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Original Article

Radical Prostatectomy Versus Stereotactic Radiotherapy for Clinically Localised Prostate Cancer: Results of the PACE-A Randomised Trial

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Abstract

Background and objective: Randomised data on patient-reported outcomes (PROs) for stereotactic body radiotherapy (SBRT) and prostatectomy in localised prostate cancer are lacking. PACE-A compared patient-reported health-related quality of life after SBRT with that after prostatectomy.

Methods: PACE is a phase 3 open-label, randomised controlled trial. PACE-A randomised men with low- to intermediate-risk localised prostate cancer to SBRT or prostatectomy (1:1). Androgen deprivation therapy (ADT) was not permitted. The coprimary outcomes were the Expanded Prostate Index Composite (EPIC-26) number of absorbent urinary pads required daily and bowel domain score at 2 yr. The secondary endpoints were clinician-reported toxicity, sexual functioning, and other PROs.

Key findings and limitations: In total, 123 men were randomised (60 undergoing prostatectomy and 63 SBRT) from August 2012 to February 2022. The median follow-up time was 60.7 mo. The median age was 65.5 yr and the median prostate-specific antigen (PSA) value 7.9 ng/ml; 92% had National Comprehensive Cancer Network (NCCN) intermediate-risk disease. Fifty participants received prostatectomy and 60 received SBRT. At 2 yr, 16/32 (50%) prostatectomy and three of 46 (6.5%) SBRT participants used one or more urinary pads daily ($p < 0.001$; 15 and two, respectively, used one pad daily); the estimated difference was 43% (95% confidence interval [CI]: 25%, 62%). At 2 yr, bowel scores were better for prostatectomy (median [interquartile range] 100 [100–100]) than for SBRT (87.5 [79.2–100]; $p < 0.001$), with an estimated mean difference of 8.9 between these (95% CI: 4.2, 13.7); sexual scores were worse for prostatectomy (18 [13.8–40.3])

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than for SBRT (62.5 [32.0–87.5]). The limitations were slow recruitment and incomplete 2-yr PRO response rates.

Conclusions and clinical implications: SBRT was associated with less patient-reported urinary incontinence and sexual dysfunction, and slightly more bowel bother than prostatectomy. These randomised data should inform treatment decision-making for patients with localised, intermediate-risk prostate cancer.

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ADVANCING PRACTICE

What does this study add?

To our knowledge, PACE-A is the first phase 3 randomised control trial to compare stereotactic body radiotherapy (SBRT) with prostatectomy in men with early-stage localised prostate cancer. Unlike earlier trials, PACE-A evaluated contemporary radical treatment options of SBRT and robotic prostatectomy. The PACE-A results provide level 1 evidence of lower rates of urinary pad use and sexual dysfunction, with a slight increase in bowel bother for SBRT compared with prostatectomy. PACE-A provides an understanding of contemporary toxicity rates for the current treatment options offered in newly diagnosed localised prostate cancer. These findings will serve to guide patients and clinicians when making treatment decisions.

Clinical Relevance

The PACE-A randomized trial provides valuable insights into the management of localized prostate cancer by directly comparing stereotactic body radiotherapy with radical prostatectomy. Although the study involved a relatively small patient cohort recruited over a 10-year period, its significance lies in being the first phase 3 trial to assess these contemporary treatments in low- to intermediate-risk patients. The results suggest that stereotactic body radiotherapy may lead to lower rates of urinary incontinence and sexual dysfunction compared to radical prostatectomy, albeit with a potential increase in bowel dysfunction. These findings highlight the importance of considering side effects associated with both treatment options, emphasizing the potential benefits of active surveillance for men with low-risk, and select men with favourable intermediate-risk, disease. Ultimately, these outcomes are critical for guiding patient-centred treatment decisions, enabling clinicians and patients to select treatment options that best align with individual preferences and quality of life considerations.

Patient Summary

The PACE trial enrolled patients with early localised prostate cancer who had not previously received any treatment for their cancer. We found that men treated with five doses of radiotherapy described less incontinence and less sexual problems at 2 yr, with slightly worse bowel bother, than men treated with prostatectomy. These results will help newly diagnosed patients make informed decisions when given a treatment choice.

1. Introduction

Men presenting with localised prostate cancer (LPCa) have multiple management options such as prostatectomy, radiotherapy including stereotactic body radiotherapy (SBRT), and active surveillance. The ProtecT trial long-term outcomes, demonstrating similar overall survival across management strategies, emphasised the significance of patient-led decision-making. In ProtecT, there were a significantly higher number of patients with metastatic disease in the active surveillance cohort, but no difference in overall or metastasis-free survival was observed between prostatectomy and radiotherapy, suggesting that some men may benefit from radical treatment [1]. Advancements in technology and the shift towards patient-centred care underscore the importance of prioritising long-term quality of life (QoL) and patient preferences when making LPCa treatment decisions.

Modern treatment options, such as robotic prostatectomy, are now available widely, and advanced radiotherapy techniques such as SBRT offer improved precision and efficacy in treating LPCa. Historically, radiotherapy has been associated with better urinary and sexual outcomes than prostatectomy, with a higher risk of bowel toxicity. However, this has not been demonstrated in a randomised setting with contemporary treatment modalities [2–4].

The PACE-A trial aims to evaluate QoL outcomes following SBRT compared with prostatectomy. Here, the primary results of PACE-A, based on a comprehensive set of patient-reported and clinician-assessed outcomes at 2 yr, are presented.

