

Observational Study

Patient-reported outcome measures for technology assessment: A comparison between three-dimensional conformal and intensity-modulated radiotherapy in prostate cancer

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Abstract

BACKGROUND

Technological innovation in radiotherapy demands evaluation not only through dosimetric or clinician-reported outcomes, but also through patient-centred measures. Patient-reported outcome measures (PROMs) provide a unique insight into how advances such as intensity-modulated radiotherapy (IMRT) affect daily functioning and quality of life, compared to conventional techniques. Despite the clear dosimetric benefits over three-dimensional conformal radiotherapy (3D-CRT), evidence on whether IMRT translates into superior patient-reported outcomes remains inconsistent. PROM-based assessment offers a robust framework to evaluate the real clinical value of radiotherapy technologies and their impact on long-term quality of life in localized prostate cancer.

AIM

To compare 3D-CRT and IMRT using PROMs and to examine the influence of image-guided techniques on outcomes.

METHODS

The observational study compared two independent cohorts of localized prostate cancer patients followed for five years: (1) 92 were treated with 3D-CRT (2003-2005); and (2) 106 with IMRT (2013-2019). PROMs were assessed using the expanded prostate cancer index composite and short form-36 health survey before treatment and annually, *via* centralized telephone interviews. Propensity score-weighted Generalized Estimating Equation models were constructed with adjustment for baseline differences. Within the IMRT cohort, a multivariate regression explored associations between image guidance, fractionation, and dose escalation and urinary outcomes 12 months post-treatment.

RESULTS

Both radiotherapy techniques were associated with sustained high long-term health-related quality of life, according to patient-reported data. Significant differences between modalities emerged from the second year or third year post-treatment in the expanded prostate cancer index composite urinary, bowel, and sexual domains. Patients treated with IMRT reported better trajectories in mental health (short form-36 health survey) compared with those treated with 3D-CRT. Within the IMRT cohort, the use of Cone-Beam Computed Tomography-based image guidance and reduced planning margins (≤ 5 mm) was associated with improved preservation of urinary continence ($P = 0.048$). Conversely, higher equivalent dose in 2-Gy fractions doses (> 78 Gy) and hypofractionation (≥ 3 Gy/fraction) were associated to greater short-term deterioration in urinary incontinence ($P = 0.030$) and irritative/obstructive symptoms ($P = 0.006$).

CONCLUSION

PROMs reveal the real-world impact of radiotherapy advances from the patient's perspective. IMRT improved urinary and bowel outcomes, supporting PROMs as valid tools for technology assessment and patient-centred treatment optimization.

Key Words: Prostate cancer; Radiotherapy; Patient-reported outcome measures; Three-dimensional conformal radiotherapy; Intensity-modulated radiotherapy; Quality of life

Core Tip: This study demonstrates the utility of patient-reported outcome measures in assessing technological advances in radiotherapy for localized prostate cancer. By comparing long-term quality-of-life outcomes between three-dimensional conformal radiotherapy and intensity-modulated radiotherapy, it reveals that intensity-modulated radiotherapy – especially when combined with image guidance and reduced margins – was associated with better preservation of urinary continence and bowel function. Conversely, hypofractionation and dose escalation may transiently worsen urinary symptoms. Patient-reported outcome measures capture nuances in patient-centred effects of radiotherapy innovations, supporting their integration into technology assessment frameworks and guiding future optimization strategies.

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INTRODUCTION

The evaluation of new technologies in radiation oncology increasingly requires patient-centred endpoints beyond dosimetry or clinician reports. Patient-reported outcome measures (PROMs) offer critical insight into symptoms, functioning, and quality of life, and have become integral to value-based healthcare and technology assessment in oncology[1,2], increasingly guiding clinical decision-making in radiotherapy.

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy among men in Europe and the United States[3]. Most cases are localized with long-term survival[4], which emphasizes the need to minimize treatment-related morbidity. Over the past two decades, radiotherapy for localized prostate cancer has evolved from three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), which allows higher conformity and better organ sparing[5]. However, does this technological transition translate into sustained long-term improvements in patients' quality of life? This critical question remains insufficiently explored in PROM-based comparative effectiveness research.

While IMRT facilitates dose escalation, its clinical value must be judged not only by its biochemical control or physician-rated toxicity, but also by PROMs reflecting the quality of life achieved. Previous comparative studies of 3D-CRT and IMRT have yielded inconsistent results – some showing no differences[6], others transient benefits for IMRT[7] – highlighting the need for long-term PROM-based evaluations. Clarifying whether technological advances translate into meaningful patient-perceived benefits is therefore essential.

