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ORIGINAL REPORT

Quality-of-Life Impact of Primary Treatments for Localized Prostate Cancer in Patients Without Hormonal Treatment

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ABSTRACT

Purpose
Earlier studies evaluating the effect on quality of life (QoL) of localized prostate cancer interventions included patients receiving adjuvant hormone therapy, which could have affected their outcomes. Our objective was to compare the QoL impact of the three most common primary treatments on patients who were not receiving adjuvant hormonal treatment.

Patients and Methods
This was a prospective study of 435 patients treated with radical prostatectomy, external-beam radiotherapy, or brachytherapy. QoL was assessed before and after treatment with the Short Form-36 and the Expanded Prostate Cancer Index Composite. Differences between groups were tested by analysis of variance. Distribution of outcome at 3 years was examined by stratifying according to baseline status. Generalized estimating equation models were constructed to assess the effect of treatment over time.

Results
Compared with the brachytherapy group, the prostatectomy group showed greater deterioration on urinary incontinence and sexual scores but better urinary irritative-obstructive results (−18.22, −13.19, and +6.38, respectively, at 3 years; $P < .001$). In patients with urinary irritative-obstructive symptoms at baseline, improvement was observed in 64% of those treated with nerve-sparing radical prostatectomy. Higher bowel worsening (−2.87, $P = .04$) was observed in the external radiotherapy group, with 20% of patients reporting bowel symptoms.

Conclusion
Radical prostatectomy caused urinary incontinence and sexual dysfunction but improved preexisting urinary irritative-obstructive symptoms. External radiotherapy and brachytherapy caused urinary irritative-obstructive adverse effects and some sexual dysfunction. External radiotherapy also caused bowel adverse effects. Relevant differences between treatment groups persisted for up to 3 years of follow-up, although the difference in sexual adverse effects between brachytherapy and prostatectomy tended to decline over long-term follow-up. These results provide valuable information for clinical decision making.

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INTRODUCTION

Prostate cancer is the most common cancer in men in the United States[1] and the second most common in the European Union.[2] Increased detection (incidence) associated with the widespread use of prostate-specific antigen testing has enabled diagnosis at earlier disease stages.[1,3] A recent systematic review of localized prostate cancer treatment effectiveness[4] concluded that all treatments caused urinary, bowel, or sexual dysfunction with different frequency, duration, and severity, but they were insufficiently characterized to facilitate clinical recommendations.

The occurrence of relevant treatment adverse effects combined with otherwise good results in terms of cancer control[5-9] have led to a growing interest in evaluating the impact of treatment on quality of life (QoL). Previous longitudinal QoL studies[10-15] included patients receiving hormone therapy, particularly as an adjunct to external or interstitial radiotherapy, which could have affected the results obtained for these primary treatments. Recently, Sanda et al[14] showed that adjuvant

androgen suppression exacerbated the adverse effects of external radiotherapy or brachytherapy on sexuality and vitality. Therefore, evidence is needed on the impact of the common primary treatments for localized prostate cancer on patients' QoL when used without hormone therapy.

Most longitudinal studies have only followed patients for up to 1[16-18] or 2 years,[13-15,19,20] whereas treatment adverse effects and QoL may change further with longer follow-up.[10,11,21,22] Long-term studies could be particularly relevant in external or interstitial radiotherapy, as adverse effects might appear later as a result of chronic damage to adjacent tissues. Patients treated with external radiotherapy showed later worsening in incontinence[21] and sexual dysfunction.[11,21] However, the only long-term follow-up study that included brachytherapy showed recoveries[21] in urinary irritative symptoms and bowel function.

The objective of this study was to compare the QoL impact of radical prostatectomy, three-dimensional external-beam radiotherapy, and prostate brachytherapy on patients with localized prostate cancer who were not receiving adjuvant hormonal treatment, from pretreatment to 3 years after the intervention.

PATIENTS AND METHODS

Study Design and Participants

This was a prospective study of a clinically localized prostate cancer cohort treated with radical prostatectomy, external-beam radiotherapy, or brachytherapy.

Participants included in the Spanish Multicentric Study of Clinically Localized Prostate Cancer were followed for 3 years after treatment. Details of the study are described elsewhere.[15] Briefly, consecutive outpatients from 10 Spanish hospitals were enrolled from April 2003 to March 2005. Inclusion criteria were stages T1 or T2[23] and no previous transurethral prostate resection. For the purpose of this analysis, patients who received neoadjuvant or adjuvant hormonal therapy were excluded. Decisions on treatment options were made jointly by patients and physicians. The surgery group underwent radical retropubic prostatectomy, and the nerve-sparing technique was used at the surgeon's discretion. External-beam radiation was 3D conformal. Treatment was delivered with 1.8 Gy to 2.0 Gy daily fractions to a mean dose of 73.7 Gy (standard deviation [SD] = 5.0) to the prostate planning target volume. In the brachytherapy group, participants received ^{125}I, and the prescription dose was 144 Gy to the reference isodose (100%) according to the Task Group 43 (TG-T43).[24] The median dose of D90 and V100% was 158 Gy and 93%, respectively.

Research protocols were approved by the ethics review boards of the participating hospitals, and written informed consent was required for each participant according to the 2000 revision of the Declaration of Helsinki.