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2. Patients and methods

2.1. Participants

Eligible participants were men medically fit for prostatectomy, with histologically confirmed prostate adenocarcinoma with ten or more biopsy cores within 18 mo of randomisation and National Comprehensive Cancer Network (NCCN) low- to intermediate-risk LPCa (stage T1c–T2c, N0-X, M0-X, TNM sixth edition) of Gleason grade $\leq$3 + 4 and prostate-specific antigen (PSA) $\leq$20 ng/ml. Participants had World Health Organization performance (WHO) status 0–2. The exclusion criteria included previous pelvic radiotherapy, noncutaneous malignancy within 2 yr, and bilateral hip prosthesis. Progression on active surveillance was included if eligibility was otherwise fulfilled.

Participants were staged using magnetic resonance imaging (MRI) of the pelvis. Distant metastasis staging was not mandatory. Androgen deprivation therapy (ADT) was not permitted.

2.2. Trial design and randomisation

PACE-A was a multicentre, parallel-group, randomised controlled trial. Participants were assigned randomly 1:1 to prostatectomy or SBRT. Randomisation was done centrally by the Institute of Cancer Research Clinical Trials and Statistics unit (ICR-CTSU, London, UK) using computer-generated random permuted blocks (size 4 and 6), stratified by NCCN risk group and randomising centre. Treatment was not masked.

2.3. Treatment and assessments

For SBRT, insertion of prostatic fiducial markers was recommended. Bladder filling and bowel preparation (enemas) were advised for treatment planning. Computed tomography scan and radiotherapy planning MRI were completed, and images were fused with fiducial matching. Clinical target volume (CTV) was defined as prostate only for low-risk participants or prostate plus proximal 1 cm of seminal vesicles for intermediate-risk participants. CTV to planning target volume (PTV) margin was 4–5 mm isotropic, except 3–5 mm posteriorly. A dose of 36.25 Gy in five fractions (1–2 wk) was delivered to 95% of PTV, and a secondary target dose of 40 Gy was delivered to CTV. SBRT was permitted on CyberKnife (Accuray Incorporated, Sunnyvale, CA, USA) and (since protocol version 5.0, August 2014) conventional linear accelerator platforms.

A comprehensive quality assurance programme for prostatectomy and SBRT ensured consistency to trial protocol across centres. The minimum annual surgical caseload was specified as at least 25 cases. The predominant approach was robotic assisted, but non–robotic-assisted laparoscopic prostatectomy was permitted. Treatment was mandated to start within 12 wk of randomisation.

Participants were assessed using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [5], and in the SBRT group, using the Radiation Therapy Oncology Group (RTOG) criteria prior to treatment, at the end of treatment, at weeks 2, 4, 8, and 12 after treatment completion, and then 3-monthly up to 24 mo. Prostatectomy participants had a Clavien score [6] recorded on the day of discharge, and at weeks 2 and 4.

Patient-reported outcomes (PROs) were assessed at baseline, weeks 4 and 12, and months 6, 9, 12, and 24, using the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) [7], the International Prostate Symptom Score (IPSS) [8], the Vaizey faecal incontinence score [9], and the International Index of Erectile Function 5 (IIEF-5) questionnaire, omitting week 4 and month 9 [10]. IPSS was additionally collected at weeks 2 and 8. PROs were collected via paper questionnaires distributed in clinic or posted by centres.

2.4. Trial oversight

PACE is an investigator-initiated trial approved by the London Chelsea Research Ethics Committee (11/LO/1915) in the UK. From protocol version 5.0, August 2014, the trial was sponsored by the Royal Marsden NHS Foundation Trust and co-ordinated by the ICR-CTSU. Prior to this, the trial was sponsored by Accuray. Accuray had no role in data collection (managed by a third party before February 2014) or statistical analysis (ICR-CTSU). The trial was conducted in accordance with the principles of Good Clinical Practice. Participants were recruited by their clinical teams and provided written, informed consent before enrolment. The Trial Management Group (TMG) was overseen by an Independent Data Monitoring Committee (IDMC), and an independent Trial Steering Committee (TSC; Supplementary material). The protocol is available online [11].

2.5. Outcome measures

The coprimary endpoints were PROs of the number of absorbent urinary pads required per day to control leakage (defined as none versus one or more absorbent pads required per day; EPIC-26 question 27) and EPIC-26 bowel domain score. The time point of primary interest was 2 yr from completing treatment.

Gastrointestinal and genitourinary side effects, and erectile function were of primary interest, and secondary endpoints were chosen to capture these. The clinician-reported secondary endpoints were worst-grade acute and late genitourinary and gastrointestinal CTCAE toxicities (specific adverse events listed in the Supplementary material) and, in the SBRT group, RTOG genitourinary and gastrointestinal toxicities. The secondary PRO endpoints were IIEF-5 score, IPSS total and domain scores, Vaizey faecal incontinence score, other EPIC-26 domain scores, and single-item EPIC questions for overall bowel (question 55), urinary (question 34), and sexual (question 68) bother.

2.6. Statistical analysis

Power calculations were originally based on a primary endpoint of freedom from biochemical failure. From protocol version 9.0 (June 2017), the trial was redesigned with the coprimary PRO endpoints. This amendment, motivated by

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slow recruitment, was approved by the TMG (including patient advocates), IDMC, TSC, and funders. The revised target sample size of 234 participants was driven by EPIC question 27, categorised as "any use of urinary pads". We assumed that 15% of prostatectomy participants required pad use at 2 yr and anticipated it to be 4% with SBRT; calculations were based on a comparison of proportions, with 5% two-sided alpha, 80% power, and 5% dropout [4]. This sample size provided over 90% power to detect a 5-point difference in the mean EPIC bowel domain score (assuming a mean of 95 at 2 yr with prostatectomy and a standard deviation of 9.4). Following IDMC and TSC recommendations, the trial stopped recruitment in February 2022 before reaching target accrual.

