therapy, prostate cancer radiation therapy outcomes, prostate cancer radiation therapy biochemical failure, prostate cancer radiation therapy biochemical free survival
	IMRT prostate cancer, IMRT prostate cancer outcomes, IMRT prostate cancer biochemical failure, IMRT prostate cancer biochemical failure, intensity modulated radiation therapy prostate cancer, intensity modulated radiation therapy prostate cancer outcomes, intensity modulated radiation therapy prostate cancer biochemical failure, intensity modulated radiation therapy prostate cancer biochemical free survival
Cryotherapy	cryotherapy, prostate cancer, prostate cryo therapy, prostate cancer cryo therapy

HDR, high dose radiation; HIFU, high intensity focused ultrasound; IMRT, intensity modulated radiation therapy.

PATIENTS AND METHODS

A literature search of prostate cancer papers published during 2000–2010 was conducted to find studies related to treatment of localized prostate cancer. The following four databases were searched: PubMed, Medline, Google Scholar and Elsevier. The keywords used in the searches are shown in Table 1. The search resulted in the identification of over 18 000 prostate cancer related abstracts and papers, which were then screened by the PCRSG for evidence of treatment outcomes. Each paper accepted for inclusion in this comparison study was required to meet a set of minimum criteria established by the PCRSG (Table 2).These criteria were unanimously agreed upon by the expert panel to allow for adequate comparison purposes. The number of patients, the reported period of follow-up, the categorization of patients according to the D'Amico *et al.* [1], Zelefsky *et al.* [2] or the National Comprehensive Cancer Network [3] risk group categories of low, intermediate and high risk were determined from the selected publication. Extracted from each paper were the prostate-specific antigen (PSA) results at reported follow-up. Patients reported as relapse free or reaching surgical definitions of free of disease were considered progression free. Results were then categorized into low-, intermediate- or high-risk groups. Data were plotted by treatment modality or regimen according to the reported duration of follow-up and plotted as PSA progression-free survival.

Statistical analysis of the data involved calculating the standard deviational ellipse (SDE) for each treatment group using R (Package aspace, version 3.0, 2011; http://cran.r-project.org/web/packages/aspace/index.html). The SDE was centred on the weighted mean for all the data points in the treatment group. The ellipse generated represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE.

TABLE 2 Criteria for inclusion of a study on treatment of localized prostate cancer

- Patients must be stratified into recognizable pretreatment risk groups, low, intermediate and high risk, using D'Amico, Zelefsky or NCCN stratification
- Standard endpoint used to measure biochemical relapse-free survival: ASTRO, Phoenix and PSA < 0.2 ng/mL (for surgery)
- Clinical staging conducted and not pathological staging alone
- EBRT must be minimum 72 Gy IMRT/conformal
- All treatment modalities considered: brachytherapy (including HDR), surgery, IMRT, HIFU, cryotherapy, protons
- Results published in peer-reviewed journals only
- Low risk accepted minimum number of patients was 100
- Intermediate risk accepted minimum number of patients was 100
- High risk accepted minimum number of patients was 50
- Minimum median follow-up was 5 years

NCCN, National Comprehensive Cancer Network; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; HDR, high dose rate; HIFU, high intensity focused ultrasound.

TABLE 3 Number of patients in each treatment group and according to risk group category

	No. of patients (no. of studies)		
Treatment type	Low risk	Intermediate	High
RP	6447 (6)	3696 (4)	5149 (11)
Robotic RP	706 (1)	479 (1)	200 (1)
Seeds alone	8133 (17)	5808 (15)	295 (1)
Seeds + EBRT	726 (1)	1554 (6)	2864 (15)
EBRT + seeds + ADT	–	–	1231 (6)
HDR (seeds)	226 (2)	607 (4)	869 (5)
Protons	388 (2)	162 (1)	–
EBRT alone	4735 (9)	2969 (10)	3828 (11)
HIFU	227 (1)	–	–
Cryotherapy	–	175 (1)	357 (2)
Seeds + ADT	–	165 (1)	–

