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Comparative effectiveness of new treatment modalities for localized prostate cancer through patient-reported outcome measures

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ABSTRACT

Purpose: There is scarce comparative effectiveness research on the new treatment modalities for localized prostate cancer. We aim to compare through Patient-Reported Outcome Measures (PROMs) the impact of active surveillance, robot-assisted radical prostatectomy (RARP), intensity-modulated radiotherapy (IMRT), and real-time brachytherapy, considering side effects (incontinence, irritative/obstructive urinary symptoms, sexual dysfunction and bowel symptoms) and physical and mental health.

Materials and Methods: Prospective cohort of men diagnosed with clinically localized prostate cancer (age 50-75y, T1-T2, and low risk including Gleason 3 + 4 in T1c) from 18 Spanish hospitals, followed up to 24 months. Treatment decisions were jointly made by patients and physicians (n = 572). The Expanded Prostate cancer Index Composite (EPIC-26) and Short-Form 36 (SF-36v2) were administered through telephone interviews before and three, six, 12, and 24 months after treatment. To account for correlation among repeated measures, generalized estimating equation models were constructed. All analyses were performed with propensity score weights to solve treatment selection bias.

Results: The PROMs completion rate at 24 months was 95.0 %. Active surveillance entails the fewest side effects, but with significant sexual (0.4 standard deviations [SD], $p < 0.001$) and physical health deterioration (0.5 SD, $p < 0.001$); and moderate mental health improvement (0.4 SD, $p = 0.001$) at 24 months. Compared with active surveillance, RARP presented greater urinary incontinence ($p = 0.030$), and IMRT and real-time brachytherapy worse bowel symptoms ($p = 0.027$ and $p = 0.007$) at 24 months.

Conclusions: Most side effects of the new treatment modalities seem to be limited to short-term deteriorations, except for moderate-large urinary incontinence in patients who had undergone RARP and moderate bowel deterioration in patients treated with IMRT or with real-time brachytherapy. Furthermore, patients under active surveillance, IMRT, and real-time brachytherapy showed a moderate improvement in mental health.

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1. Introduction

Prostate cancer is the most frequently diagnosed non-cutaneous cancer among men in USA and Europe [1], and most patients are diagnosed in localized stages [2], becoming long-term survivors [3]. Randomized controlled trials of curative intention treatments for localized prostate cancer are mainly restricted to the ProtecT (Prostate Testing for Cancer and Treatment) trial [4,5]. This study showed similar very high rates of survival at ten years of follow-up [4] for radical prostatectomy, external beam radiotherapy and active monitoring, though differing in their side effects' patterns, evaluated with Patient-Reported Outcome Measures (PROMs) [5]. ProtecT patients were treated in the early 2000s with open retropubic radical prostatectomy, external beam 3D-conformal radiotherapy (delivered at 74 Gy in 37 fractions), and active monitoring.

New modalities of the same treatments are being widely used, such as robot-assisted radical prostatectomy (RARP), intensity-modulated radiation therapy (IMRT), or real-time brachytherapy, with the theoretical justification that they are less aggressive and could achieve maximum efficacy in oncological results with a lower rate of side effects. RARP has shown to be an easily acquired laparoscopic technique, with shorter learning curves than the open procedure [6]. IMRT has allowed treating patients with higher doses of radiation, without increasing toxicity in surrounding healthy tissues [7]. Real-time brachytherapy allows correcting radioactive seed distribution and doses at the time of their implantation, achieving better target coverage and sparing normal tissues [8].

The rapid adoption of newer modalities has introduced additional uncertainty to the decision-making process. On the one hand, despite the theoretical advantages, the randomized clinical trial comparing RARP with open radical prostatectomy did not find significant benefits in PROMs [9]. On the other hand, the randomized clinical trial comparing IMRT with 3-D conformal radiotherapy reported differences in urinary, bowel and other treatment-related symptoms, in favor of the new technique [7]. The only recent study comparing real-time with pre-planned low-dose rate brachytherapy as a monotherapy did not show any differences in toxicity, though PROMs were not included [8].

There is scarce comparative effectiveness research assessing PROMs of the four most established new modalities of treatment [10–13] (active surveillance, RARP, IMRT, and real-time brachytherapy), and groups were composed by a combination of modalities. The proportion of new techniques was only reported in two studies: 87 % [10] and 81 % [13] of patients treated with RARP, and 95 % [10] and 76 % [13] with IMRT. None of these studies provided information on the proportion of patients treated with real-time and pre-planned brachytherapy [10–13]. As far as we know, no study has reported comparative data of patients strictly treated with the four new treatment modalities.

Therefore, the aim of this study was to compare through Patient-Reported Outcome Measures (PROMs) the impact of active surveillance, RARP, IMRT, or real-time brachytherapy on patients with localized prostate cancer, considering side effects (incontinence, irritative/obstructive urinary symptoms, sexual dysfunction and bowel symptoms) and physical and mental health.

2. Materials and methods

2.1. Patients

This was a prospective cohort of Spanish men diagnosed with clinically localized prostate cancer in 18 Spanish hospitals, between 2014 and 2021 (ClinicalTrials.gov Identifier: NCT05523856). Patient inclusion criteria were 50–75 years old; clinical stage T1 or T2, N0/Nx and M0/Mx; Gleason $\leq$ 6 or 7 (if 3 + 4 with T1c); Prostate-Specific Antigen (PSA) $\leq$ 10 ng/ml; and to be treated with active surveillance, RARP, IMRT or real-time brachytherapy as monotherapy. Patients were excluded when body mass index was $>$ 33, they had undergone neoadjuvant hormone treatment, previous pelvic treatments, and/or had presence of serious comorbidities. The ethics review boards of the 18 participating hospitals approved the study (Research Ethics Committee with medicines (CREm) at Bellvitge University Hospital: PR086/14), and written informed consent was requested from patients. The decision regarding treatment selection was made jointly by the patients and physicians after diagnosis. Treatment group assignment was based on the initial primary treatment, regardless of any further adjuvant or salvage therapy.