The number of urinary pads are presented as a binary outcome (none vs any) and absolute number, and compared using the chi-square test; 95% confidence interval (CI) for the difference in the proportion was calculated using the Wilson score method. EPIC bowel domain scores were compared using the Mann-Whitney *U* test, descriptive statistics were presented for EPIC domain scores, and difference in the mean EPIC bowel domain scores was compared using *t* test. The minimal clinically important differences (MCIDs) in EPIC-26 domain scores were urinary incontinence (8 points), urinary irritative/obstructive (6 points), bowel (5 points), and sexual (11 points) [12]. Single-item EPIC question scores (none/very small/small vs moderate/severe) were tabulated. Statistical comparisons for secondary outcomes were made at 12 wk and 24 mo using the Mann-Whitney *U* test for continuous scores, chi-square trend test for ordinal data, and chi-square (or Fisher's exact) test for binary data. Significance was $p < 0.05$ for the coprimary endpoints and $p < 0.01$ for the secondary endpoints. Analyses were by treatment received, with all available data reported for a time point included. Sensitivity analyses for the coprimary endpoints were performed (1) by replacing 2-yr missing data with responses from 3-yr questionnaire, where available, and (2) in the intention-to-treat population. Analyses were based on a data snapshot taken on April 17, 2023, and conducted using Stata version 17.0 (Stata Corp., College Station, TX, USA). The study is registered at ClinicalTrials.gov (NCT01584258).

3. Results

3.1. Participants

From August 2012 to February 2022, 123 men (60 undergoing prostatectomy and 63 SBRT) were randomised from eight UK centres (Fig. 1 and Supplementary material). Forty-eight of 60 participants assigned to prostatectomy had prostatectomy (one received SBRT, three received conventional radiotherapy, and eight withdrew consent). Fifty-nine of 63 participants assigned to SBRT completed at least one fraction of SBRT (two received prostatectomy and two withdrew consent). Eight participants who started treatment were later reported not to meet all the eligibility criteria but were included in the analysis (five participants with only nine-core biopsies, one with PSA >60 d from randomisation, one with prostate volume not measured within 6 mo of randomisation, and one with biopsy not performed within 18 mo of consent).

The baseline characteristics are shown in Table 1. The median age was 65.5 yr (interquartile range [IQR] 60.8–68.4), median pretreatment PSA was 7.9 ng/ml (IQR 5.9–11.0), 97/123 (79%) participants had a Gleason score of 3 + 4, and 116/123 (94%) had NCCN intermediate risk. The median follow-up was 60.7 mo (IQR 43.9–75.3); 95/110 (86%) participants have at least 2 yr of follow-up data, with 24-mo PRO questionnaire return rates of 34/50 (68%) for prostatectomy and 49/60 (82%) for SBRT (Supplementary material).

All 50 prostatectomy participants were treated laparoscopically; 42/50 (84%) had robotic-assisted prostatectomy (surgical details are presented in the Supplementary material). SBRT was delivered using robotic noncoplanar radiotherapy (CyberKnife) for 45/60 (75%) and linear accelerator-based volumetric modulated arc therapy for 15/60 (25%). Most participants (50/60, 83%) had fiducial markers placed; all patients starting SBRT completed five fractions as planned (Supplementary material).

3.2. Patient-reported urinary symptoms

No patient reported the use of absorbent pads at the baseline. At 24 mo, 16/32 (50%) prostatectomy and three of 46 (6.5%) SBRT participants reported any use of absorbent pads ($p < 0.001$), with an estimated difference in proportion of 43% (95% CI: 25%, 62%). Of the 16 participants with prostatectomy using pads at 24 mo, 15 used one pad per day and one used three or more pads. In the SBRT group, two used one pad and one used two pads per day. The use of pads was reported consistently more often for prostatectomy (Fig. 2A and Supplementary material) and in sensitivity analyses (Supplementary material). EPIC urinary incontinence domain scores at 24 mo were worse for prostatectomy (median 77.3 [58.5–100]) than for SBRT (100 [79.3–100], $p = 0.003$; Supplementary material). The median urinary irritative/obstructive domain score was 100 (IQR 93.8–100) for prostatectomy compared with 93.8 (IQR 87.5–100) for SBRT ($p = 0.01$; Fig. 3A and Supplementary material). We did not see evidence of a difference ($p = 0.8$) in overall urinary bother, with one of 32 (3.1%) prostatectomy participants and two of 46 (4.4%) SBRT participants reporting moderate/severe problems (Supplementary material). A higher proportion of prostatectomy participants reported a reduction in incontinence scores from baseline of greater than the MCID at 24 mo (prostatectomy: 21/31 [68%] vs SBRT: 13/41 [32%], $p < 0.001$), a pattern that held when more clinically relevant differences of 2 × MCID were considered (post hoc; Supplementary material).

The 24-mo IPSS total scores indicated less moderate/severe symptoms with prostatectomy (five of 31, 16%) than with SBRT (16/42, 38%). This was driven by the median IPSS voiding score of 0 (IQR 0–2) for prostatectomy and 2.5 (IQR 1–4) for SBRT ($p < 0.001$; Supplementary material). However, IPSS QoL score indicated no evidence of a difference in QoL (median 1, IQR 1–2 for prostatectomy and median 1, IQR 0–2 for SBRT, $p = 0.2$; Supplementary material).