Measurement Instruments

Participants' clinical characteristics evaluated at baseline included: T stage, prostate-specific antigen (PSA), Gleason histological grading scores, prostate volume, and reported chronic conditions. The definition of D'Amico et al[5] was used to classify patients according to risk group. QoL instruments were administered centrally by telephone interviews before and 1, 3, 6, 12, 24, and 36 months after treatment.

Generic and prostate cancer–specific QoL questionnaires were included. The Short Form-36 Health Survey (SF-36) version 2[25,26] was used. Scores for the two summary components (physical and mental component scores) were calculated using the recommended standardized procedure.[25,26] The Expanded Prostate Cancer Index Composite (EPIC)[27] includes 50 items grouped into two urinary subscales (incontinence and irritative-obstructive) and three summary scores (bowel, sexual, and hormonal), with scores ranging from 0 to 100. The International Prostate Symptom Score[28,29] contains seven items measuring urinary obstruction, with scores ranging from 0 (no symptoms) to 35. With the exception of the International Prostate Symptom Score, higher scores indicate better QoL.

In addition to the EPIC continuous scores, we classified distressful levels of symptoms following the strategy proposed by Talcott et al[22,30] "No relevant problem" describes a patient with no distressful symptoms, "small to moderate problem" describes a patient reporting at least one distressful symptom, and "severe problem" describes a patient with at least one extremely distressful symptom. Within each EPIC domain, only the severity items were considered to construct this classification. These items and the level of distress associated with each response category are specified in the Appendix Table A1 (online only).

Statistical Analysis

Between-group differences on QoL mean scores at each assessment and changes in mean QoL scores (from baseline to 3 years after treatment) were tested using analysis of variance and Tukey's studentized range for post hoc comparisons.

To facilitate the interpretability of results, the percentages of patients with no relevant, small to moderate, and severe problems at 3 years after treatment were shown in bar charts. To examine the effect of pretreatment symptoms on the occurrence of treatment adverse effects, these bar charts were constructed after we stratified patients according to their symptoms severity at baseline.[13]

To assess the effect of treatment on QoL and adverse effects over time while accounting for correlation among repeated measures, we constructed separate generalized estimating equation (GEE) models for each EPIC scale and for the SF-36 physical component score (included as dependent variables). Age, risk group, and prostate volume at baseline were included in the models as adjusting factors. So as not to assume a linear association, we included time in the model as a categorical variable with four categories: pretreatment (reference), and months 12, 24, and 36. Regarding treatment, brachytherapy patients were used as the reference group in these models, and interactions between treatment and time were also included. The statistical analyses were carried out using SPSS 12.0 and SAS 9.1 software.

RESULTS

A total of 179 patients were excluded as a result of having received hormone treatment, resulting in a final sample of 435 patients (Table 1). There were statistically significant differences by treatment group at baseline for age, PSA, T stage, risk group, and prostate volume. Those receiving radical prostatectomy tended to be younger, whereas the lowest values for PSA, T stage, risk group, and prostate volume were seen in the prostate brachytherapy group. However, pretreatment QoL scores were similar among treatment groups.

Figure 1 shows QoL mean scores over the follow-up period by treatment group. Scores on the SF-36 mental component were quite stable, whereas a slight decrease was observed on the physical component. In the radical prostatectomy group, there was a notable decline in the urinary incontinence and sexual scores after treatment, with subsequent partial recovery. Sexual recovery was higher after nerve-sparing radical prostatectomy (NSRP) than after non–nerve-sparing radical prostatectomy (NNSRP). Compared with patients treated with surgery, the brachytherapy and external radiotherapy groups showed significantly lower (worse) urinary irritative-obstructive and bowel scores, respectively, during the last 2 years of follow-up. Mean changes in QoL scores from baseline to 3 years of follow-up are shown in Table 2. Sexual and urinary incontinence deterioration was greater in patients treated with radical prostatectomy (mean change, −23.9 and −25.1, respectively) than in the other groups, though this group showed fewer changes in urinary irritative-obstructive symptoms.

Table 1. Patient Characteristics and Quality-of-Life Scores at Pretreatment Evaluation and Response Rate at Each Follow-Up Assessment

Variable	Radical Prostatectomy		External-Beam Radiotherapy		Brachytherapy		*P*
	No.	%	No.	%	No.	%	
Participants	123	28.3	127	29.2	185	42.5	
Clinical characteristics							
Age, years							< .001*†‡
Mean	64.2		69.5		66.0		
SD	5.5		5.4		7.0		
PSA, ng/mL							< .001†‡
Mean	8.0		8.2		6.8		
SD	3.3		4.7		2.1		
Gleason score							.150
Mean	6.9		5.9		5.9		
SD	6.4		1.0		5.3		
T stage							
1	82	66.7	73	57.5	152	82.2	< .001†‡
2	41	33.3	53	41.7	33	17.8	
Unknown	0	0	1	0.8	0	0.0	
Risk group							
Low	52	42.3	72	57.1	165	89.2	< .001*‡
Intermediate	67	54.5	44	34.9	19	10.3	
High	4	3.3	10	7.9	1	0.5	
Prostate volume, cm^3							< .001
Mean	52.4		45.2		34.0		
SD	27.7		25.3		9.8		
No. of chronic conditions							.486
Mean	2.33		2.5		2.3		
SD	1.5		1.8		1.6		
Quality-of-life scores							
SF-36							
PCS							.016‡
Mean	53.1		52.4		54.2		
SD	6.2		5.8		4.9		
MCS							.141
Mean	54.1		54.6		53.3		
SD	5.9		5.2		6.7		
EPIC							
Urinary							
Incontinence							.404
Mean	94.5		96.3		96.1		
SD	15.1		9.9		11.1		
Irritative/obstructive							.304
Mean	93.4		95.5		94.4		
SD	11.1		9.5		11.1		
Bowel							.036
Mean	97.9		97.8		96.5		
SD	3.7		4.5		7.2		
Sexual							.246
Mean	59.0		54.1		55.9		
SD	23.5		23.2		23.3		
Hormonal							.197
Mean	94.0		95.7		95.5		
SD	9.1		8.4		8.0		
IPSS							.221
Mean	6.8		5.8		5.7		
SD	6.1		5.6		5.3		