2.2. Treatments

Patients in active surveillance were monitored with regular tests including PSA and digital rectal examination every 6 months, and a magnetic resonance imaging and prostate biopsy during the first year. Thereafter, physicians scheduled the regular tests, based on clinical information, progression and/or physical examination at 6–12 monthly intervals, and repeat biopsy regularly at 1–4 yearly intervals. Triggers for transition to another treatment included Gleason or local TNM progression, significant increase of PSA values and/or PSA doubling time in less than 36 months, or the patient's choice.

The RARP applied consisted in a prostate extraction procedure carried out through a six-port transperitoneal approach, using the four-arm Da Vinci Si Robotic Surgical System. Nerve-sparing procedure was applied in 90 % of the patients, and modifications of the technique including lymphadenectomy were performed according to the final pathological report only in nine patients.

IMRT was carried out with volumetric modulated arc therapy (VMAT) under daily image-guided radiation therapy (IGRT). The planning target volume of the prostate was defined as the entire prostate plus a 5 mm margin in all directions except posteriorly, where a 3 mm margin was used. The treatment was delivered in 3 Gy daily fractions, 5 days per week, with a prescription dose of 60 Gy.

All patients in the real-time interstitial radiotherapy group underwent low-dose-rate brachytherapy with I^{125} permanent seeds implantation, with a prescribed dose of 145 Gy to the target volume. The prescription dose (V100) applied in the dosimetry prostate volume was at least 95 %, and the dose received by 90 % of the prostate (D90) was 100 %.

2.3. Patient-Reported Outcome Measures

The collection of data was carried out per the present recommendations of the International Consortium for Health Outcomes Measurement for localized prostate cancer [14]. The 26-item version of the Expanded Prostate cancer Index Composite (EPIC-26) [15,16] and the 36-item Short-Form Health Survey version 2 (SF-36v2) [17–19] were administered centrally through telephone interviews, before treatment and three, six, 12 and 24 months after treatment or after starting active surveillance.

The EPIC-26 measures urinary, sexual, bowel, and hormonal domains, ranging from 0 to 100, higher scores indicating better outcomes. In addition to the EPIC scores, we selected some of the key items proposed by the ProtecT trial [5] to help interpreting clinical relevance. Responses to these key EPIC items were all dichotomized to show the percentage of men reporting problems, except for the erection firmness item, which shows the percentage of men reporting sexual potency. The SF-36v2 physical and mental component summaries (PCS and MCS) were obtained using the developers' algorithms [17], standardized to have a mean of 50 and a standard deviation (SD) of 10 in the US general population.

2.4. Sample size calculation

The sample size calculated to detect small differences between groups (0.3 SD) on the EPIC or SF-36v2 scores was of 90 patients per

Table 1
Unweighted and weighted descriptive of patient characteristics and quality of life scores before treatment (n = 572).