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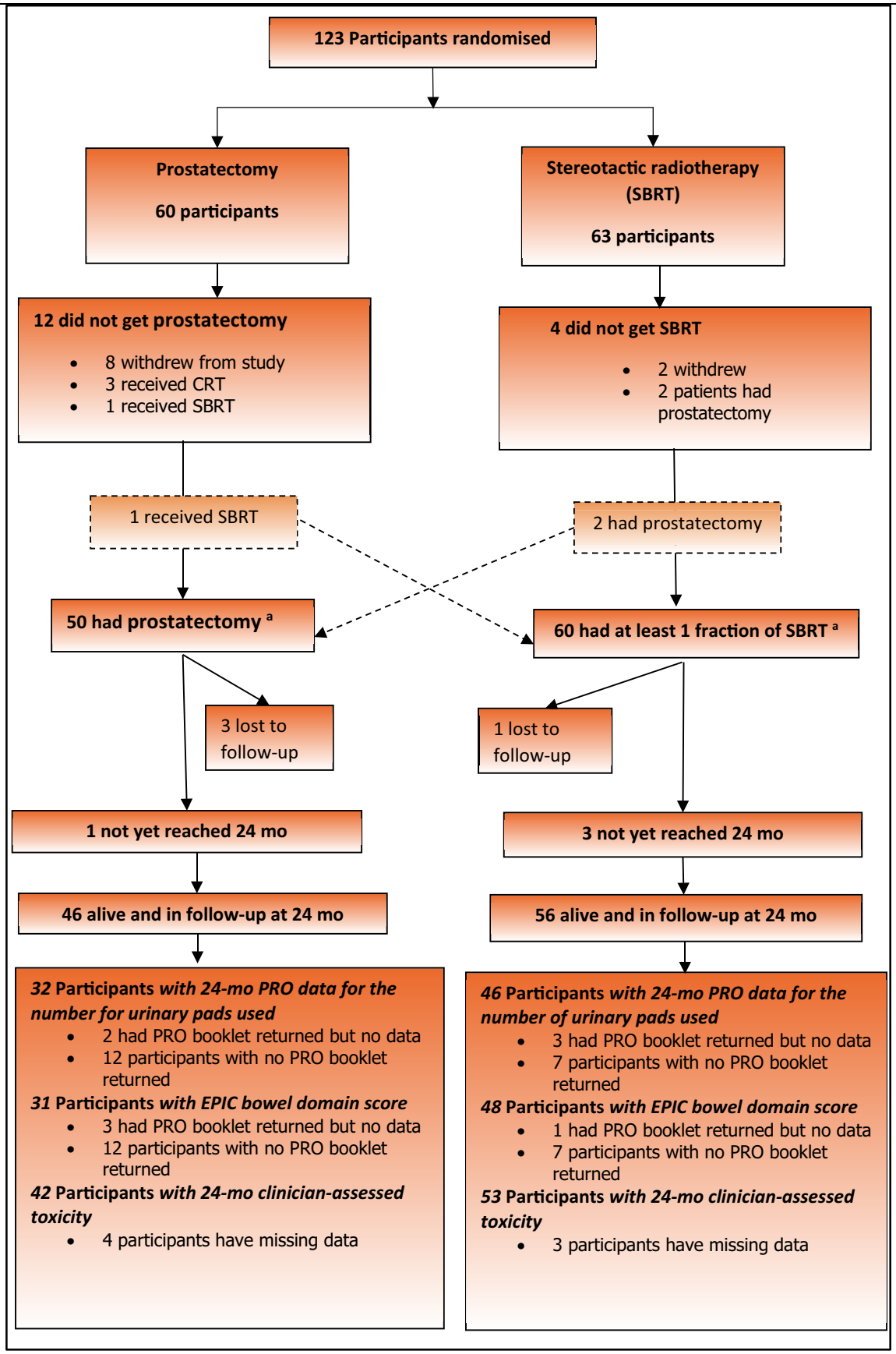

Fig. 1 – CONSORT flow chart. CRT = conventional radiotherapy; EPIC = Expanded Prostate Index Composite; PRO = patient-reported outcome; SAP = statistical analysis plan; SBRT = stereotactic body radiotherapy. [a] Eight patients (four in the prostatectomy and four in the SBRT group) started treatment and were later reported not to meet all the eligibility criteria (five participants with only nine core biopsies, one with PSA >60 d from randomisation, one with prostate volume not measured within 6 mo of randomisation, and one with biopsy not performed within 18 mo of consent). As per the SAP (all randomised patients who received at least one fraction of the protocol radiotherapy or had surgery), these patients have been included in the analysis.

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Table 1 – Baseline characteristics of the study participants

Baseline characteristics	Prostatectomy (*N* = 60)		SBRT (*N* = 63)	
Age at randomisation, median (IQR)	65.5	(60.8, 68.4)	65.0	(59.3, 68.7)
Ethnic origin, *n* (%)				
White British	52	(87)	53	(84)
Any other White	5	(8.3)	3	(4.8)
Asian	1	(1.7)	2	(3.2)
Caribbean	0		3	(4.8)
African	1	(1.7)	0	
Chinese	1	(1.7)	0	
Not disclosed	0		2	(3.2)
T stage, *n* (%)				
T1c	6	(10)	2	(3.2)
T2a	22	(37)	26	(42)
T2b	7	(12)	10	(16)
T2c	24	(41)	24	(39)
Gleason score, *n* (%)				
3 + 3	12	(20)	14	(22)
3 + 4	48	(80)	49	(78)
NCCN risk group, *n* (%)				
Low	3	(5.0)	4	(6.4)
Intermediate	57	(95)	59	(94)
Pretreatment PSA (ng/ml), median (IQR)	7.8	(6.2, 11.0)	7.9	(5.7, 11.0)
Pretreatment testosterone (nmol/l)[a], median (IQR)	12.0	(9.2, 14.4)	11.3	(9.4, 15.0)
ASA grade[b], *n* (%)				
I—normal healthy individual	26	(48)	–	–
II—Mild systemic disease that does not limit activity	27	(50)	–	–
III—Severe systemic disease that limits activity but is not incapacitating	1	(1.9)	–	–
Unobtainable	5		–	–
Not answered	1		–	–
Patients on concomitant medication at randomisation, *n* (%)				
Alpha blockers—yes	3	(5.0)	3	(4.8)
Anticholinergic—yes	0		4	(6.3)
5-Alpha-reductase inhibitors—yes	0		1	(1.6)
PDE5 inhibitors—yes	3	(5.0)	0	–

ASA = American Society of Anesthesiologists; IQR = interquartile range; NCCN = National Comprehensive Cancer Network; PDE5 = phosphodiesterase-5; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy.