This study applies a PROM-driven technology assessment framework to compare 3D-CRT and IMRT in localized prostate cancer patients, using validated measures of urinary, bowel, and sexual function, and their overall physical and mental health over 60 months. It also examines how image-guided radiation therapy (IGRT), hypofractionation, and dose escalation influence patient-reported outcomes, offering a comprehensive view of the real-world impact of technological progress. Beyond evaluating clinical outcomes, this study explores the feasibility of integrating PROMs into radiotherapy technology assessment frameworks, bridging technical advances with patient-centred endpoints relevant for clinical decision-making. Specifically, it addresses whether IMRT provides sustained long-term advantages over 3D-CRT from the patient's perspective.

MATERIALS AND METHODS

Design and primary endpoints

An observational study was conducted comparing two cohorts of patients with newly diagnosed localized prostate cancer treated with radiotherapy and followed for five years. Both cohorts were enrolled prospectively in a multicentre database using a standardized platform, with data collection and follow-up planned in advanced to ensure consistency and comparability (Supplementary Figure 1).

The cohorts were recruited in different decades, under a similar design and protocol to allow comparative effectiveness research (active surveillance, radical prostatectomy, brachytherapy, and external radiotherapy), except for their inclusion criteria. Because the risk criteria were stricter in the IMRT cohort, the 103 patients in the 3D-CRT cohort with prostate-specific antigen > 10 or T > 2a were excluded. The final analysis included 92 patients diagnosed in 2003-2005 and treated with 3D-CRT, and 106 patients diagnosed in 2013-2019 and treated with IMRT. Treatment decisions were made jointly by patients and physicians. Although the 3D-CRT cohort was recruited two decades earlier, its prospective follow-up with standardized PROMs provides unique long-term data to assess the transition from 3D-CRT to IMRT. Cohorts' details and treatment modalities characteristics have been described elsewhere[8,9].

The study was approved by the ethics review boards of the participating centres, and written informed consent was obtained from all patients, following the 2000 revision of the Helsinki Declaration. In both cohorts, demographic and clinical characteristics were recorded at the clinical sites before treatment. According to the patient-centred outcome measures set for localized prostate cancer of the International Consortium for Health Outcomes Measurement[10], the expanded prostate cancer index composite (EPIC)-26[11,12] and the short form-36 health survey (SF-36)[13] were administered centrally through telephone interviews before treatment and during follow-up at three, six, and 12 months after treatment in the first year, and annually thereafter.

EPIC-26 evaluates urinary, sexual, bowel, and hormonal domains, scoring 0-100, with higher scores indicating better outcomes. In addition to EPIC scores, key EPIC items previously selected in the ProtecT study[14] were analysed to enhance clinical interpretability. As the EPIC-26 items of the bowel domain only ask for problems related to bloody stools and faecal incontinence, the two items of EPIC-50 measuring their frequency were also administered and analysed. Responses to all these items were dichotomized to reflect the proportion of men reporting any problem.

The SF-36 generates Physical Component Summary and Mental Component Summary scores standardized to have a mean of 50 and SD of 10 in the general United States population[15], with higher scores indicating better results.

Treatments

In the first cohort, patients were treated with 3D-CRT delivered using an isocentric technique with typically six MLC-shaped fields and X-ray energies of 15-18 megavoltage. Patients were treated in the supine position, using foot and leg immobilization and a full bladder and empty rectum. The clinical target volume (CTV) was limited to the prostate gland and CTV to planning target volume (PTV) margins were set to 10.5 mm isotropic, reduced to 5 mm posterior. Multileaf collimators ensured $\geq 95\%$ dose coverage of the PTV. No pelvic lymph node irradiation was included. Treatment was delivered in daily fractions of 1.8-2.6 Gy, 5 days per week, to a mean prostate dose of 73.4 Gy (range 65-76 Gy). Weekly setup verification was performed using orthogonal portal images compared with digitally reconstructed radiographs.

In the second cohort, patients were treated with IMRT. Both step-and-shoot and sliding window techniques were used. The X-ray beam energy was 6 megavoltages. Patients were treated in the supine position using the leg and foot immobilisation and with a full bladder and empty rectum. The CTV involved the prostate, and the PTV definition of margins was institution-specific (mean = 6.0 mm, SD = 1.7). No pelvic lymph node irradiation was included. Daily fractions were used, with 56.6% of the patients receiving ≥ 3 Gy (moderate hypofractionation). The dose prescription was set so that D95 $\geq 98\%$. The number of treatment fractions ranged from 19 to 38. The mean equivalent dose in 2 Gy fractions (EQD2) to the CTV was 77.7 Gy (range 72.5-88.3), calculated using the linear-quadratic model, according to the formula: $EQD2 = D \times (2 + \alpha/\beta)/(d + \alpha/\beta)$, where D is the total physical dose, d is the dose per fraction, and an $\alpha/\beta = 1.5$ Gy[16].