	Unweighted					Weighted applying propensity scores					
	Active Surveillance	RARP	IMRT	Brachytherapy	p-value	All	Active Surveillance	RARP	IMRT	Brachytherapy	p-value
Participants (n)	87	194	111	180							
Age (y), mean (SD)	68.5 (5.1)	60.3 (5.0)	69.6 (4.9)	64.8 (6.4)	<0.001	68.1 (5.5)	68.5 (5.1)	65.9 (5.7)	68.2 (5.4)	68.6 (5.5)	0.059
PSA, mean (SD)	6.0 (1.7)	6.1 (1.8)	6.3 (1.8)	6.0 (1.8)	0.488	6.0 (1.7)	6.0 (1.7)	5.5 (1.8)	6.0 (1.7)	6.0 (1.8)	0.330
Gleason, mean (SD)	6.1 (0.3)	6.5 (0.5)	6.1 (0.3)	6.1 (0.3)	<0.001	6.1 (0.4)	6.1 (0.3)	6.2 (0.4)	6.1 (0.4)	6.0 (0.4)	0.086
≤6	77 (88.5 %)	88 (45.4 %)	98 (88.3 %)	169 (93.9 %)	<0.001	86.1 %	88.5 %	77.8 %	85.2 %	88.1 %	0.417
7	10 (11.5 %)	106 (54.6 %)	13 (11.7 %)	11 (6.1 %)		13.9 %	11.5 %	22.2 %	14.8 %	11.9 %	
Clinical tumour stage T, n (%)											
T1c	78 (89.7 %)	194 (100.0 %)	92 (82.9 %)	131 (72.8 %)	<0.001	82.8 %	89.7 %	100.0 %	78.7 %	72.6 %	<0.001
T2a	9 (10.3 %)	0 (0.0 %)	19 (17.1 %)	49 (27.2 %)		17.2 %	10.3 %	0.0 %	21.3 %	27.4 %	
Tumoral risk, n (%)											
Low	77 (88.5 %)	87 (44.8 %)	96 (86.5 %)	167 (92.8 %)	<0.001	86.1 %	88.5 %	77.8 %	85.2 %	88.1 %	0.417
Intermediate	10 (11.5 %)	107 (55.2 %)	15 (13.5 %)	13 (7.2 %)		13.9 %	11.5 %	22.2 %	14.8 %	11.9 %	
Working status, n (%)											
Working	10 (11.6 %)	128 (67.0 %)	11 (10.2 %)	61 (34.9 %)	<0.001	14.6 %	11.6 %	36.1 %	11.4 %	11.9 %	0.028
Retired	69 (80.2 %)	50 (26.2 %)	92 (85.2 %)	100 (57.1 %)		76.9 %	80.2 %	61.1 %	78.4 %	78.6 %	
Unemployed	2 (2.3 %)	3 (1.6 %)	1 (0.9 %)	9 (5.1 %)		3.1 %	2.3 %	0.0 %	5.7 %	2.4 %	
Other	5 (5.8 %)	10 (5.2 %)	4 (3.7 %)	5 (2.9 %)		5.4 %	5.8 %	2.8 %	4.5 %	7.1 %	
Missing	1	3	3	5							
BMI, n (%)											
Normal weight (18.5 – 24.9)	26 (29.9 %)	66 (34.0 %)	14 (12.6 %)	47 (26.1 %)	<0.001	31.2 %	29.9 %	18.9 %	33.0 %	36.1 %	0.551
Overweight (25 – 29.9)	53 (60.9 %)	107 (55.2 %)	66 (59.5 %)	100 (55.6 %)		60.3 %	60.9 %	75.7 %	58.0 %	55.4 %	
Obesity (30 – 32.9)	8 (9.2 %)	21 (10.8 %)	31 (27.9 %)	33 (18.3 %)		8.5 %	9.2 %	5.4 %	9.1 %	8.4 %	
EPIC-26, mean (SD)											
Urinary Incontinence	89.7 (20.0)	94.9 (14.1)	90.4 (17.4)	95.5 (13.2)	0.003	90.3 (18.0)	89.7 (20.0)	86.2 (17.6)	88.9 (19.1)	94.2 (14.2)	0.094
Urinary Irritative/Obstructive	89.8 (16.5)	87.6 (17.7)	88.7 (17.3)	91.9 (14.3)	0.091	89.3 (18.0)	89.8 (16.5)	80.8 (27.1)	89.7 (16.1)	91.9 (15.6)	0.019
Sexual	65.2 (26.5)	75.4 (21.5)	63.5 (27.9)	64.5 (28.5)	<0.001	66.6 (26.8)	65.2 (26.5)	68.7 (27.9)	66.0 (26.5)	67.6 (27.3)	0.895
Bowel	97.2 (7.5)	97.7 (7.1)	97.9 (6.6)	97.1 (9.4)	0.803	97.1 (8.6)	97.2 (7.5)	93.1 (15.0)	98.4 (5.5)	97.1 (8.1)	0.017
Hormonal	91.0 (12.7)	88.6 (13.2)	90.3 (12.5)	90.1 (13.4)	0.490	90.5 (12.5)	91.0 (12.7)	89.1 (10.9)	89.7 (12.6)	91.2 (12.9)	0.760
SF-36v2, mean (SD)											
Physical Component Summary	49.9 (6.4)	52.8 (5.1)	49.1 (7.4)	51.6 (6.1)	<0.001	50.7 (7.2)	49.9 (6.4)	53.9 (4.5)	48.6 (9.6)	52.2 (5.1)	<0.001
Mental Component Summary	51.0 (9.0)	49.8 (8.4)	50.7 (9.3)	50.3 (9.0)	0.727	50.3 (9.2)	51.0 (9.0)	49.3 (9.0)	49.8 (10.0)	50.7 (8.8)	0.720

BMI: Body Mass Index; EPIC-26: Expanded Prostate cancer Index Composite 26; IMRT: Intensity-Modulated Radiotherapy; PSA: Prostate-Specific Antigen; RARP: Robot-Assisted Radical Prostatectomy; SD: Standard Deviation; SF-36v2: 36-item Short-Form Health Survey version 2;