(continued on following page)

Table 1. Patient Characteristics and Quality-of-Life Scores at Pretreatment Evaluation and Response Rate at Each Follow-Up Assessment (continued)

Variable	Radical Prostatectomy		External-Beam Radiotherapy		Brachytherapy		*P*
	No.	%	No.	%	No.	%	
Response rate (quality-of-life questionnaires)							
Pretreatment	123	100.0	127	100.0	185	100.0	
Month 1	66	53.7	43	33.9	100	54.1	.001*‡
Month 3	114	92.7	117	92.1	172	93.0	.961
Month 6	107	87.0	108	85.0	163	88.1	.732
Month 12	111	90.2	112	88.2	169	91.4	.654
Month 24	111	90.2	108	85.0	161	87.0	.457
Month 36	109	88.6	100	78.7	155	83.8	.107

NOTE. One-way analysis of variance for continuous variables among the three treatment groups; Tukey studentized range post hoc comparisons. The response rate at month 1 was lower, resulting in scheduled evaluations at month 1 and 3 having a high concentration of interviews in a short period of time. Evaluations at month 3 were prioritized.

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component score; MCS, mental component score; EPIC, Expanded Prostate Cancer Index Composite; IPSS, International Prostate Symptom Score.

*$P < .005$ for radical prostatectomy *v* external-beam radiotherapy.

†$P < .005$ for radical prostatectomy *v* brachytherapy.

‡$P < .005$ for brachytherapy *v* radiotherapy.

Bowel and hormonal deterioration were mainly observed in the radiotherapy group (mean change, −3.2 and −5.0, respectively).

To expand the information represented by mean score changes, Figure 2 shows the distribution of patients with no relevant, small to moderate, and severe problems at 3 years according to baseline status, which indicates the proportion of patients who improved, preserved status, or worsened. Considering patients with no relevant sexual problem at baseline, approximately 40% of patients in the external and interstitial radiotherapy groups had preserved pretreatment sexual status compared with less than 10% in the surgery group; the proportion of patients with any severe problem after NNSRP (83%) was higher than after NSRP (64%). Among patients with any small to moderate sexual problem at baseline, deterioration was observed in 89% of patients after NNSRP and 67% after NSRP, compared with 50% for the brachytherapy group.

Because not enough patients (n = 9-18) had severe urinary or hormonal problems at baseline for a separate analysis, they were analyzed jointly with those patients who reported small to moderate problems. At 3 years, almost 75% of patients in the external and interstitial radiotherapy groups had preserved pretreatment urinary continence, compared with 45% of NSRP and 31% of NNSRP patients. Brachytherapy resulted in the highest proportion of patients who experienced urinary irritative-obstructive symptoms (35%), whereas in patients with pretreatment small to severe urinary irritative-obstructive symptoms, improvement over baseline was observed in 64% of those treated with NSRP. Most of the patients did not present relevant bowel problems at baseline, and 23% of patients treated with external radiotherapy reported bowel problems at 3 years. The proportion of patients with hormonal adverse effects was similar among treatment groups, approximately 20% in those with no relevant problem at baseline.

Table 3 shows the results from the GEE models constructed to assess treatment impact at different follow-up evaluations. In the urinary incontinence model, patients in the prostatectomy group showed significantly greater deterioration than those in the brachytherapy reference group throughout follow-up ($\beta = -20.10, -17.33$, and -18.22 at 1st, 2nd, and 3rd year, respectively; $P < .001$). On irritative-obstructive symptoms, the difference from pretreatment (mean, 93.4; SD, 11.1) was significantly lower in the prostatectomy group at each year of follow-up ($\beta = +5.14, +5.56$, and $+6.38$, respectively for 1st, 2nd, and 3rd year), with positive coefficients indicating less deterioration from pretreatment than among patients in the brachytherapy group. In the sexual summary model, scores for patients in the brachytherapy group were lower (worse) than pretreatment, and deterioration increased ($\beta = 5.74, 7.26$ and 10.03, respectively, at the end of the 1st, 2nd, and 3rd years). Deterioration from pretreatment was significantly larger in the prostatectomy group throughout follow-up ($P < .001$), though differences with the brachytherapy group decreased somewhat over time ($\beta = 21.30, 19.74$ and 13.19, respectively, at the 1st, 2nd, and 3rd year).

Standard categorization of effect size (ES) was applied to understand the magnitude or clinical importance of these GEE β coefficients. ES was calculated as adjusted mean differences (β) divided by SD at baseline. The guidelines define an ES of 0.2 as small, 0.5 as moderate, and 0.8 as large.[31,32] For example, the ES for significant differences between surgery and brachytherapy on the EPIC urinary incontinence, sexual, and urinary irritative-obstructive symptoms ($\beta = 18.2, 13.2$, and $+6.4$, respectively, at the 3rd year) was large for incontinence (ES, 1.2), and moderate for sexuality and urinary irritative-obstructive symptoms (ES, −0.6 and +0.6).