[a] Missing: prostatectomy, *n* = 6; SBRT, *n* = 5.

[b] There were no participants in grade IV—incapacitating systemic disease that is constantly life threatening, and grade V—moribund, not expected to survive 24 hours with or without prostatectomy category.

3.3. *Patient-reported bowel symptoms*

At baseline, the median (IQR) EPIC bowel domain score was 100 (95.8–100) in each group. At 24 mo, prostatectomy participants reported statistically significantly better EPIC bowel domain scores (median 100, IQR 100–100) than SBRT participants (median 87.5, IQR 79.2–100, $p < 0.001$), with a difference in mean score of 8.9 (95% CI: 4.2, 13.7; Fig. 2B and 3C, and Supplementary material). The results held in sensitivity analyses (Supplementary material). A lower proportion of prostatectomy participants (four of 29 [14%]) had a reduction from baseline in bowel domain scores of greater than the MCID at 24 mo compared with SBRT participants (21/47 [45%], $p < 0.001$), with a similar pattern seen for worsening bowel scores of >2 × MCID (Supplementary material). We did not see evidence of a difference in overall bowel bother, with moderate/severe problems reported in 0/31 prostatectomy and one of 48 (2.1%) SBRT participants ($p > 0.9$; Supplementary material). The 24-mo Vaizey incontinence total scores indicated no statistically significant differences between the treatment groups ($p = 0.1$; Supplementary material).

3.4. *Patient-reported sexual function*

Prostatectomy participants reported clinically and statistically significantly worse 24-mo EPIC sexual domain scores, with a median value of 18 (IQR 13.8–40.3) compared with 62.5 (IQR 32.0–87.5) for SBRT ($p < 0.001$; Fig. 3D and Supplementary material). A higher proportion of prostatectomy participants reported a reduction from baseline in sexual domain scores of greater than the MCID at 24 mo (prostatectomy: 21/28 [75%] vs SBRT: 20/42 [48%], $p = 0.045$; Supplementary material).

The proportions of men reporting moderate/severe problems with overall sexual bother were ten of 30 (33%) with prostatectomy and eight of 45 (18%) with SBRT ($p = 0.1$; Supplementary material). IIEF-5 erectile dysfunction was higher in prostatectomy participants ($p = 0.002$; Supplementary material).

3.5. *Clinician-reported toxicity*

CTCAE grade ≥2 genitourinary toxicity was low across all late time points (Supplementary material). At 24 mo, we

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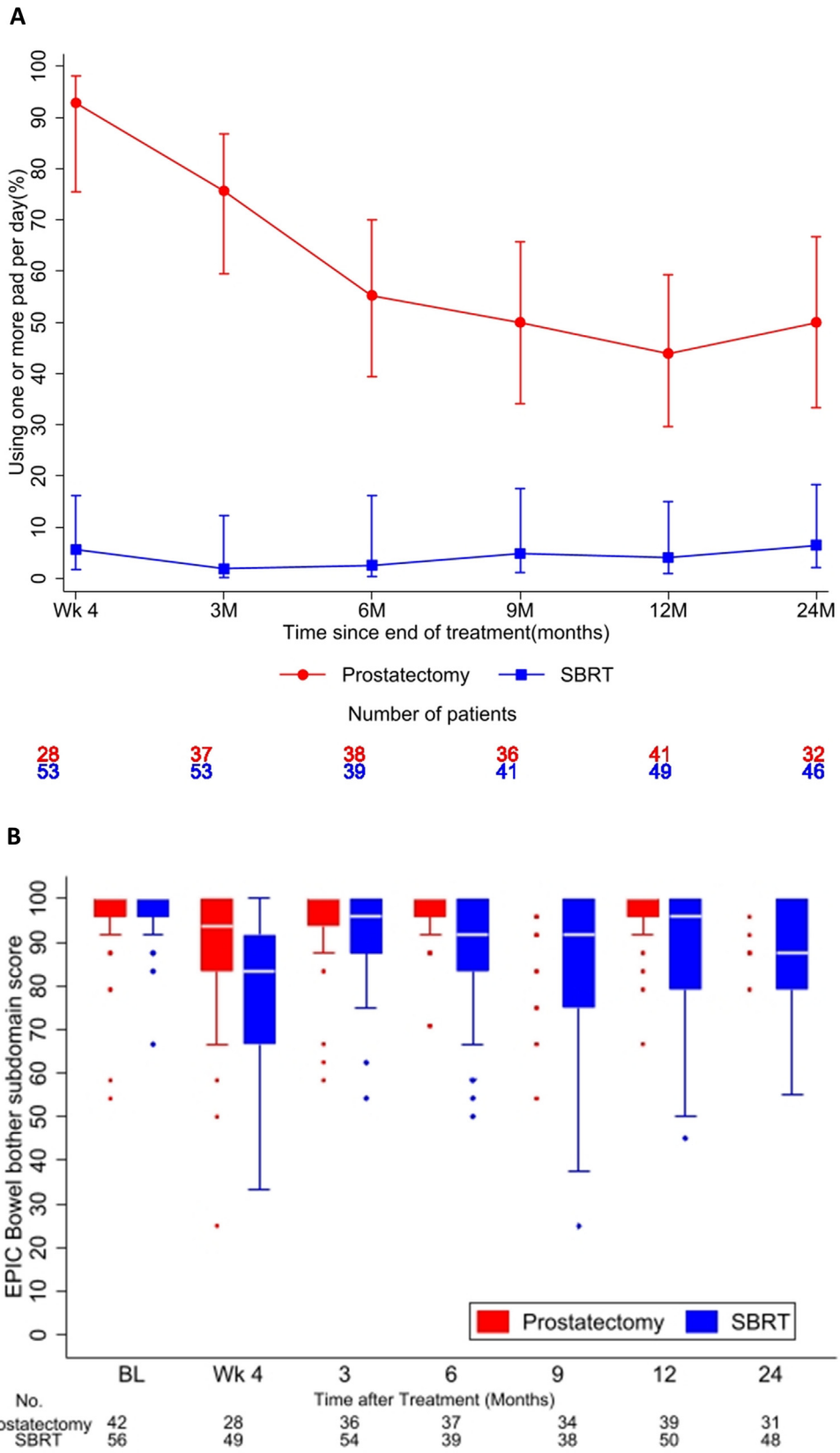

