

Clinical Investigation

Comparative Effectiveness Research in Localized Prostate Cancer: A 10-Year Follow-up Cohort Study



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Purpose: Long-term comparative effectiveness research on localized prostate cancer treatments is scarce, and evidence is lacking especially for brachytherapy. The aim of this study was to assess the long-term impact of the side effects of radical prostatectomy, brachytherapy, and external radiation therapy on patients with localized prostate cancer at 10 years, using propensity score analyses.

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Methods and Materials: This was a prospective observational study of a cohort of men who received a diagnosis of clinically localized prostate cancer (clinical stage T1 or T2, low and intermediate risk group) and were treated with radical prostatectomy ($n = 139$), brachytherapy ($n = 317$), or external radiation therapy ($n = 194$). Treatment decisions were jointly made by patients and physicians. Patient-reported outcome (PRO) evaluation included the Expanded Prostate Cancer Index Composite and Short Form-36, administered centrally by telephone interviews before and annually after treatment. The Expanded Prostate Cancer Index Composite covers urinary, bowel, sexual, and hormonal domains. To assess PRO changes over time, while accounting for correlation among repeated measures, generalized estimating equation models adjusted by propensity scores were constructed.

Results: The PRO completion rate at 10 years was 85.8%. Generalized estimating equation models showed that the pattern of radical prostatectomy side effects, with substantial urinary incontinence and sexual dysfunction, remained until 10 years after treatment (standard deviation [SD], -1.1 and -1.3 , respectively). Brachytherapy produced late deterioration in urinary continence (SD, -0.4) and sexual function (SD, -0.9) that appeared midterm, but the differences from radical prostatectomy remained statistically significant at 10 years ($P < .001$ after adjusting by propensity score). External radiation therapy showed similar results to brachytherapy, but with bowel bother (SD, -0.3).

Conclusions: Although late deterioration in radiation therapy groups attenuated differences from radical prostatectomy, relevant PRO differences still remained after 10 years. Our findings support that brachytherapy is the treatment option that causes the least impact on PROs; it is therefore an alternative to be considered when making evidence-based decisions on localized prostate cancer treatment. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Prostate cancer is the most frequently diagnosed cancer among men in the United States and Europe.¹ Currently, most patients with prostate cancer are diagnosed in localized stages² and will probably be long-term survivors.³

Randomized controlled trials of curative intention treatments for localized prostate cancer are mainly restricted to the Prostate Testing for Cancer and Treatment (ProtecT) trial.^{4,5} This study showed similar very high rates of survival at 10 years of follow-up⁴ for radical prostatectomy, external radiation therapy, and active monitoring; however, treatments differed in side-effect patterns as measured by patient-reported outcomes (PROs).⁵ These results have been confirmed by an analysis of the trial results according to the treatment received and including patients who refused the randomization.⁶ Long-term PRO follow-ups have been also reported by the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)⁷ trial and Prostate Cancer Outcomes Study,⁸ but CaPSURE is the only study to evaluate brachytherapy.

A systematic review of PROs in clinically localized prostate cancer treatments⁹ identified 6 studies evaluating brachytherapy with follow-ups of 5 to 6 years, and their combined results indicated a reduced adverse effect profile. In contrast, 5 and 10 years after treatment, patients undergoing brachytherapy in the CaPSURE study⁷ presented a similar risk of sexual deterioration compared with those who received radical prostatectomy, a lower risk of urinary function worsening, and a higher risk of bowel dysfunction. Since that review and up to the present, no other study on brachytherapy has shown relevant evidence on this treatment. Three articles have published data at 12 to 14,¹⁰ 8,¹¹ and 8 to 9¹² years of follow-up, but they presented relevant

limitations: a small sample size (42¹⁰ or 6¹² patients in the brachytherapy group at the last follow-up), a very low response rate (13%),¹¹ or only covering bowel impact.¹² Therefore, evidence on brachytherapy remains scarce and controversial in the long term.

The aim of this study was to assess the long-term impact of the side effects of radical prostatectomy, brachytherapy, and external radiation therapy on patients with localized prostate cancer 10 years after treatment, using propensity score analyses.