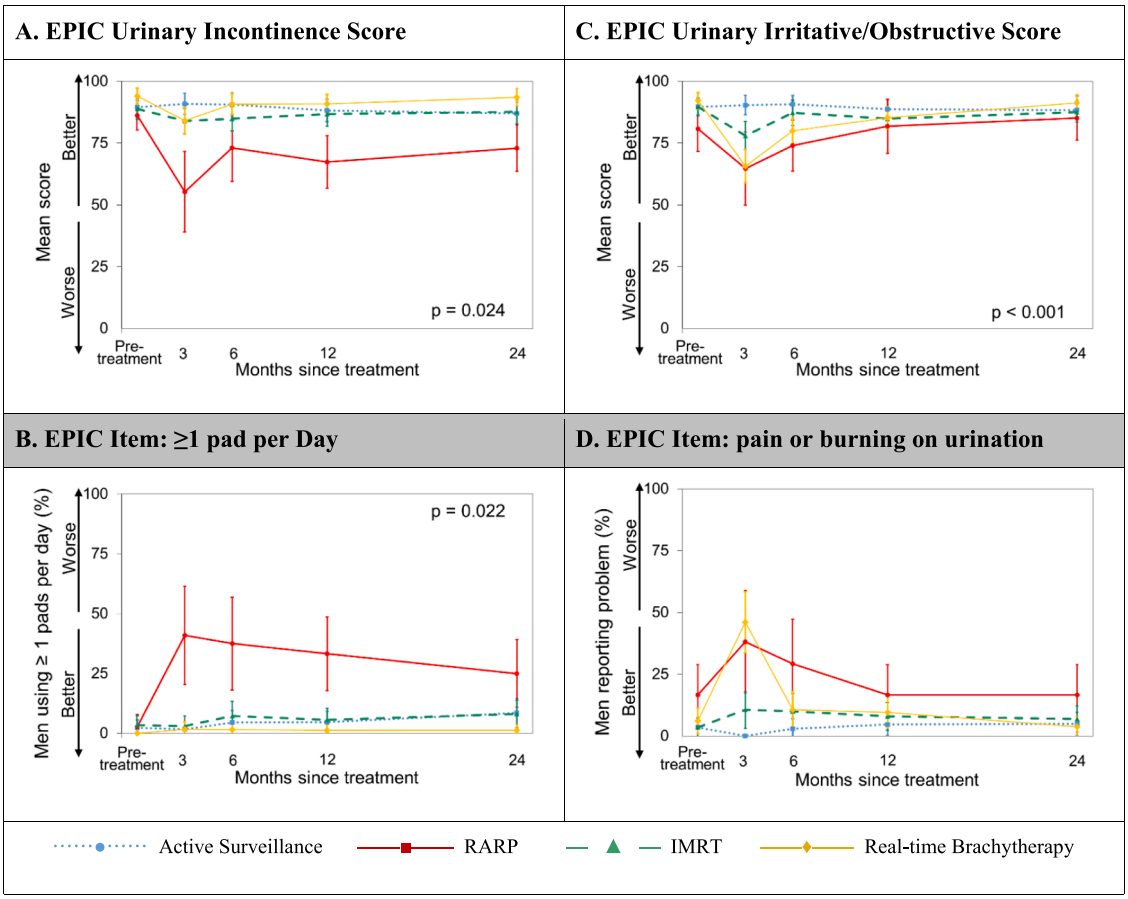

Fig. 1. Follow-up results of the Urinary domain weighted by propensity score measured with the Expanded Prostate cancer Index Composite-26 (EPIC-26). Panel A shows the EPIC-26 score mean for Urinary Incontinence and Panel B the results of one of the items included in that score: the percentage of men who used one or more absorbent pads per day for urinary incontinence. The EPIC Urinary Irritative/Obstructive score is shown in Panel C, and Panel D shows the percentages of men who reported a moderate-to-severe pain or burning on urination. The p-values show the trend differences over 24 months of follow-up among the four groups, weighted by propensity score. I bars represent 95 % confidence intervals.

treatment group, given a statistical power of at least 80 % at a significance level of 5 %, and loss to follow-up of 10 %.

2.5. Statistical analysis

To account for treatment selection bias, propensity scores were obtained from the predicted probabilities estimated in separate logistic regression models (Supplementary Material, Table S1), contrasting active surveillance with each of the other three treatment groups (RARP, IMRT, and real-time brachytherapy). The c-statistics obtained for each model were 0.97 for RARP, 0.77 for IMRT, and 0.82 for real-time brachytherapy, indicating good discriminant ability. For standardized morbidity ratio (SMR) weighting [20], patients in active surveillance are given a weight of one, while weights for patients in other treatment groups are defined as the ratio of the estimated propensity score to one minus the estimated propensity score.

Summary statistics and 95 % confidence intervals (95 %CI) are reported per treatment group, and the differences were tested using Chi squared test for categorical variables or one-way analysis of variance (ANOVA) for continuous variables. All analyses were performed with propensity score weights, except for the comparison of patients' characteristics at baseline, which were also described with unweighted estimates.

To assess PROMs changes over time, while accounting for correlation among repeated measures, separate Generalized Estimating Equation (GEE) models were constructed for EPIC-26 and SF-36v2 scores as dependent variables. Treatment and time were included in the models as categorical variables, and interactions between them were considered in order to test differences in trends among the four treatment groups (with active surveillance as reference group). The remaining unbalanced variables after applying weights of propensity scores were also included in the GEE models as covariates. Models were constructed with SAS software, version 9.4.

3. Results

Of the 583 participants, 11 did not want to answer the PROM interviews, and they were excluded from the analysis (Supplementary Material, Fig. S1). The PROMs completion rate before treatment and at three, six, 12, and 24 months was 94.3 % (n = 550), 58.3 % (n = 340), 64.8 % (n = 378), 96.6 % (n = 563) and 95.0 % (n = 554), respectively, with a median follow-up of 24.8 months. Table 1 summarizes the demographic and clinical characteristics of patients (n = 572) at baseline per treatment groups: 87 in active surveillance, 194 who underwent RARP, 111 IMRT, and 180 real-time brachytherapy. Fifteen patients in the active surveillance group initiated some treatment before the 24-month evaluation: eight underwent IMRT, six RARP, and one a combination of IMRT and a boost of low-dose rate real-time brachytherapy. All characteristics presented statistically significant differences among treatment groups, which disappeared after applying propensity score weights, except for clinical stage T, working status, and some PROM scores at pretreatment: in the RARP group, all patients were diagnosed with T1c tumoral stage, the proportion of workers was higher (36.1 %), and they presented lower (worse) EPIC irritative/obstructive and bowel