DISCUSSION

This comparative study of the three primary treatments for localized prostate cancer when used without hormone therapy shows a distinctive pattern of adverse effects for these treatments. Radical prostatectomy caused considerable urinary incontinence and sexual dysfunction, interstitial and external radiotherapy caused moderate urinary irritative-obstructive symptoms and sexual dysfunction, and external radiotherapy also produced moderate bowel-related adverse effects. Long-term modifications of adverse effects, such as an increase in urinary-related adverse effects after external radiotherapy or sexual adverse effects with brachytherapy, tended to reduce

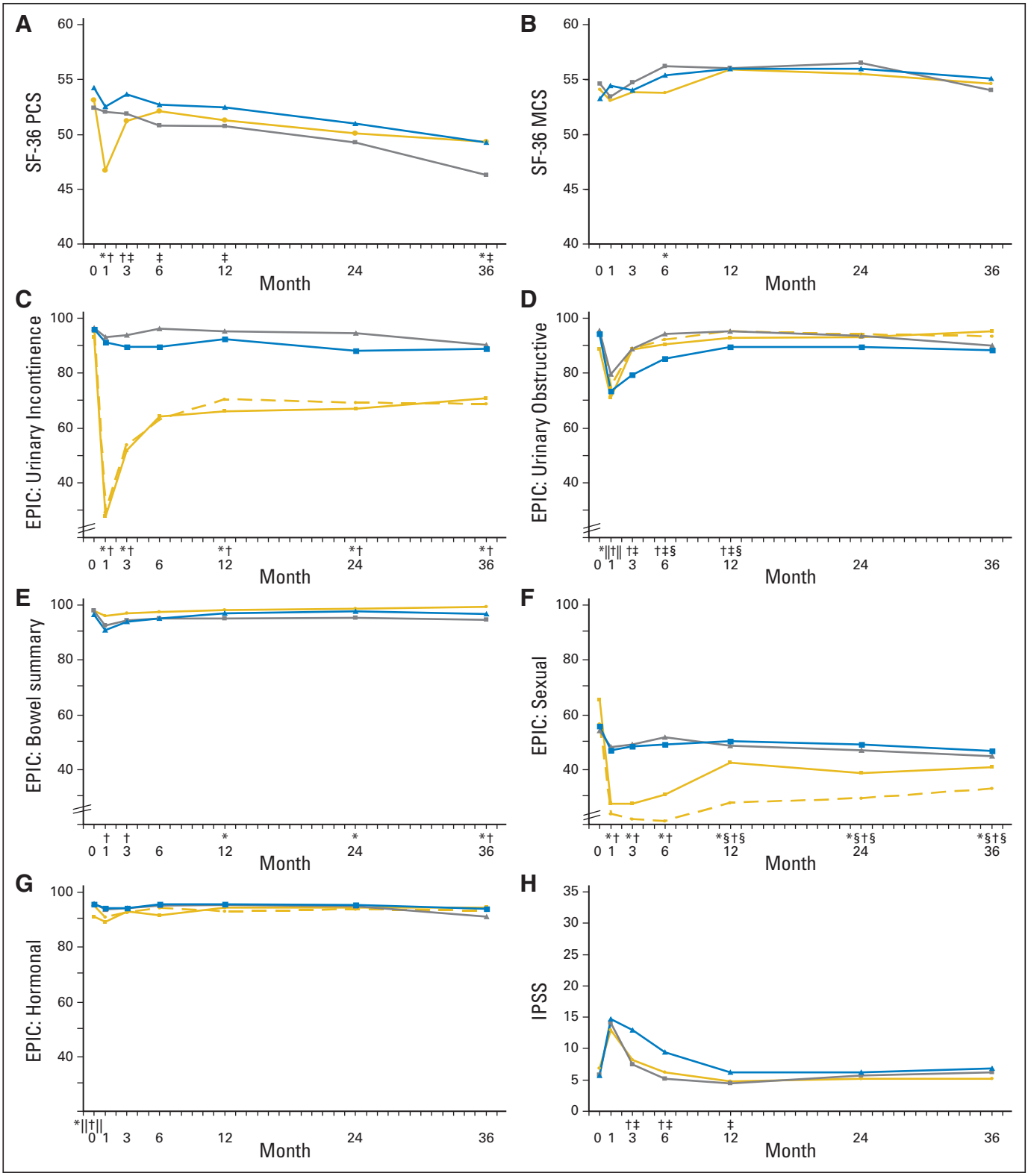

Fig 1. Mean quality-of-life (QoL) scores by treatment group—radical prostatectomy, external-beam radiotherapy, and brachytherapy—for Short Form-36 (SF-36) physical component score (PCS; A); SF-36 mental component score (MCS; B); Expanded Prostance Cancer Index Composite (EPIC) urinary incontinence (C), urinary obstructive (D), bowel (E), sexual (F), and hormonal (G) domains; and International Prostate Symptom Score (IPSS). The surgery group is shown separately, as a solid line for nerve-sparing radical prostatectomy (NSRP) and as a dashed line for non–nerve-sparing radical prostatectomy (NNSRP), for EPIC urinary, sexual, and hormonal domains. One-way analysis of variance of QoL scores among the three treatment groups for each follow-up assessment. Tukey studentized range post hoc comparisons: (*) $P < .05$ for radical prostatectomy versus external-beam radiotherapy; (†) $P < .05$ for radical prostatectomy versus brachytherapy; (‡) $P < .05$ for brachytherapy versus radiotherapy; (§) $P < .05$ for non–nerve-sparing radical prostatectomy only; (‖) $P < .05$ for nerve-sparing radical prostatectomy only.