Methods and Materials

This was a prospective observational study (ClinicalTrials.gov Identifier: NCT01492751) of a cohort of men who received a diagnosis of clinically localized prostate cancer and were treated with radical prostatectomy ($n = 193$), brachytherapy ($n = 317$), or external radiation therapy ($n = 194$). Study details have been described elsewhere.¹³⁻¹⁵ Briefly, eligible patients were those with clinical stage T1 or T2, low and intermediate D'Amico risk group disease,¹⁶ treated at one of the participating centers, and without previous prostate transurethral resection. Decisions regarding treatment were made jointly by patients and physicians. The study was approved by the ethics review boards of the participating hospitals, and written informed consent was obtained from patients per the 2000 revision of the Helsinki Declaration.

The Expanded Prostate Cancer Index Composite (EPIC)^{17,18} and Short Form-36 (SF-36)^{19,20} were administered centrally by telephone interviews before treatment and during follow-up at 1, 3, 6, and 12 months after treatment during the first year and annually thereafter. EPIC covers urinary, bowel, sexual, and hormonal domains, with

50 items and scores ranging from 0 to 100.¹⁷ The SF-36 (version 2) generates physical and mental component summaries, scored as recommended by developers and standardized to have a mean of 50 and standard deviation (SD) of 10 in the general US population.¹⁹ Higher scores indicate better results in both instruments. In addition to the EPIC scores, we selected the key EPIC items already identified in the ProtecT study⁵ to aid in the interpretation of clinical relevance. Responses to these key items were all dichotomized to show the percentage of men reporting problems, except for the erection firmness item (percentage of men reporting sexual potency).

The sample size was calculated to detect between-group differences of 5 points on the urinary irritative–obstructive score of the EPIC questionnaire.¹³

Statistical analysis

Summary statistics and 95% confidence intervals (CIs) are reported by treatment group. To account for treatment selection bias, previously estimated propensity scores,¹⁵ which had already been demonstrated to balance the distribution of possible confounders among treatment groups, were incorporated into multivariate analyses.

To assess PRO changes over time, while accounting for correlation among repeated measures, separate generalized estimating equation (GEE) models were constructed for each EPIC score or key item (included as dependent variables). Time was included in the model as a categorical variable, and interactions between treatment and time were considered to test differences on trends among the treatment groups. The GEE models were constructed with the use of SAS/STAT software, version 9.4.

Results

At baseline, the treatment groups presented statistically significant differences in age (means from 64.2 years in radical prostatectomy to 70.1 years in external radiation therapy; $P < .001$), prostate-specific antigen level (means from 7.0 ng/mL in brachytherapy to 8.1 ng/mL in external radiation therapy; $P < .001$), and Gleason score (means from 5.5 in brachytherapy to 6.3 in radical prostatectomy; $P < .001$). After propensity score adjustment,¹⁵ the differences in baseline clinical characteristics among treatment groups disappeared.

The flow chart in Figure E1 shows that at 10 years after treatment, 149 of 704 participants had died, 74 missed the interview, 5 were lost to follow-up, and 476 completed the PRO questionnaires. The completion rate at 10 years was 85.8% (median, 10.24 years; interquartile range, 10.28–10.14).

Figure 1 shows the annual results of the EPIC urinary domain with unadjusted means or percentages with their 95% CI and P -values adjusted by propensity scores. Urinary incontinence (Fig. 1A) presented statistically significant time–trend differences among the treatment groups,

with patients who underwent radical prostatectomy presenting the greatest deterioration. The use of absorbent pads (Fig. 1B) was null before treatment and increased 10 years after to 34.3% in the prostatectomy group, 6.9% in the brachytherapy group, and 7.8% in the external radiation therapy group. Although the urinary irritative–obstructive score was quite stable during follow-up (Fig. 1C), the radiation therapy groups presented statistically lower (worse) means than radical prostatectomy. Figure 1D shows the rate of men reporting pain or burning with urination, which was quite low during the whole follow-up ($<7\%$ for all groups).

All scores and selected key items from the EPIC sexual domain showed statistically significant different results over 10 years of follow-up across the treatment groups (Fig. 2). The sexual function score decreased (deteriorated) with radical prostatectomy and external radiation therapy, but patients treated with brachytherapy showed stability during the first 5 years after treatment and deterioration thereafter (Fig. 2A). Before surgery, 58.1% of men reported erections firm enough for intercourse, but this rate fell to 9.4% after 1 year (Fig. 2B). In the brachytherapy group, this rate remained stable at around 40% from before treatment to the fifth year and declined thereafter.

Figure 3 shows that only the key item about loose stools (Fig. 3B) and the bowel summary score (Fig. 3G) presented statistically significant differences among treatments over time ($P = .027$ and $P = .032$), both indicating worse results in the external radiation therapy group. Calculating the P -value of trend differences for fecal incontinence (Fig. 3C) and bloody stools (Fig. 3D) was not possible, because in some evaluations no men reported these problems.