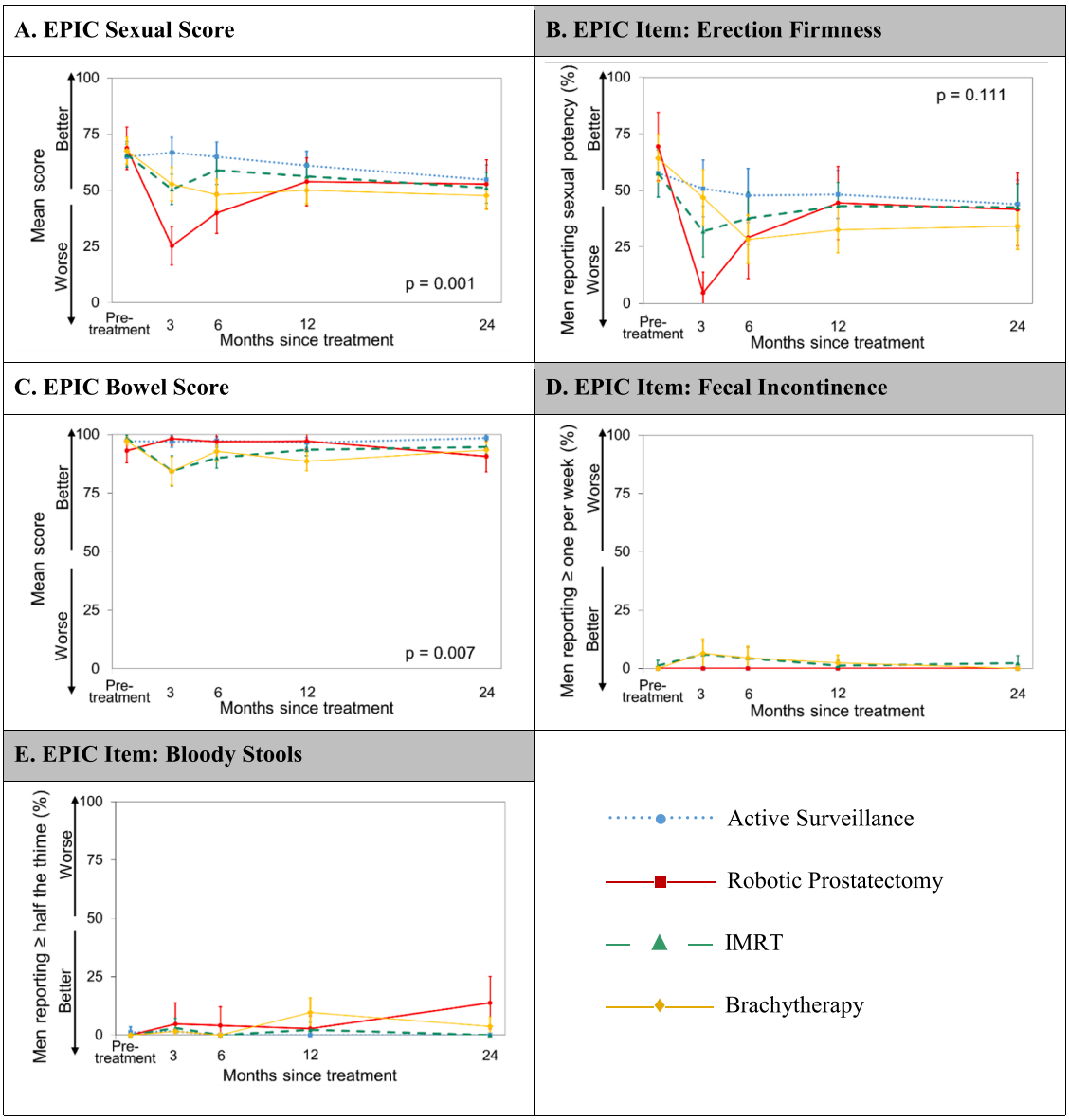

Fig. 2. Follow-up results of the Sexual and Bowel domains weighted by propensity score measured with the Expanded Prostate Cancer Index Composite-26 (EPIC-26). Panel A shows the EPIC-26 Sexual score mean, and Panel B the results of one of the items included in that score: the percentage of men reporting erections firm enough for intercourse. Panel C shows the EPIC-26 Bowel score mean, and Panel D and E show the percentages of men who reported: D) fecal incontinence at least once per week; and E) bloody stools half of the time or more. The p-values show the trend differences over 24 months of follow-up among the four groups, weighted by propensity score. I bars represent 95 % confidence intervals.

scores, but greater (better) SF-36v2 physical component summary.

Fig. 1 shows the results of the EPIC urinary domain with means or percentages and p-values weighted by propensity scores. Urinary incontinence (Fig. 1A) presented differences among treatment groups ($p = 0.024$), mainly since RARP patients showed the greatest deterioration. Daily use of one or more absorbent pads (Fig. 1B) was near zero before treatments, and lower than 10 % throughout the follow-ups, except for RARP, which was 40.9 % at three and 25.0 % at 24 months. Fig. 1C shows that patients treated with RARP or brachytherapy presented the greatest urinary irritative/obstructive deterioration ($p < 0.001$), but recovered at 24 months. Similar trends are shown in the rate of men reporting pain or burning with urination (Fig. 1D).

Fig. 2A shows that the greatest sexual deterioration along the first year after treatment was observed in patients who underwent RARP ($p = 0.001$), with partial recovery. All treatment groups presented lower scores at 24 months than before treatment. The proportion of men who reported erections firm enough for intercourse before RARP was 69.4 % (Fig. 2B), which fell to 4.8 % at three months, and gradually recovered to 43.9 % after 24 months. This rate decreased to a lesser extent in the brachytherapy group, but without an observed recovery. Fig. 2C shows differences in EPIC bowel scores ($p = 0.007$), indicating worse short-term results for brachytherapy and IMRT. Fig. 2D and 2E showed a very low proportion of patients reporting fecal incontinence or bloody stools; in fact, it was not possible to estimate the p-value of trend differences because in some evaluations no men reported these problems.

Fig. 3A presents the time-trends in EPIC hormonal score, and Fig. 3B and 3C show the physical and mental component summaries of SF-36v2, without statistically significant differences among groups.