Fig. 2 – (A) Proportion of patients requiring at least one urinary pad per day to control leakage by treatment received over time. (B) Distribution of the EPIC bowel domain scores over time for both treatment groups: quartiles with median (box), 1.5 × interquartile range (whiskers), and any outliers (•) beyond the whiskers. BL = baseline; EPIC = Expanded Prostate Index Composite; M = months; SBRT = stereotactic body radiotherapy; Wk = weeks.

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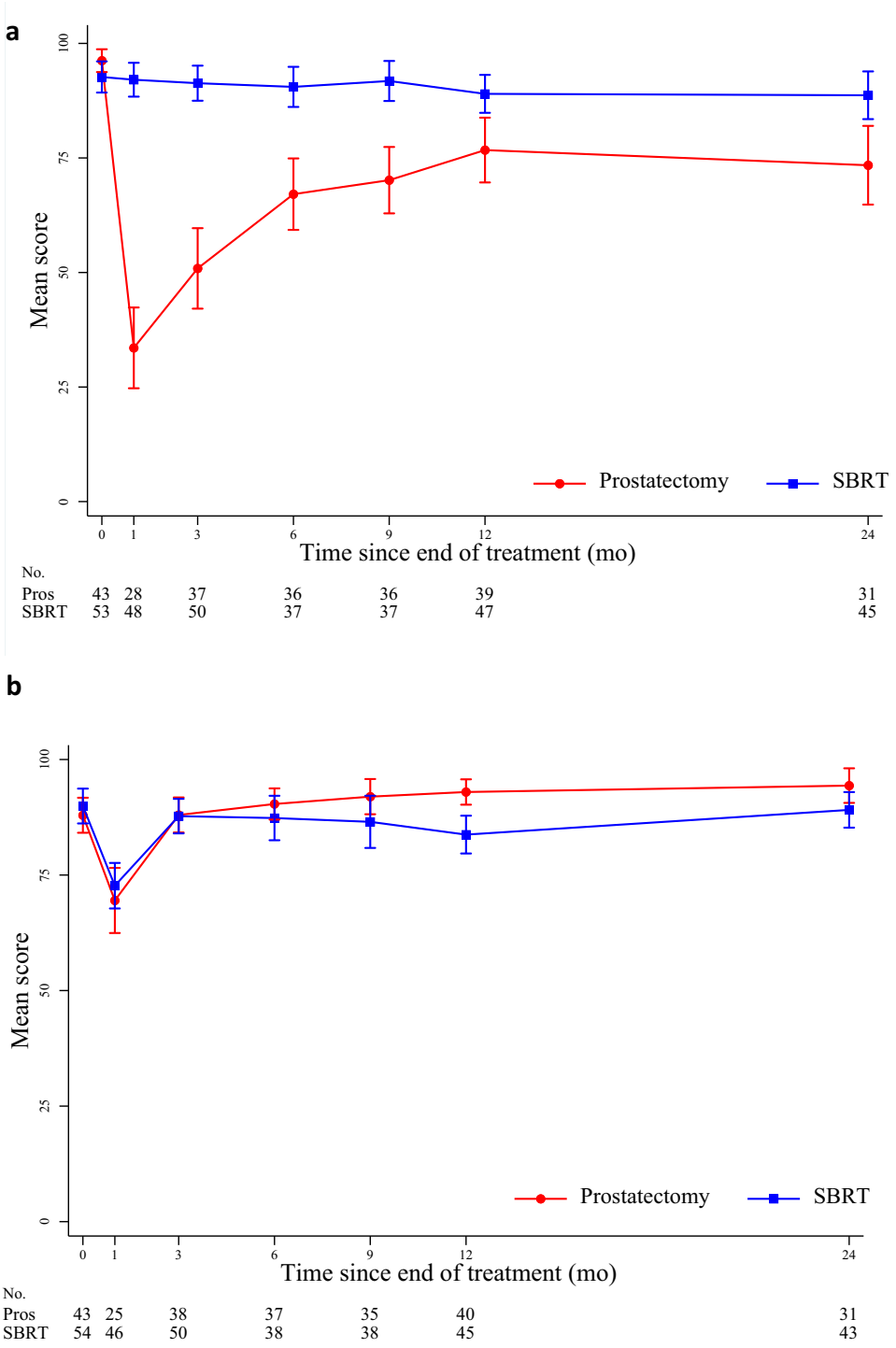