Figure 4 shows the changes at 10 years obtained by GEE models constructed to assess treatment impact on PROs after adjusting by propensity scores. The GEE models with all the coefficients and P -values are available in the Table E1. Units of change on the left of the figure are EPIC scores and those on the right SDs (change: moderate = 0.5 SD and large = 1 SD, indicated by gray lines).²¹ On average, 10 years after radical prostatectomy, patients scored 29.9 points less than before treatment (Fig. 4A). This change of 30 points is greater than 1 SD (large deterioration). Patients treated with brachytherapy fared +17.4 points (95% CI, 11.0–23.9) better (positive sign) than those who underwent radical prostatectomy (reference group) and, similarly, those who underwent external radiation therapy. Urinary continence deterioration in the brachytherapy and external radiation therapy groups has an near 0.5 SD (moderate deterioration).

Figure 4B shows that both radiation therapy groups presented worse results than radical prostatectomy on the urinary irritative–obstructive score (−3.9 points for brachytherapy; −5.5 points for external radiation therapy). Figure 4C shows substantial worsening of the EPIC sexual function score at 10 years in the 3 treatment groups, but patients treated with brachytherapy fared +10.8 points (95% CI, 4.8–16.8) better than those in the radical

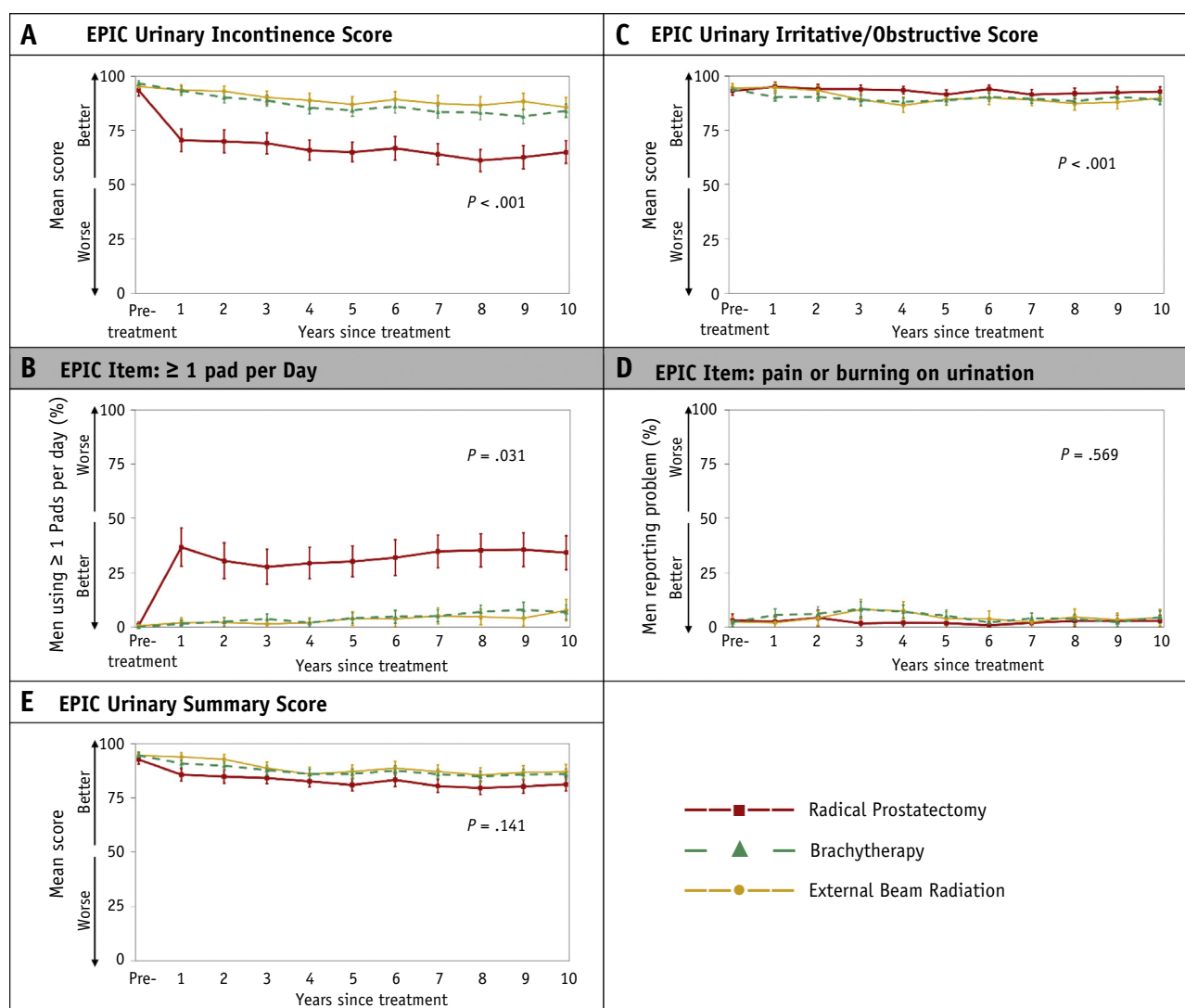


Fig. 1. Ten years of annual results in the urinary domain. Effects of treatments on the urinary domain measured with the Expanded Prostate Cancer Index Composite (EPIC) instrument. EPIC urinary scores comprise several urinary items and are formed by linear transformation of raw scores, ranging from 0 to 