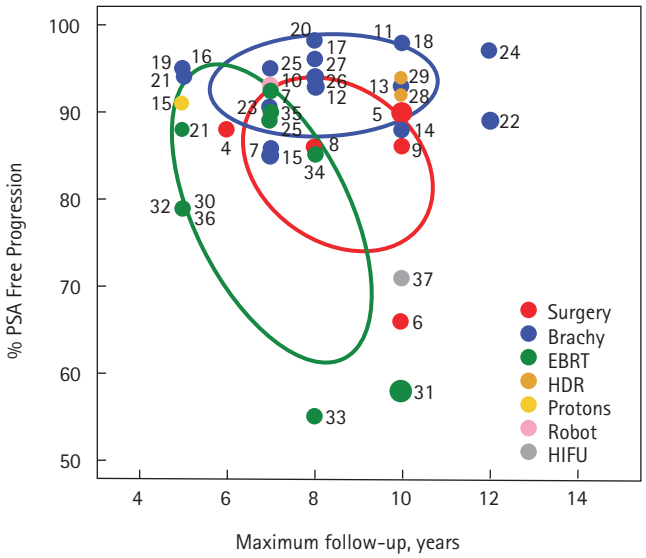
ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation.

RESULTS

A total of 848 of the batch of over 18 000 published abstracts were initially identified as treatment-related papers. The percentage of papers by treatment modality meeting PCRSG criteria was as follows: high intensity focused ultrasound 1/30 (3%); robotic radical prostatectomy 3/59 (5%); radical prostatectomy 24/260 (9%); proton therapy 2/13 (15%); cryotherapy 5/31 (16%); EBRT 39/222 (18%); and brachytherapy 66/213 (31%). The total number of patients for each treatment type is shown in Table 3. In total, the studies analysed reported on 52 087 patients.

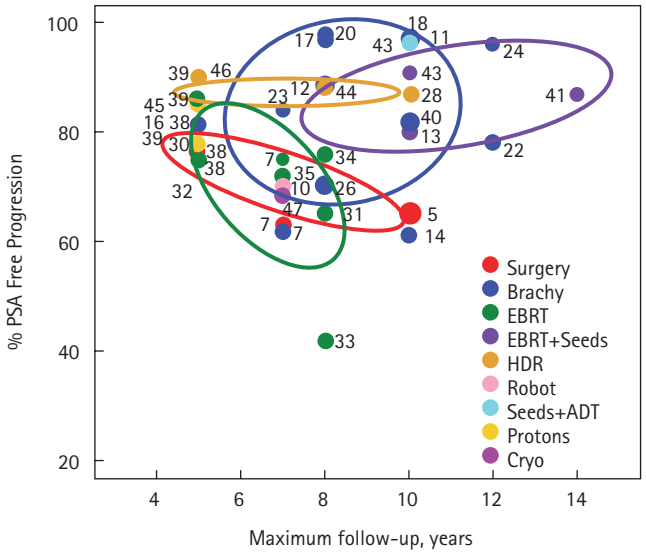
Outcome from the first analysis is shown in Figs 1–3 and represents the PSA progression-free survival outcomes by treatment modality for low-, intermediate- and high-risk groups [4–69]. In low-risk patients, higher average PSA progression-free survival was reported for brachytherapy than for RP or EBRT. There was limited reporting with the other therapies although some of the individual studies showed comparable outcomes to RP and EBRT. In intermediate-risk patients, higher average progression-free survival was reported for brachytherapy (permanent seeds and high dose rate) approaches than for RP or EBRT. For high-risk patients combination regimens of androgen deprivation therapy, EBRT and brachytherapy had higher progression-free

FIG. 1. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with low-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound.



Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [4]	336	Brachy [17]	173	Protons [15]	124
Surgery [5]	3283	Brachy [18]	329	Protons [30]	230
Surgery [6]	346	Brachy [19]	586	EBRT [15]	134
Surgery [7]	765	Brachy [20]	173	EBRT [31]	2765
Surgery [8]	1381	Brachy [21]	108	EBRT [32]	421
Surgery [9]	336	Brachy [22]	1345	EBRT [7]	173
Robot [10]	706	Brachy [23]	260	EBRT [21]	108
Brachy [11]	475	Brachy [24]	319	EBRT [33]	485
Brachy [12]	768	Brachy [25]	448	EBRT [25]	281
Brachy [13]	726	Brachy [26]	1444	EBRT [34]	203
Brachy [14]	232	Brachy [27]	319	EBRT [35]	446
Brachy [15]	158	HDR [28]	110	EBRT [36]	227
Brachy [7]	723	HDR [29]	116	HIFU [37]	227
Brachy [16]	273				

FIG. 2. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with intermediate-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; ADT, androgen deprivation therapy; Cryo, cryotherapy; HIFU, high intensity focused ultrasound.



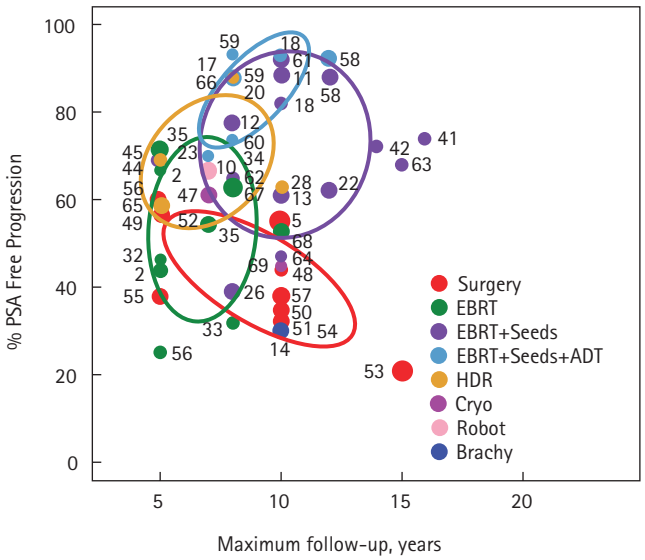
Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [5]	2795	Brachy [22]	554	HDR [46]	109
Surgery [38]	336	Brachy [23]	141	Protons [30]	162
Surgery [7]	211	Brachy [24]	144	EBRT [38]	321
Surgery [39]	354	Brachy [39]	256	EBRT [31]	349
Robot [10]	479	Brachy [26]	960	EBRT [32]	137
Brachy [11]	176	EBRT + seeds [11]	460	EBRT [7]	99
Brachy [12]	535	EBRT + seeds [13]	447	EBRT [33]	218
Brachy [14]	369	EBRT + seeds [41]	119	EBRT [33]	218
Brachy [38]	204	EBRT + seeds [42]	157	EBRT [33]	218
Brachy [7]	199	EBRT + seeds [43]	266	EBRT [39]	305
Brachy [16]	123	EBRT + seeds [7]	105	EBRT [34]	255
Brachy [17]	212	Seeds + ADT [43]	165	EBRT [35]	849
Brachy [18]	425	HDR [28]	188	Cryotherapy [47]	175
Brachy [20]	212	HDR [44]	188		
Brachy [40]	1298	HDR [45]	122		

survival than surgery, EBRT or brachytherapy alone.

DISCUSSION

Large-scale randomized studies are not yet and are unlikely to be conducted for prostate cancer. To complicate comparisons, most retrospective studies fail to provide pretreatment risk group stratification, which limits treatment comparisons. Only 17% of the reported papers in this review met the minimal inclusion criteria to allow for comparison. Many surgical studies stratified patients post-treatment and therefore true comparisons by pretreatment status could not be made. In addition, minimal cancer control endpoints have not been standardized or enforced by journal editors, further creating difficult comparison outcomes across treatment modalities.

FIG. 3. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with high-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; ADT, androgen deprivation therapy; Cryo, cryotherapy; HIFU, high intensity focused ultrasound.



Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [5]	1513	EBRT+seeds+ADT [60]	175	EBRT+seeds [26]	192
Surgery [48]	176	EBRT+seeds+ADT [23]	59	HDR [65]	256
Surgery [49]	235	EBRT+seeds [11]	243	HDR [28]	107
Surgery [50]	288	EBRT+seeds [61]	186	HDR [45]	80
Surgery [51]	265	EBRT+seeds [12]	362	HDR [66]	67
Surgery [52]	188	EBRT+seeds [13]	284	EBRT [67]	1256
Surgery [53]	1061	EBRT+seeds [41]	164	EBRT [32]	57
Surgery [54]	237	EBRT+seeds [42]	124	EBRT [56]	95
Surgery [55]	210	EBRT+seeds [44]	359	EBRT [33]	97
Surgery [56]	134	EBRT+seeds [62]	92	EBRT [68]	296
Surgery [57]	842	EBRT+seeds [58]	284	EBRT [34]	103
Robot [10]	200	EBRT+seeds [17]	127	EBRT [2]	65
Brachy [14]	295	EBRT+seeds [18]	90	EBRT [2]	193
EBRT+seeds+ADT [58]	284	EBRT+seeds [59]	107	EBRT [35]	752
EBRT+seeds+ADT [18]	60	EBRT+seeds [22]	418	EBRT [35]	752
EBRT+seeds+ADT [59]	69	EBRT+seeds [63]	114	Cryotherapy [47]	314
EBRT+seeds+ADT [20]	584	EBRT+seeds [64]	77	Cryotherapy [69]	43

This study evaluated published data from 2000 to 2011 that met the PCRSG minimum reporting criteria. All current primary treatment options for each risk group of prostate cancer were included and involved over 52 000 patients. To date only one randomized study has been conducted comparing primary treatment outcomes for brachytherapy and surgery [70], but this study failed to meet the PCRSG criteria for inclusion. The current report is the first comprehensive comparative analysis of its kind that looks at all modern treatment outcomes based on the different risk group stratifications, also weighted according to patient numbers. Of note was the observation that risk group definition was uniformly consistent only in the low-risk group. Intermediate- and high-risk group definitions demonstrated some variability. However, studies evaluating the outcomes in high-risk patients based on different definitions have not demonstrated significant differences in outcome after RP [71].

The findings of the study suggest that in terms of biochemical (PSA) free progression, brachytherapy approaches provide superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy appear equivalent to brachytherapy alone and appear superior to EBRT or surgery; however, selection issues may play a large role in outcomes between these treatment options. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT. No study was found that purely looked at the results of high-risk patients treated with planned surgery and EBRT, so extrapolation on this form of treatment could not be commented upon.

Since it is unlikely that large randomized studies will be conducted, physicians and patients will rely largely upon the use of retrospective studies to compare treatment results. Such reviews will require that studies report on similar patient populations, as determined by pretreatment measurements, and outcomes measured primarily in terms of treatment effect (e.g. PSA). Since only a small percentage of studies in this work met minimum comparable reporting standards, the PCRSG encourages editors and reviewers to advocate that future authors be required to report results based on standardized pretreatment risk classification and PSA-based outcome measures. One of the limitations of the current study is that, despite attempts to compare data by using pre-selected rigorous inclusion and exclusion criteria, we found that some of the included studies may not be directly comparable based on other factors.

This study should provide cancer control information to physicians and patients attempting to make an ultimate treatment decision. It is acknowledged that other factors can also significantly affect a patient's and physician's decision on the type of prostate cancer treatment. This report is based on accepted standard surgical and radiation definitions of PSA failures. It is also acknowledged that differences between definitions of PSA outcomes between various treatment modalities make the final conclusion less certain. As part of an ongoing process, the literature review will be updated bi-yearly by the PCRSG and further information is provided on the website: http://www.prostatecancertreatmentcenter.com/.

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CONFLICT OF INTEREST

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Abbreviations: **RP**, radical prostatectomy; **EBRT**, external beam radiation; **PCRSG**, Prostate Cancer Results Study Group; **SDE**, standard deviational ellipse.