Table 2. Mean (and standard deviation) Changes in Quality-of-Life Scores From Pretreatment to 3-Year Follow-Up by Treatment Group

Score	Radical Prostatectomy: Non–Nerve Sparing Mean	Non–Nerve Sparing SD	Radical Prostatectomy: Nerve Sparing Mean	Nerve Sparing SD	Conformal External Radiotherapy Mean	Conformal External Radiotherapy SD	Brachytherapy Mean	Brachytherapy SD	*P*
SF-36 PCS									
PCS	−3.9	8.7	−3.2	7.4	−6.2	8.3	−5.2	7.6	.167
MCS	−0.2	9.7	2.2	7.8	−0.7	9.1	1.3	8.8	.215
EPIC									
Urinary incontinence	−26.3	28.8	−21.4	25.2	−6.7	17.8	−7.4	20.7	< .001*†
Urinary irritative/obstructive	−1.8	14.4	7.0	13.1	−5.6	15.9	−5.9	21.0	.002*‡†‡
Bowel	1.3	3.1	1.7	4.5	−3.2	11.1	0.3	11.8	.006*§‖
Sexual	−23.4	25.7	−25.3	28.2	−10.6	22.4	−9.9	23.5	< .001*†
Hormonal	−1.7	12.8	2.4	15.5	−5.0	14.1	−2.0	10.7	.034*‡
IPSS	0.9	7.0	2.7	4.7	−0.4	6.3	−1.1	7.0	.017†‡

One-way analysis of variance for the differences in quality-of-life scores from baseline to 3-year follow-up, by treatment group. Tukey studentized range post hoc comparisons.

Abbreviations: SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component score; MCS, mental component score; EPIC, Expanded Prostate Cancer Index Composite; IPSS, International Prostate Symptom Score.

*$P < .05$ for radical prostatectomy *v* radiotherapy.

†$P < .05$ for radical prostatectomy *v* brachytherapy.

‡$P < .05$ for nerve-sparing radical prostatectomy only.

§$P < .05$ for non–nerve-sparing radical prostatectomy only.

‖$P < .05$ for brachytherapy *v* radiotherapy.

differences between treatments over time. However, these modifications were only slight and did not imply a real change in the characteristic pattern.

Sexual dysfunction was a common adverse effect of treatments, but it was also the most frequent concurrent symptom previous to treatment. In our sample, half of the patients presented severe sexual problems at baseline, almost 30% presented small to moderate problems, and only 22% did not present any relevant sexual problem. Differences in sexual adverse effects between patients with normal or poor pretreatment sexual functioning were reported previously.[11,13,22] These studies showed that adverse effects were more severe in patients with better pretreatment sexual functioning, possibly because patients with sexual dysfunction may leave little margin for additional, treatment-related worsening. Consistent with this finding, out of the patients treated with surgery in our study, more than 90% of those without any relevant sexual problems at baseline presented sexual adverse effects, compared with 67% of patients with small to moderate sexual problems at baseline who received nerve-sparing procedures. Brachytherapy presented lower levels of sexual adverse effects than prostatectomy, with approximately half of patients worsening, independently of whether they experienced no relevant or small to moderate pretreatment sexual problems. These results provide useful evidence to inform patients regarding expected treatment adverse effects according to their levels of pretreatment sexual functioning.

Regarding urinary treatment–related effects, the prostatectomy group showed worse adverse effects for incontinence, but better results on urinary irritative-obstructive symptoms compared with brachytherapy at 3 years after treatment. The prostatectomy group presented approximately twice as many patients with urinary incontinence adverse effects (69% for NNSRP and 54% for NSRP), compared with 25% of those treated with external or interstitial radiotherapy without relevant pretreatment incontinence problems. Among patients with urinary obstructive-irritative symptoms at baseline, improvement was observed in 64% of patients treated with NSRP, 44% with brachytherapy, and 28% with external radiotherapy. Our results confirm previously reported improvement in urinary obstruction-irritation in patients treated with prostatectomy, and also for those treated with radiotherapy.[14,22] It has been argued that external and interstitial radiotherapy may lead to small improvements because of a reduction in prostate size. This potential clinical benefit of radical prostatectomy may simplify clinical decision making for patients who have pre-existing irritative-obstructive urinary symptoms.

Only the group of patients treated with external radiotherapy presented a statistically significant moderate worsening of bowel symptoms (ES, −0.6). If we analyze these results at the individual level,[33] 8% of patients presented severe bowel problems, and 15% small to moderate ones, at 3 years. Finally, only a small deterioration in hormonal summary scores (ES, 0.2) was observed at 3 years. Although statistically significant differences in changes between treatment groups were observed in the bivariate analysis, they were not significant in the GEE model. Consistent with this finding, the distribution of patients with hormonal adverse effects was similar in the three treatment groups.