100 (from worse to better). (A) EPIC score for urinary incontinence. (B) Results for one of the items included in that score: Percentage of men who used ≥ 1 absorbent pads per day for urinary incontinence. (C) EPIC urinary irritative-obstructive score. (D) Percentages for men who reported moderate-to-severe pain or burning on urination. (E) EPIC urinary summary score. P -values show the strength of evidence for a difference in mean response over 10 years of follow-up across the 3 groups, adjusted by propensity score. I bars represent unadjusted 95% confidence intervals.

prostatectomy group. Finally, worsening was not observed in the bowel function domain (Fig. 4E), and the small worsening presented in bowel bother (<0.5 SD) did not statistically differ among treatments (Fig. 4F).

Discussion

Our findings show that the main traits of radical-prostatectomy side-effect patterns, with large urinary incontinence and sexual dysfunction, remain until 10 years after treatment. Brachytherapy produced substantial deterioration

in sexual function and moderate urinary incontinence that appears at midterm (5 and 7 years after treatment). External radiation therapy showed results similar to brachytherapy, but with bowel bother. Although late deterioration in the radiation therapy groups attenuated their differences from radical prostatectomy, they remained relevant at 10 years.

The main limitation of this study is its observational design. The main concern regarding this design is treatment selection bias where, for example, brachytherapy is preferentially prescribed to patients with lower tumor risk and surgery to younger patients.¹³⁻¹⁵ In our cohort, the propensity scores balanced treatment selection bias.¹⁵ Results