Fig. 3 – Mean EPIC-26 domain scores by treatment received at each time point assessed: (A) urinary incontinence domain scores, (B) urinary obstruction domain scores, (C) EPIC bowel domain scores, and (D) EPIC sexual domain scores. EPIC domain scores range from 0 to 100, with higher scores indicating better quality of life. Error bars show 95% confidence interval for estimates of mean subdomain scores. Week 0 is the baseline toxicity score taken before the start of radiotherapy. EPIC-26 = Expanded Prostate Cancer Index Composite (26 question); Pros = prostatectomy; SBRT = stereotactic body radiotherapy.

did not see evidence of a difference between treatments (p = 0.7; Supplementary material). Grade ≥2 gastrointestinal toxicity was also low across time, with no grade ≥2 events at 24 mo. There were similarly very low levels of moderate/severe genitourinary or gastrointestinal RTOG toxicity with SBRT (Supplementary material). CTCAE erectile dysfunction was reported consistently as a worst grade in prostatectomy participants, with more grade ≥2 events at 24 mo—24/38 (63%) compared with nine of 50 (18%) for SBRT (p < 0.001; Supplementary material).

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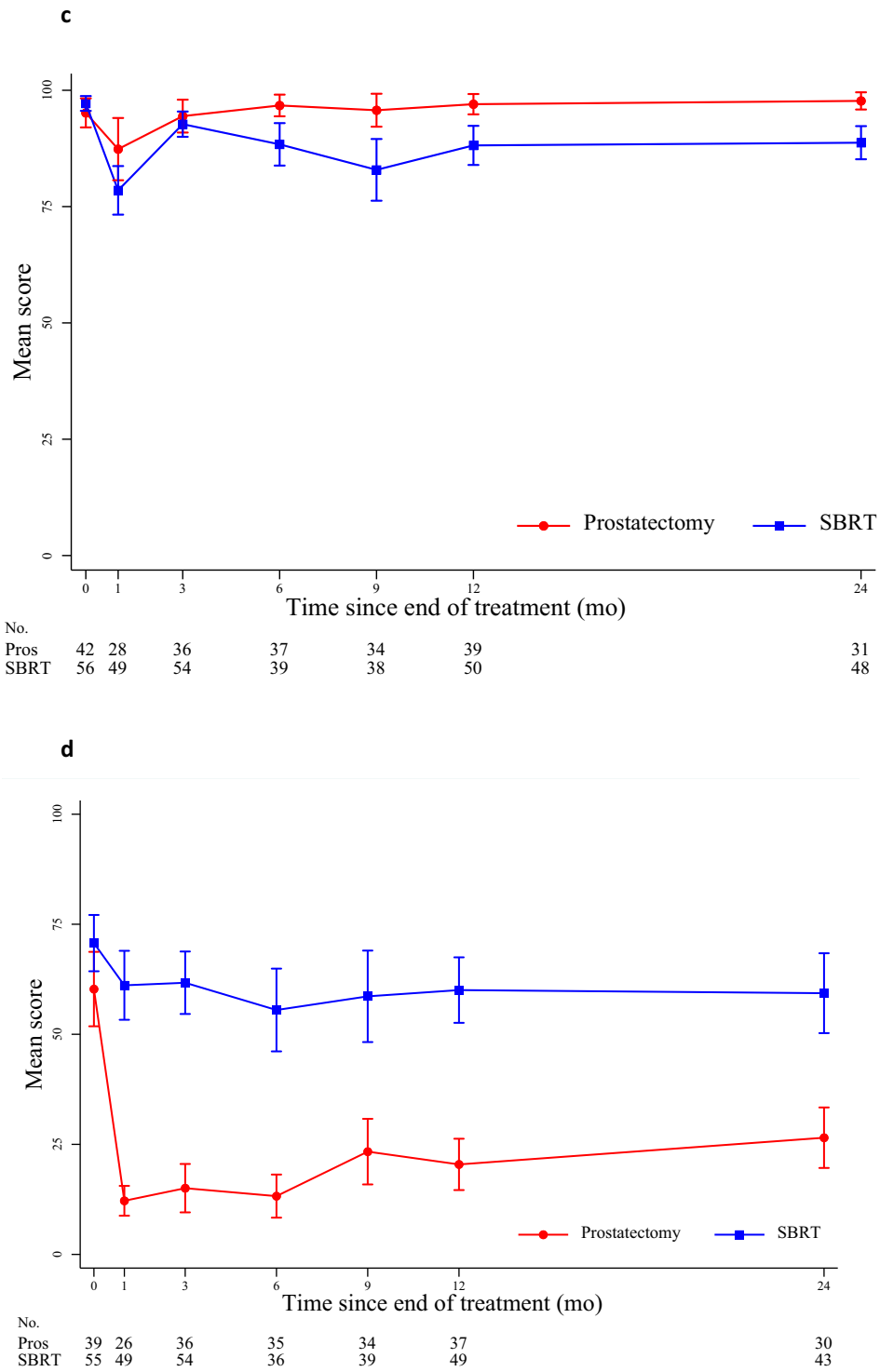

Fig. 3 (*continued*)

4. Discussion

Most patients presenting with intermediate-risk LPCa can expect good outcomes and excellent survival rates with appropriate radical treatment. It is therefore crucial to minimise treatment-related toxicity. PACE-A is the first randomised trial comparing toxicities of SBRT with those of prostatectomy in LPCa.