Table 2 shows the means of EPIC and SF-36v2 scores weighted by propensity scores and adjusted by clinical tumour stage and working status, as well as the comparison with values before treatment and with active surveillance (reference group) at each evaluation. No differences were found among treatments in any EPIC score before treatment, once adjusted by these variables. Urinary incontinence significantly worsened

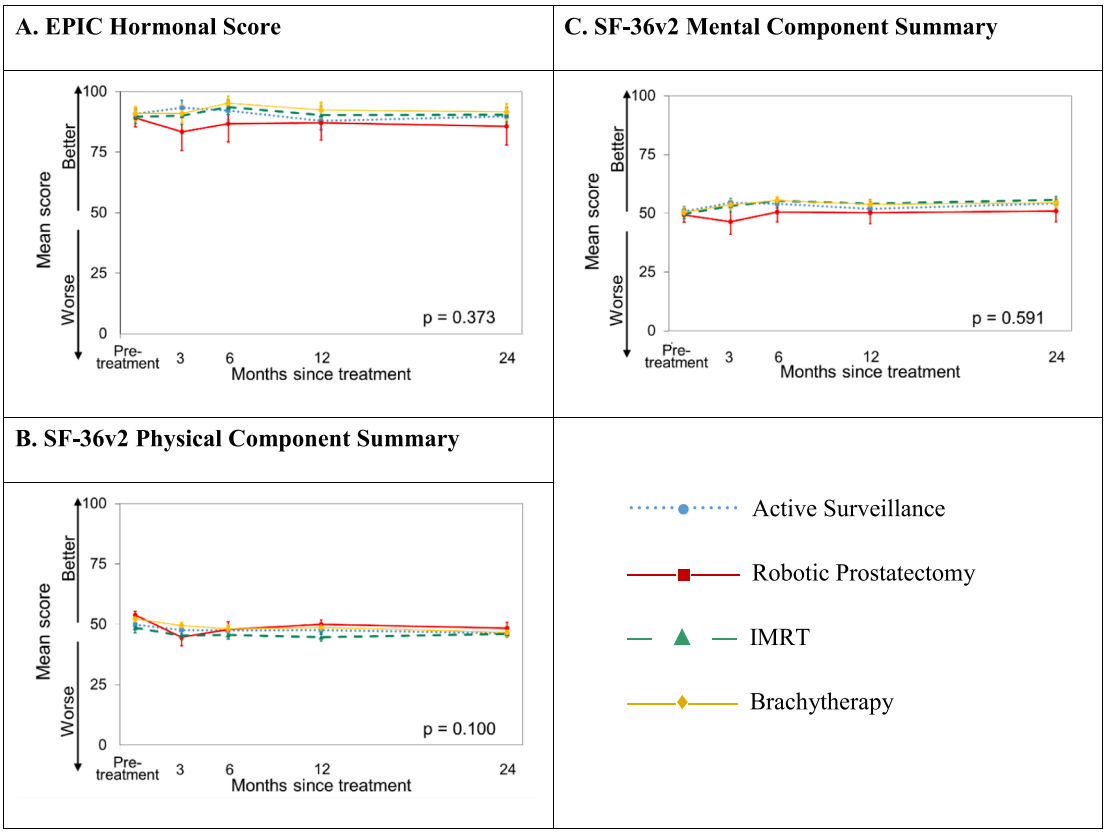

Fig. 3. Follow-up results of the Hormonal domain, and Physical and Mental Component Summaries weighted by propensity score measured with the Expanded Prostate cancer Index Composite-26 (EPIC-26) instrument, and with the 36-item Short-Form Health Survey (SF-36v2). Panel A shows the EPIC-26 Hormonal score mean, and Panel B and C show the SF-36v2 physical and mental component summaries' score means. The p-values show the trend differences over 24 months of follow-up among the four groups, weighted by propensity score. I bars represent 95 % confidence intervals.

(lower scores) in most follow-ups of the RARP and real-time brachytherapy groups, but only RARP presented significant higher worsening than the active surveillance group (73.0 vs 88.0 at 24 months). Deterioration of urinary irritative/obstructive symptoms was only statistically significant in the real-time brachytherapy group until month 12.

The mean of sexual scores in patients under active surveillance gradually worsened and became significantly lower, from 66.0 after diagnosis, to 56.0 at month 24. Other treatment groups significantly worsened throughout follow-ups, but differences with active surveillance (reference group) were not statistically significant at 24 months.

Both radiotherapy groups presented a statistically significant worsening during the whole follow-up in bowel scores, which was also significantly different from active surveillance (reference group). The hormonal score did not present changes over time in any treatment group.

Finally, SF-36v2 shows that physical health worsened over follow-up in all treatment groups, mostly without significant differences compared to active surveillance. Mental health significantly improved in most follow-up evaluations of patients under active surveillance, IMRT, and real-time brachytherapy.

4. Discussion

Our findings provide short- and mid-term comparative effectiveness evidence among some of the new treatment modalities for localized prostate cancer, to characterize their distinct patterns of side effects. Active surveillance served as a natural control group for this study, to help inform the decision of men about treatment options. As expected, active surveillance is the treatment that entails the fewest side effects, with preserved urinary and bowel domains. RARP presented the greatest deterioration in urinary continence, while IMRT and real-time brachytherapy in bowel symptoms. All treatment groups presented significant deterioration in the sexual domain and physical health from diagnosis to 24 months follow-up.