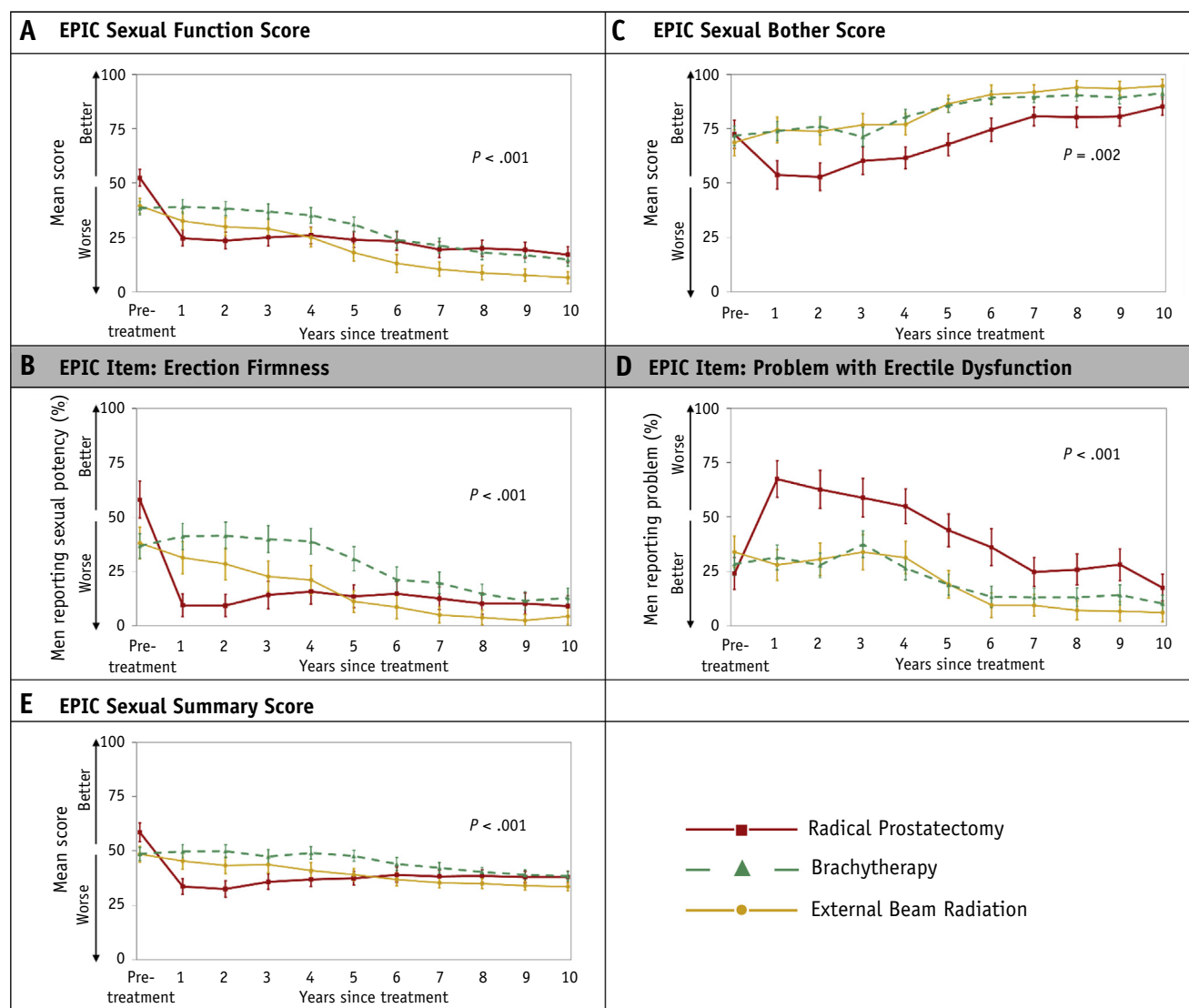


Fig. 2. Ten years of annual results in the sexual domain. Effects of treatments on the sexual domain measured with the Expanded Prostate Cancer Index Composite (EPIC) instrument. EPIC sexual scores comprise several sexual items and are formed by linear transformation of raw scores, ranging from 0 to 100 (from worse to better). (A) EPIC sexual function score. (B) Results for one of the items included in this score: Percentage of men reporting erections firm enough for intercourse. (C) EPIC sexual bother score. (D) Percentages for men who reported a moderate-to-severe problem with erectile dysfunction. (E) EPIC sexual summary score. P -values show the strength of evidence for a difference in mean response over 10 years of follow-up across the 3 groups, adjusted by propensity score. I bars represent unadjusted 95% confidence intervals.

adjusted by propensity scores were consistent with those from traditional models adjusted by baseline clinical variables (Table E2), likely allowing an estimation of the true treatment effects.²² Second, the treatments were applied >1 decade ago; since then, diagnostic techniques and treatments for prostate cancer have evolved.

The strengths of the study include the collection of data per the present recommendations of the International Consortium for Health Outcomes Measurement for localized prostate cancer, which were developed in 2015,²³ the use of a propensity score adjustment for comparative effectiveness research,²² regular follow-up with high rates of response (median, 83.3%; interquartile range, 85.7-74.0),

and the consistency of interpretation based on the magnitude of change with previously established minimally important differences for EPIC scores.²⁴ This is the first study to provide robust evidence on the long-term outcomes of brachytherapy because only 85 of 684 patients treated with this therapy in the CaPSURE registry were evaluated 10 years after treatment.⁷ Of the 317 patients treated with brachytherapy in our cohort, 69 died and 217 completed the 10-year evaluation.