In PACE-A, participants treated with SBRT reported clinically and statistically significantly better urinary continence and less sexual bother at 2 yr than prostatectomy participants. However, SBRT was associated with worse bowel bother than prostatectomy.

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Pad use with prostatectomy was higher in PACE-A than in ProtecT, which was noted to be 23–34% at 2 yr [4]. PACE-A was similar to PIVOT, in which just under 40% reported pad use, with 17% incontinence rates at 2 yr with prostatectomy [13]. LAPPRO reported 52% were not pad-free or not leakage-free at 2 yr post prostatectomy [14]. SPCG-4 reported 27% urinary leakage at 4 yr [15]. One interpretation is that men who underwent prostatectomy were regularly using pads as a "security" measure irrespective of severity of incontinence; however, only 4% treated with SBRT required a pad even if just for security.

PACE-A reports worse bowel outcomes with SBRT, with overall low bowel toxicity for both the arms. However, the median 2-yr EPIC bowel domain score was higher in PACE-B at 100 for SBRT compared with 87.5 in PACE-A, so the true difference between prostatectomy and SBRT in PACE-A may be overstated [16]. In the future, bowel toxicity seen with SBRT could be mitigated with a number of strategies, including margin reduction with motion management and potentially the use of perirectal spacer insertion [17,18].

PACE-A shows worse clinician and patient-reported sexual function for prostatectomy. Similarly, high erectile dysfunction rates of 81% were observed with prostatectomy at 2 yr in PIVOT using SF-12 scoring and 66% with a study-specific score in SPCG-4 [13,15]. Sexual function appears static between 2 and 5 yr after treatment in previous studies, suggesting that 2 yr is sufficient to capture differences [13,19].

Patient-reported genitourinary or gastrointestinal toxicity was not reflected in clinician reporting. Overall clinician-reported genitourinary and gastrointestinal toxicity was low in both arms. Evidence suggests that standard clinician reporting can be discordant with patient self-reporting with a risk of under-reported symptoms [20]. Therefore, where toxicity is an important outcome measure, PROs should be a key component of future trials.

Strengths of this study include the randomised design, multicentre recruitment, modern radiotherapy techniques, and consistent quality assurance standards.

The trial has limitations. It is challenging to recruit to randomised trials where considerable differences exist between the randomised interventions, and PACE-A was no exception. Whilst target sample size was not achieved, the IDMC advised that continued recruitment was unlikely to yield additional information and advised study closure and reporting of 2-yr data. The impact of a smaller sample size was mitigated by the observed coprimary endpoint (absorbent pad use) event rate in the prostatectomy arm (50%), which we underestimated at 15% in the power calculations. Differential dropout from allocated treatment was seen and may have introduced some bias in the comparisons. Another limitation was data completeness; PRO questionnaire return rates were 67% (83/123) at 2 yr (Supplementary material). This could have, in part, been affected by the COVID-19 pandemic as PRO booklets were distributed in clinic and many participants were switched to telephone follow-up. However, the results held for the coprimary endpoints in a sensitivity analysis imputing 3-yr data for missing 2-yr assessments (Supplementary material). There was no evidence of a difference in baseline demographics of participants who returned and those who did not return 2-yr PRO booklets (Supplementary material).

5. Conclusions

PACE-A provides level 1 evidence of better outcomes of urinary continence and sexual function with worse bowel bother for SBRT, compared with prostatectomy. Overall serious bowel and incontinence symptoms were uncommon. For men with intermediate-risk LPCa facing treatment decisions, the fear of incontinence and loss of sexual function are frequent drivers of treatment choice. PACE-A provides contemporary toxicity estimates to optimise treatment decisions and maximise individual QoL.

Author contributions: Nicholas van As had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van As, Tree, Hall, Burnett.
Acquisition of data: van As, Tree, Ostler, van der Voet, Ford, Tolan, Wells, Mahmood, Winkler, Chan, Ogden, Thompson, Pugh, Manning, Brown, Burnett.
Analysis and interpretation of data: van As, Yasar, Griffin, Patel, Tree, Hall.
Drafting of the manuscript: van As, Yasar, Griffin, Patel, Tree, Hall.
Critical revision of the manuscript for important intellectual content: van As, Yasar, Griffin, Patel, Tree, Ostler, van der Voet, Ford, Tolan, Wells, Mahmood, Winkler, Chan, Thompson, Ogden, Naismith, Pugh, Manning, Brown, Burnett, Hall.
Statistical analysis: Hall, Yasar, Griffin, Patel.
Obtaining funding: van As, Tree, Hall, Burnett.
Administrative, technical, or material support: van As, Tree, Pugh, Manning, Brown, Burnett, Hall.
Supervision: van As, Tree, Hall.
Other: TMG, Ostler, van der Voet, Ford, Tolan, Chan, Naismith; surgical quality assurance, Winkler, Thompson; physics quality assurance group lead, Naismith.

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ogy and Physics, chair of the MRlinac Consortium Steering Committee (Elekta reimbursement via institution for time); declares her role as a member of the ESTRO Prostate Core Group, Prostate Cancer UK Clinical Advisory Group, and the European Multidisciplinary Congress on Urological Cancers Planning Committee (unpaid); and declares her participation (unpaid) in the Data Safety and Monitoring Board for the KORTUC and NEPTUNES academic trials. D. Ford declares that he is employed by Genesiscare as an advisor or a clinician in an MRLinac facility. S. Tolan declares support for attending meetings and/or travel from Janssen. M. Winkler declares his role in the Surgical Safety Monitoring Group. E. Hall declares grants received by the Institute of Cancer research from Astra Zeneca, Janssen-Cilag, Bayer, Roche Products Ltd, and Merck Sharp & Dohme.

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Supplementary data

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