With regard to the long-term modification of adverse effects, it is noticeable that the patterns of urinary adverse effects in external radiotherapy and brachytherapy became more similar over time. During the first 2 years, positive coefficients in the incontinence and irritative-obstructive models indicated that patients treated with external radiotherapy had better results than those treated with brachytherapy. Nevertheless, the differences were no longer statistically significant at year 3 ($\beta = +5.2$ and .6 at 2 and 3 years, respectively, for incontinence). Worsening incontinence among patients treated with external radiotherapy was also reported by Miller et al[21] from year 2 to year 6 of follow-up. The reduction of the differences in sexual dysfunction between the prostatectomy and brachytherapy groups was also noteworthy ($\beta = -19.7$ and -13.2 at year 2 and year 3, respectively). This reduction could be partly explained by the long-term sexual

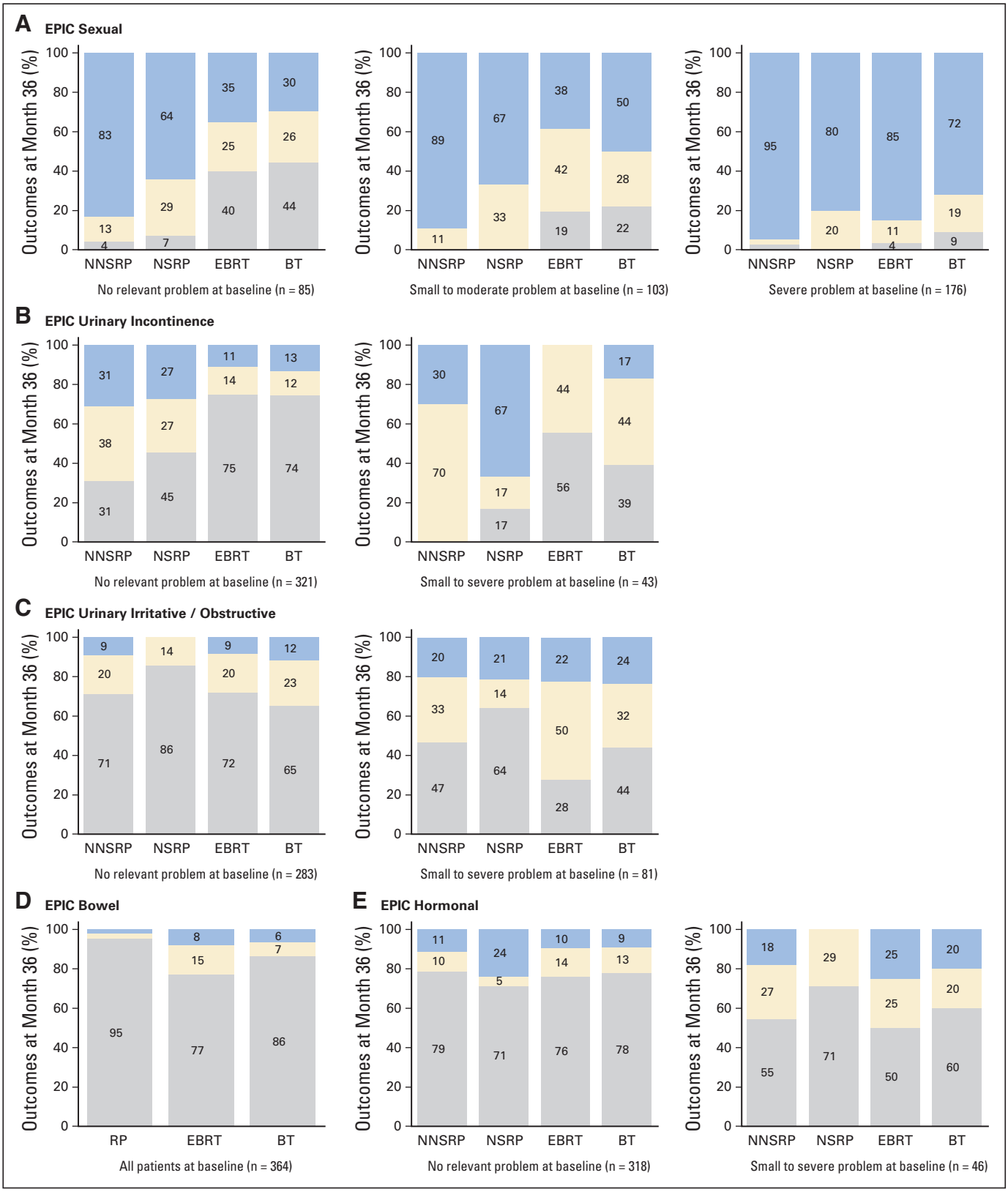

Fig 2. Distribution of patients with no relevant problems (light gray), small to moderate problems (light tan), or severe problems (light blue) at 3 years after treatment, stratified by baseline symptoms on Expanded Prostate Cancer Index Composite (A) sexual, (B) urinary incontinence, (C) urinary irritative-obstructive, (D) bowel, and (E) hormonal domains. EPIC, Expanded Prostate Cancer Index Composite; NNSRP, non–nerve-sparing radical prostatectomy; NSRP, nerve-sparing radical prostatectomy; EBRT, external-beam radiation therapy; BT, brachytherapy; RP, radical prostatectomy. Sample size was not large enough to perform bowel outcome analysis of the groups with small to moderate problems (n = 14) and severe problems (n = 5) at baseline separately.