CaPSURE applied the University of California, Los Angeles, Prostate Cancer Index to measure clinically meaningful declines in PROs (defined as 0.5 SD) after treatment.⁷ To facilitate the comparison with CaPSURE, we

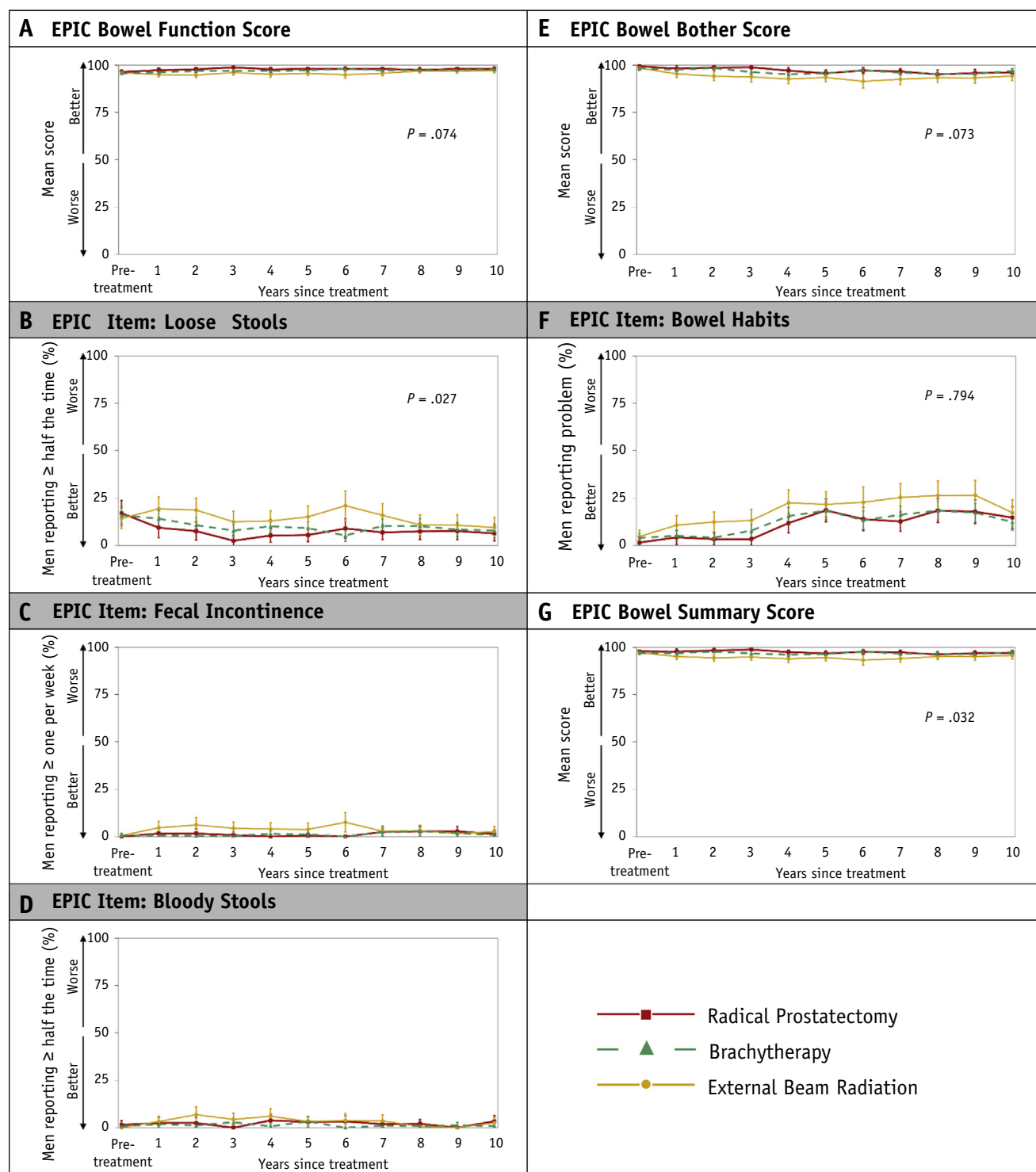


Fig. 3. Ten years of annual results in the bowel domain. Effects of the treatments on the bowel domain measured with the Expanded Prostate Cancer Index Composite (EPIC) instrument. EPIC bowel scores comprise several bowel items and are formed by linear transformation of raw scores, ranging from 0 to 100 (from worse to better). (A) EPIC score for bowel function. (B-D) Results for items included in that score as percentages of men who reported having (B) loose stools half the time or more, (C) fecal incontinence at least once per week, and (D) bloody stools half the time or more. (E) EPIC bowel bother score. (F) Percentages for men who reported a moderate-to-severe negative effect on bowel habits. (G) EPIC bowel summary score. P -values show the strength of evidence for a difference in mean response over 10 years of follow-up across the 3 groups, adjusted by propensity score. I bars represent unadjusted 95% confidence intervals.