The significant deterioration in urinary incontinence observed after RARP is in accordance with other studies on contemporary techniques showing that worsening remained significant at 12 [10, 12, 13] and 24 months after treatment [10,11]. The moderate-large magnitude of the deterioration at 24 months in our study (0.7 SD) is consistent with that observed in patients with favorable-risk disease from another study based on registries [13] which also measured PROMs with EPIC. The randomized clinical trial of robotic and open radical prostatectomy [9] found a negligible urinary deterioration at 24 months, but it was reported as the urinary summary, without distinguishing between incontinence and irritative/obstructive symptoms.

Similar to RARP, real-time brachytherapy also produced short-term deterioration in urinary incontinence, although moderate in magnitude at three months (0.6 SD) and small at six (0.2 SD), with full recovery at 12 months. Only the abovementioned study based on registries [13] found a similar pattern in brachytherapy patients, while worsening was not significant in other two [10,12], and another study reported almost moderate (0.4 SD) significant deterioration during the 24 months, also measured with EPIC [11].

Consistently with the study based on registries [13], patients who underwent RARP in our study also presented a small improvement in urinary irritative/obstructive symptoms at 24 months after treatment, although not statistically significant. Real-time brachytherapy was associated with a large significant deterioration of these symptoms up to 6 months after treatment (1.5 and 0.7 SD), which decreases until a subsequent recovery of the patients at 24 months. IMRT also presented a

Table 2
Results of EPIC and SF-36v2 over time across different treatment groups. Estimated with GEE models: means weighted applying propensity scores and adjusted by clinical tumour stage and work status.

	Urinary Incontinence		Irritative/Obstructive		Sexual		Bowel		Hormonal		SF-36v2 PCS		SF-36v2 MCS	
	Adjusted mean	95% CI	Adjusted mean	95% CI	Adjusted mean	95% CI	Adjusted mean	95% CI	Adjusted mean	95% CI	Adjusted mean	95% CI	Adjusted mean	95% CI
Active Surveillance														
Baseline	90.2	[86.0–94.4]	90.2	[86.7–93.6]	66.0	[60.3–71.7]	97.5	[95.9–99.1]	91.7	[89.1–94.4]	50.5	[49.1–51.8]	50.8	[48.9–52.7]
3 months	91.5	[87.5–95.4]	89.8	[86.0–93.6]	67.6	[61.7–73.5]	97.5	[95.3–99.8]	94.1	[91.5–96.8]	48.0[a]	[46.5–49.5]	54.6[a]	[52.9–56.2]
6 months	90.9	[86.5–95.4]	90.0	[86.5–93.4]	66.0	[60.2–71.8]	97.7	[95.9–99.5]	92.6	[89.0–96.2]	47.7[a]	[46.0–49.3]	54.1[a]	[52.4–55.9]
12 months	88.9	[84.4–93.4]	89.3	[85.5–93.1]	61.7	[55.6–67.8]	96.8	[94.7–98.9]	88.9	[85.4–92.4]	48.0[a]	[46.4–49.7]	51.9	[49.7–54.1]
24 months	88.0	[83.8–92.3]	89.0	[85.1–92.9]	56.0[a]	[49.6–62.5]	98.9	[97.8–99.9]	90.6	[87.3–94.0]	46.8[a]	[45.3–48.3]	54.1[a]	[52.4–55.9]
RARP														
Baseline	86.3	[77.7–95.0]	80.7	[63.4–97.9]	68.4	[54.5–82.2]	93.1	[83.4–102.7]	88.9	[83.5–94.2]	53.6[b]	[51.7–55.5]	49.3	[45.2–53.5]
3 months	56.7[ab]	[34.7–78.8]	67.4	[42.8–91.9]	28.4[ab]	[13.6–43.3]	99.7	[96.2–103.2]	84.1[b]	[74.7–93.6]	44.8[a]	[40.8–48.8]	47.9[b]	[40.2–55.5]
6 months	76.3	[57.1–95.5]	75.6[b]	[62.2–89.0]	42.7[ab]	[32.7–52.6]	97.9	[93.3–102.5]	86.9	[77.0–96.8]	47.8[a]	[42.9–52.6]	51.7	[45.9–57.5]
12 months	67.3[ab]	[50.5–84.1]	81.8	[60.5–103.1]	53.4[a]	[36.1–70.6]	97.2	[93.9–100.6]	86.9	[75.4–98.3]	49.8[a]	[47.7–51.9]	50.3	[41.6–59.0]
24 months	73.0[b]	[60.0–85.9]	85.1	[68.0–102.3]	52.4[a]	[35.2–69.5]	90.7	[78.9–102.5]	85.5	[72.0–99.0]	48.2[a]	[45.3–51.2]	51.0	[42.1–59.9]
IMRT														
Baseline	88.9	[82.5–95.3]	90.1	[86.0–94.2]	67.2	[60.5–73.9]	98.6	[97.5–99.7]	90.7	[87.2–94.2]	49.1	[45.9–52.3]	49.8	[46.9–52.7]
3 months	84.0	[76.7–91.2]	77.8[ab]	[69.1–86.4]	51.6[ab]	[43.3–59.9]	84.2[ab]	[75.3–93.1]	90.8	[85.4–96.3]	45.6[a]	[43.0–48.1]	53.2	[48.8–57.6]
6 months	84.5	[77.1–91.9]	86.9	[78.2–95.7]	59.7	[51.5–67.9]	89.8[ab]	[83.5–96.1]	94.8	[91.2–98.3]	46.1[a]	[43.7–48.6]	55.4[a]	[53.3–57.4]
12 months	86.8	[79.0–94.7]	85.4	[79.6–91.2]	57.5[a]	[49.7–65.3]	93.7[a]	[90.9–96.6]	91.4	[85.6–97.3]	45.3	[42.8–47.9]	54.1[a]	[51.1–57.1]
24 months	88.0	[80.4–95.6]	87.9	[82.1–93.7]	52.0[a]	[42.5–61.6]	94.7[ab]	[91.2–98.2]	91.5	[87.7–95.3]	46.6[a]	[44.7–48.6]	55.7[a]	[53.8–57.6]
Brachytherapy														
Baseline	94.4	[90.8–98.0]	92.8	[88.9–96.6]	69.4	[63.0–75.8]	97.7	[95.5–99.8]	92.2	[88.9–95.4]	53.0[b]	[51.7–54.2]	50.5	[48.2–52.9]
3 months	83.1[a]	[75.4–90.9]	65.3[ab]	[56.0–74.5]	51.0[ab]	[40.8–61.2]	83.6[ab]	[76.0–91.2]	91.4	[87.3–95.5]	50.0[ab]	[48.7–51.2]	53.4[a]	[51.3–55.5]
6 months	90.2[a]	[85.7–94.6]	80.0[ab]	[74.3–85.7]	47.3[ab]	[40.1–54.5]	92.1[ab]	[87.6–96.6]	95.7	[92.9–98.5]	48.6[a]	[47.2–50.0]	55.2[a]	[53.7–56.6]
12 months	91.1	[87.0–95.3]	86.0[a]	[81.5–90.5]	51.4[ab]	[44.4–58.4]	88.9[ab]	[83.3–94.6]	93.4	[89.0–97.9]	49.3[a]	[48.1–50.6]	53.8	[51.0–56.6]
24 months	93.7[b]	[89.9–97.6]	92.0	[88.5–95.6]	49.2[a]	[42.0–56.4]	93.7[b]	[90.0–97.3]	92.7	[89.0–96.5]	47.3[a]	[45.7–48.9]	54.5[a]	[52.3–56.7]