Table 3. Generalized Estimating Equation Models of the Association Between Treatment Groups and Clinical Variables, With SF-36 Physical Component Score and EPIC Scores at Each Year of Follow-Up

Variable	SF-36 Physical Component Score			EPIC Urinary Incontinence			EPIC Urinary Irritative-Obstructive		
	β	SE	P	β	SE	P	β	SE	P
Intercept	63.29	2.53	< .0001	89.1	9.29	< .0001	98.12	5.99	< .0001
Age	−0.14	0.04	< .0001	0.08	0.14	.552	−0.06	0.09	.507
Prostate volume	0	0.01	.979	0.03	0.04	.363	0	0.02	.993
Risk group									
Low	ref.		ref.	ref.		ref.	ref.		ref.
Intermediate-high	0.26	0.63	.682	2.73	1.77	.122	1.17	1.11	.29
Treatment group (differences at baseline)									
Brachytherapy	ref.		ref.	ref.		ref.	ref.		ref.
Radiotherapy	−1.67	0.71	0.018	−0.64	1.45	.66	0.83	1.41	.554
Prostatectomy	−1.75	0.78	0.026	−2.8	1.92	.146	−1.27	1.55	.412
Interaction brachytherapy × time (change from baseline)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	−1.73	0.4	< .0001	−3.75	1.34	.005	−4.62	1.29	0
24 months	−3.26	0.56	< .0001	−7.58	1.58	< .0001	−4.8	1.4	.001
36 months	−4.93	0.57	< .0001	−6.85	1.61	< .0001	−5.73	1.64	.001
Interaction radiotherapy × time (difference from brachytherapy)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	0.17	0.7	.811	2.15	1.85	.245	4.21	1.64	.01
24 months	0.44	0.91	.631	5.16	2.07	.013	2.77	1.87	.139
36 months	−0.75	1.03	.467	−0.63	2.48	.798	0.06	2.42	.981
Interaction prostatectomy × time (difference from brachytherapy)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	0.01	0.78	.985	−20.1	3.31	< .0001	5.14	1.87	.006
24 months	0.13	0.94	.889	−17.33	3.32	< .0001	5.56	2	.006
36 months	0.64	1.05	.544	−18.22	3.08	< .0001	6.38	2.16	.003

Variable	EPIC Bowel Summary			EPIC Sexual Summary			EPIC Hormonal Summary		
	β	SE	P	β	SE	P	β	SE	P
Intercept	93.74	2.74	< .0001	106.53	9.98	< .0001	85.39	3.98	< .0001
Age	0.04	0.04	.283	−0.77	0.15	< .0001	0.16	0.06	.005
Prostate volume	0	0.01	.672	0.01	0.04	.78	−0.01	0.02	.71
Risk group									
Low	ref.		ref.	ref.		ref.	ref.		ref.
Intermed.-high	1.07	0.51	.035	0.9	(2.21)	.685	0.3	0.83	.72
Treatment group (differences at baseline)									
Brachytherapy	ref.		ref.	ref.		ref.	ref.		ref.
Radiotherapy	0.88	0.76	.245	1.51	2.96	.61	−0.63	1.15	.586
Prostatectomy	1.12	0.72	.12	0.4	3.15	.9	−1.5	1.13	.185
Interaction brachytherapy × time (change from baseline)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	0.51	0.68	.454	−5.74	1.72	.001	0.14	0.58	.815
24 months	1.19	0.61	.051	−7.26	1.84	< .0001	−0.51	0.75	.498
36 months	0.2	0.91	.827	−10.03	1.85	< .0001	−1.88	0.86	.03
Interaction radiotherapy × time (difference from brachytherapy)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	−2.99	1.13	.008	−1.06	2.57	.68	−0.68	0.88	.437
24 months	−4.03	1.2	.001	−1.67	2.88	.563	−0.14	1.16	.905
36 months	−2.87	1.4	.04	−1.23	3.07	.689	−2.7	1.7	.112
Interaction prostatectomy × time (difference from brachytherapy)									
Baseline	ref.		ref.	ref.		ref.	ref.		ref.
12 months	−0.19	0.96	.843	−21.3	3.16	< .0001	−0.9	1.46	.539
24 months	−0.46	0.73	.53	−19.74	3.34	< .0001	1.07	1.37	.432
36 months	1.15	0.98	.239	−13.19	3.28	< .0001	1.97	1.66	.234

NOTE. Time was included in the model as a categorical variable with four categories so as not to assume a linear association: baseline (reference), month 12, month 24, and month 36. Interaction variables between each treatment group and time were included: for interaction with brachytherapy, the coefficients refer to the changes from baseline; and for the radiotherapy and prostatectomy groups, the coefficients refer to the difference from the brachytherapy group (reference group) on the changes from baseline.

Abbreviations: SF-36, Short Form-36; EPIC, Expanded Prostate Cancer Index Composite; ref., reference.

deterioration observed in brachytherapy patients ($\beta = -7.3$ and -10.0 at year 2 and year 3). Chen et al[22] also reported a slight tendency to deteriorate on this parameter in the brachytherapy group, compared with a tendency toward recovery in the prostatectomy group. A longer follow-up would be needed to confirm whether the worsening observed in our sample from the 2nd to the 3rd year of follow-up indicates a true trend toward later occurrence of sexual dysfunction with brachytherapy treatment.