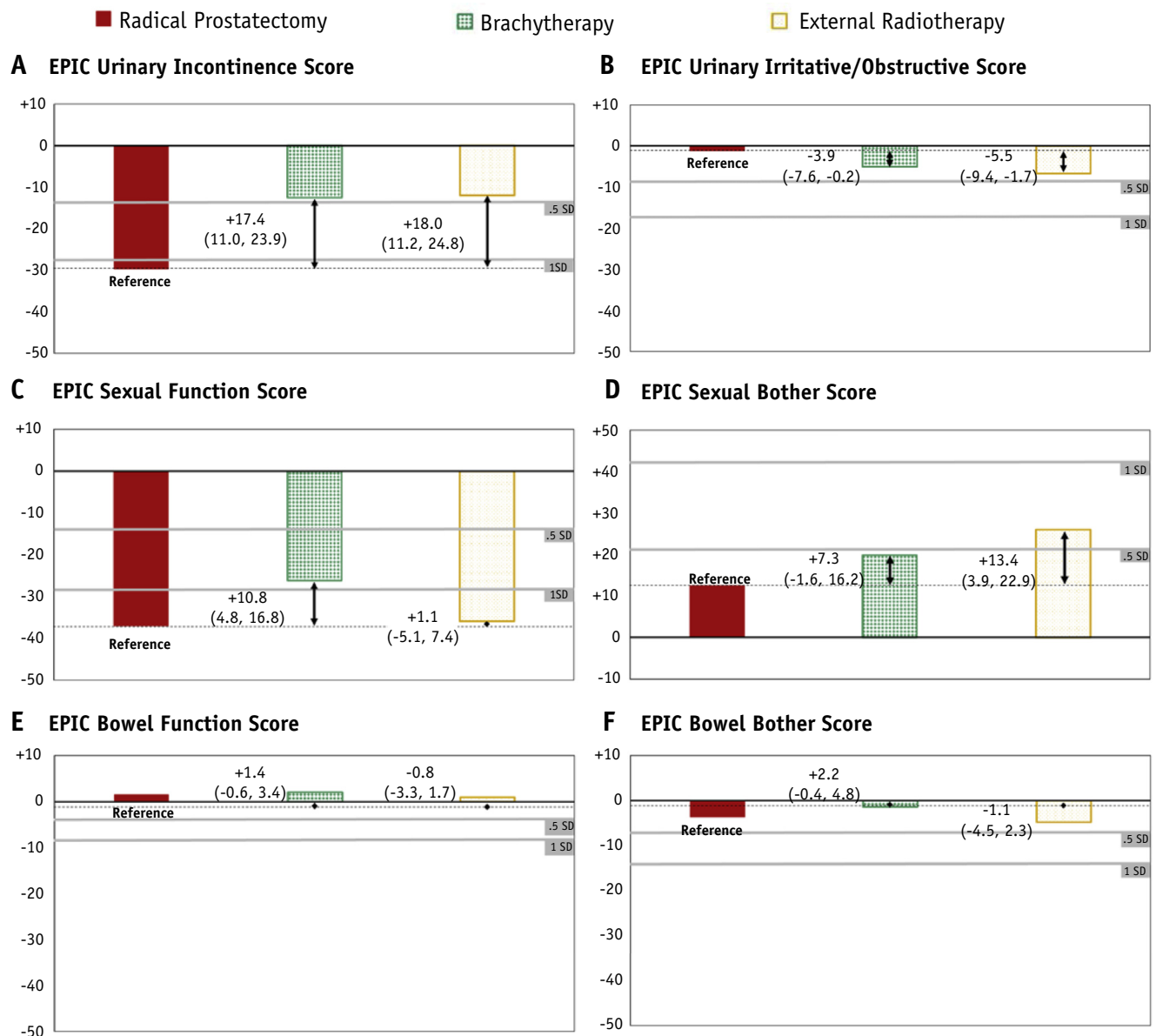


Fig. 4. Impact on patient-reported outcomes 10 years after treatment. On the left side of the figures, the units of change are EPIC scores and on the right side, they are standard deviations (moderate = 0.5 SD; large = 1 SD, indicated by gray lines). Mean changes in Expanded Prostate Cancer Index Composite instrument scores from pretreatment to 10 years of follow-up, obtained by generalized estimating equation models, are adjusted by propensity scores. Each bar is complemented with the difference compared with radical prostatectomy (mean and 95% confidence interval).

similarly calculated odds ratios adjusted by propensity scores (Table E3) with radical prostatectomy as the reference group. Because EPIC was derived from the University of California, Los Angeles, Prostate Cancer Index, mainly by transforming the urinary domain, only the sexual and bowel domains are comparable. The results for sexual function were similar for the radiation therapy groups, and differences were not statistically significant at 10 years in our cohort, nor in the CaPSURE study, with an odds ratio of 0.8 (95% CI, 0.3-1.7) and 0.9 (95% CI, 0.3-2.6)⁷ in brachytherapy and 1.3 (95% CI, 0.5-3.2) and 0.7 (95% CI, 0.2-3.4)⁷ in external radiation therapy. Our bowel results in the external radiation therapy

group were also similar to those reported by CaPSURE, but not in the brachytherapy group.