[a] p-value < 0.05 in the comparison with values before treatment.
[b] p-value < 0.05 in the comparison with active surveillance (reference group) at each evaluation. 95% CI: 95% Confidence Interval; IMRT: Intensity-Modulated Radiotherapy; MCS: Mental Component Summary; PCS: Physical Component Summary; RARP: Robot-Assisted Radical Prostatectomy.

significant and moderate-large deterioration at three months (0.7 SD), but rapid recovery, consistently with the available evidence [10,13].

All treatment groups presented statistically significant sexual deterioration. The RARP group presented a large worsening at three and six months (1.5 and 0.9 SD), which became moderate at 24 months (0.6 SD). Similarly, the randomized clinical trial comparing robotic surgery with the open radical prostatectomy also found a moderate sexual deterioration in both arms at 24 months (0.6 and 0.5 SD) [9]. Nevertheless, in our study, this worsening in the RARP group was not significantly different from that observed in the active surveillance group, which could be explained by the aging process and the transition of 15 patients (17 %) from active surveillance to treatment. Moderate deterioration (0.6 SD) in IMRT patients was significantly different from active surveillance at three months, and in the real-time brachytherapy group until month 12 (0.7 SD). This worsening across all treatment groups was consistent with other studies [10–13] but, in contrast to our findings, they reported that large deterioration in the radical prostatectomy group remained for up to 24 months. Nonetheless, RARP patients in our study presented higher sexual scores before surgery (median 87.5) than in other studies (mean = 63.5 [11], median = 80 [13]), and there is evidence [21] showing that patients with high sexual function prior to radical prostatectomy with bilateral nerve sparing had a greater initial loss of sexual function, but greater long-term improvement.

Both radiotherapy groups presented significant large deteriorations in bowel-related symptoms until six months, which became moderate at 24 months (0.5 SD). Other studies on contemporary techniques also presented a moderate deterioration with external radiotherapy [10,11,13] and brachytherapy [13] at 24 months, although results for the latter varied among studies from large [11] to negligible deterioration [10]. The only randomized clinical trial comparing external radiotherapy techniques also found a moderate bowel deterioration in the IMRT arm (0.6 SD), but large in the 3-dimensional conformational radiotherapy arm (1.4 SD) [7].

Consistently with the registry-based study, which is the only one also reporting results of generic health-related quality of life [13], physical health declined during follow-up for all treatment groups in our study. The participants' aging process could partly explain the physical worsening in all treatment groups, as it was also present in those patients under active surveillance. In contrast, we observed a moderate mental health improvement in patients under active surveillance (0.4 SD), IMRT (0.6 SD), and real-time brachytherapy (0.4 SD) after 24 months.

The main limitation of this study is its observational design, without randomized allocation. Treatment selection bias could explain statistically significant differences in socio-demographic, tumoral, and health characteristics among groups. In our study, the propensity scores weighting procedures applied allowed to balance selection bias in social and clinical variables, except for clinical tumoral stage T and working status, which were favorable to the RARP group. For example, 100 % of RARP patients were diagnosed in T1c. However, these two variables were entered in GEE models, adjusting by them.

5. Conclusions

In conclusion, in this cohort of men with localized prostate cancer strictly treated with new treatment modalities, side effects mainly disappeared by the 24-month follow-up, except for the moderate-large urinary incontinence in patients who underwent RARP and the moderate bowel deterioration in those treated with IMRT and brachytherapy. Therefore, most side effects of new treatment modalities seem to be limited to short-term deteriorations. On the other hand, patients under active surveillance, IMRT, and real-time brachytherapy showed a moderate improvement in mental health. It is important to consider each patient's preferences regarding their treatment strategy, with personalized information about the potential risks and benefits, during the shared decision-making process.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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