Some limitations of this study should be taken into account. First, this is an observational study, and participants were not randomly assigned to treatment groups. However, randomized clinical trials have presented considerable difficulties in these patients.[34] Baseline differences in clinical characteristics between treatment groups in our sample could be attributed to the observational design of the study. To account for the possible effect of clinical differences, we adjusted GEE models by the relevant clinical characteristics. Age, risk group, or prostate volume showed little impact on treatment outcomes. Second, nerve-sparing techniques were not widely applied in our study (28% of patients treated with prostatectomy), and our findings from the GEE model for the prostatectomy group as a whole could overestimate their adverse sexual effects. Nevertheless, large sexual adverse effects for prostatectomy treatment were also shown by other studies that included high proportions of patients who received nerve-sparing procedures.[13,14] Third, improvements observed in urinary incontinence, hormonal function, and sexual function, regardless of which treatment was applied, were generally experienced by a low number of patients, and may be partially explained by the regression to the mean phenomenon. Unexpected improvements have also been reported in previous studies.[11,35]

This study provides (to our knowledge) novel long-term results on QoL and adverse effects for the three common primary treatments in patients with localized prostate cancer who were not receiving adjunct hormonal treatment. Furthermore, the interpretation strategy addressed at the individual and aggregate levels followed here provides complementary useful information. Mean scores of treatment groups indicate results on average and facilitate comparison with other studies because it is the most usual approach. However, it could be a challenge to communicate the evidence to patients in a meaningful way. In fact, clinical interpretability of QoL scores has been identified as one of the barriers to the use of this type of measure.[36] The interpretation approach at an individual level shows the percentages of patients with adverse effects, and could facilitate clinical interpretation and the transmission of information to patients.

In conclusion, our findings suggest that adverse effects of external and interstitial radiotherapy could increase beyond 2 years of follow-up. Nevertheless, urinary irritative-obstructive symptoms, sexual dysfunction, and bowel-related adverse effects associated with interstitial or external radiotherapy were still moderate at 3 years of follow-up, whereas radical prostatectomy was associated with substantial urinary incontinence and sexual dysfunction over the same period. These results could provide relevant information to characterize adverse effects of primary treatments and facilitate shared clinical decision making between patients and professionals.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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CORRECTIONS

Author Corrections

The November 20, 2010, special article by Pappo et al, entitled "Infrequent Tumor Initiative of the Children's Oncology Group: Initial Lessons Learned and Their Impact on Future Plans" (J Clin Oncol 28:5011-5016, 2010), contained an error.

In the Introduction section, the second sentence was given as: "Indeed, the Rare Disease Act of 2002[1] defines a rare disease as one that affects fewer than 200,000 persons per year in the United States."

Whereas it should have read:

"Indeed, the Rare Disease Act of 2002[1] defines a rare disease as one that affects fewer than 200,000 persons in the United States."

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2011.34.7351

The December 20, 2010, article by Kunitake et al, entitled "Routine Preventive Care and Cancer Surveillance in Long-Term Survivors of Colorectal Cancer: Results From National Surgical Adjuvant Breast and Bowel Project Protocol LTS-01" (J Clin Oncol 28:5274-5279, 2010), contained an error.

The first initial of the seventh author's name was inadvertently omitted. The author's name was given as Lawrence Wickerham and should have been D. Lawrence Wickerham.

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2011.34.7369

Journal Corrections

The November 1, 2010, article by Pardo et al, entitled "Quality-of-Life Impact of Primary Treatments for Localized Prostate Cancer in Patients Without Hormonal Treatment" (J Clin Oncol 28:4687-4696, 2010), contained an error.

In the legend of Figure 1, the colors of the lines corresponding to the treatments were inadvertently omitted. The corrected legend is reprinted below in its entirety.

Mean quality-of-life (QoL) scores by treatment group—radical prostatectomy (gold), external-beam radiotherapy (gray), and brachytherapy (blue)—for (A) Short Form-36 (SF-36) physical component score (PCS); (B) SF-36 mental component score (MCS); (C) Expanded Prostate Cancer Index Composite (EPIC) urinary incontinence, (D) urinary obstructive, (E) bowel, (F) sexual, and (G) hormonal domains; and International Prostate Symptom Score (IPSS). The surgery group is shown separately, as a solid line for nerve-sparing radical prostatectomy (NSRP) and as a dashed line for non–nerve-sparing radical prostatectomy (NNSRP), for EPIC urinary, sexual, and hormonal domains. One-way analysis of variance of QoL scores among the three treatment groups for each follow-up assessment. Tukey studentized range post hoc comparisons: (*) $P < .05$ for radical prostatectomy versus external-beam radiotherapy; (†) $P < .05$ for radical prostatectomy versus brachytherapy; (‡) $P < .05$ for brachytherapy versus radiotherapy; (§) $P < .05$ for NNSRP only; (‖) $P < .05$ for NSRP only.

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

DOI: 10.1200/JCO.2011.34.7377

The May 10, 2010, article by Ziepert et al, entitled "Standard International Prognostic Index Remains a Valid Predictor of Outcome for Patients With Aggressive CD20$^+$ B-Cell Lymphoma in the Rituximab Era" (J Clin Oncol 28:2373-2380, 2010), contained an error.

The institutional affiliation for Evelyn Kuhnt should have been given as the Clinical Trial Centre, Universität Leipzig, Leipzig, Germany.

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

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