The probability of experiencing a meaningful decline after brachytherapy compared with radical prostatectomy at 10 years after treatment was higher among the CaPSURE patients than in our cohort, with odds ratios of 3.3 (95% CI, 1.4-7.4)⁷ versus 2.3 (95% CI, 0.8-6.7) in bowel function and 2.3 (95% CI, 1.0-5.2)⁷ versus 1.5 (95% CI, 0.5-4.0) in bowel bother. Therefore, discrepancies compared with CaPSURE were mainly restricted to the better results obtained in our study for brachytherapy in the bowel domain. Although CaPSURE is a nationwide prostate cancer registry, it is

important to highlight the low number of patients in the brachytherapy group with results at 10 years⁷ ranged from 76 to 85 according to the domain evaluated. Follow-up losses could have produced some bias in CaPSURE, which may explain the differences when compared with our study. For example, completion rate could be higher among patients with worse PRO results, because patients without problems may tend to disregard clinical encounters.

In addition, patients who underwent brachytherapy in our cohort presented a similar sexual pattern to results reported by Keyes et al²⁵ in a large cohort of almost 3000 patients followed for a median of 3.5 years and a maximum of 14 years, when focusing on patients with full potency before treatment and without neoadjuvant androgen deprivation therapy: a gradual and continuous erectile function decline. In our study, the percentage of men reporting sexual potency in this selected subsample went from 64% at 1 year after treatment to 53% after 4 years and 34% after 7 years. In the study by Keyes et al, the most significant drop in erectile function among patients with full potency before treatment was also during the first months: approximately 65% reported full potency 1 year after treatment, approximately 55% at 4 years, and 40% at 7 years after treatment.²⁵ This similarity is especially noteworthy because the erectile function measurement in both studies has a different nature. Ours is an item response in a PRO (EPIC), and Keyes et al assessed erectile function through a physician-reported 3-point scale.²⁵

Our long-term findings in PROs confirm those reported by the ProtecT trial at 6 years^{5,6} regarding the distinct impact of localized prostate-cancer treatment side effects, but similar general health. Figure E2 and Table E1 show the stability of the SF-36 summaries until the sixth year of follow-up. Both studies show a very similar negative effect of prostatectomy on sexual domain (ie, only 14.7% of men reported sexual potency at year 6 in our study and 15% in the ProtecT trial).⁶ Regarding radical prostatectomy's impact on urinary continence, the percentage of patients who required the use of pads was lower in the ProtecT trial than in our cohort (21%⁶ vs 32% by year 6). In both studies, external radiation therapy is related to bowel bother and function deterioration at 6 years after treatment (ie, 5.9% of men reporting bloody stools more than half the time in the ProtecT trial⁶ and 3.8% in our study).

Of note, the ProtecT trial's inclusion criteria were limited to patients diagnosed by screening. As a consequence, the baseline tumor characteristics of patients in the ProtecT trial and our cohort are very different, including median prostate-specific antigen levels of 4.8 versus 8.1 ng/mL, 78% versus 43.3% of patients with Gleason score 6, and 79% versus 58.2% with clinical T1 stage.⁴

Conclusions

Novel long-term results are provided on the impact of brachytherapy adverse effects in patients with localized

prostate cancer 10 years after treatment compared with radical prostatectomy and external radiation therapy. Our findings support that, despite some late deterioration in urinary continence and sexual function around 5 years after treatment, brachytherapy is the treatment option causing the least impact on PROs. These results provide patients, clinicians, and health care planners with clear information to make evidence-based decisions and facilitate shared clinical decision-making, taking into account patients' perspective. Although no single treatment can be considered the preferred strategy for managing all patients, our study supports brachytherapy as a possible alternative for patients with localized prostate cancer seeking attempted curative treatment while avoiding bowel effects and postponing the risk for urinary incontinence and sexual dysfunction.

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