IGRT varied: (1) Cone-beam computed tomography (CBCT) in 83 patients (76.8%); (2) Fiducial markers with kilovoltage portal imaging in 14 (13.2%); (3) Bone frame in 3 (2.8%); and (4) Combinations of the aforementioned methods in 6.

Statistical analysis

Considering a statistical power of 80% and a 5% significance level, the sample size ($n = 92$ and $n = 106$) was sufficient to detect small-to-moderate group differences (effect size 0.4 SD) in EPIC-26 and SF-36v2 scores.

To account for treatment selection bias, propensity scores were obtained from the predicted probabilities estimated in logistic regression models (Supplementary Table 1), contrasting the 3D-CRT with the IMRT cohort, and the c-statistic obtained was 0.851. These logistic regression models included the following variables at baseline to maximize comparability between the 3D-CRT and IMRT cohorts: (1) Age; (2) Prostate volume; (3) T stage; (4) Prostate-specific antigen; (5) Gleason score; (6) Risk group; (7) Neural permeation; (8) Lymphatic permeation; (9) Urological and bowel antecedents; (10) Familiar antecedents; (11) Comorbidities; (12) Erectile aids; (13) Smoking habits; (14) Study level; and (15) Marital status. The standardized morbidity ratio weighting[17] based on the average treatment effect on the treated was applied. A weight of one was given to patients treated with 3D-CRT, while inverse probability of treatment weighting (IPTW) was applied to patients treated with IMRT. All analyses were performed with propensity score weights, except for patient characteristics, which were also described with unweighted estimates.

Summary statistics were obtained through weighted analysis of a complex design using the R package Survey, and the differences between both cohorts were tested using either the χ^2 test, for categorical variables, or the *t*-test, for continuous variables. To show results over time from pre-treatment to 5 years after treatment, figures were constructed with either means of EPIC-26 and SF-36 scores or percentages of key EPIC items, and with 95%CI.

To assess patient-reported outcomes over time, while accounting for the correlation among repeated measures, separate Generalized Estimating Equation (GEE) models weighted with IPTW were constructed for each EPIC-26 and SF-36 score as dependent variables. The 'survey' package was used to apply robust weights estimated from propensity scores. Although the repeated-measures models constructed through this package are mixed models, they interpret weights as precision weights – affecting the residual variances rather than properly weighting individuals. Therefore, we constructed GEE models (implemented through the 'geepack' package) that correctly incorporate IPTW to estimate marginal population-averaged effects with robust variance. Gleason score was included as a covariate in the models due to their remaining residual imbalance after propensity score weighting, to minimize its potential effect on the outcomes. Treatment and time were included in the models as categorical variables, and the interaction between them was considered in order to test the difference in trends of both groups. When this trend's value was significant, the *t*-test was used for cross-sectional comparisons at each assessment time. The bootstrapping method was used to assess uncertainty in the sampling distribution of the EPIC-26 and SF-36 mean scores. All analyses were performed using R version 4.2.2.

Finally, linear regression models were constructed with the patients treated with IMRT to explore the association between technique characteristics and patient-reported outcomes scores 12 months after treatment (as dependent variables).

RESULTS

The study included 92 patients treated with 3D-CRT and 106 with IMRT. At five years, PROMs completion was 87.2% among survivors. A total of 11 of the 198 patients had died and 24 were lost to follow-up (Supplementary Figure 1). Table 1 summarizes baseline characteristics.

At diagnosis, cohorts differed in their smoking status (20.9% *vs* 61.2%; $P < 0.001$), Gleason score [mean (SD): 5.3 (1.1) *vs* 6.1 (0.3); $P < 0.001$], and comorbidity (88.4% *vs* 75.5%; $P = 0.037$). After propensity weighting, only the Gleason score remained significant [mean (SE): 5.3 (0.1) *vs* 6.1 (0.0); $P < 0.001$]. Statistically significant differences over time or between

Table 1 Unweighted and weighted description of patient characteristics before treatment, *n* (%) / mean (SD or SE)

	Unweighted			Weighted		
	3D-CRT cohort	IMRT cohort	<i>P</i> value	3D-CRT cohort	IMRT cohort	<i>P</i> value
Age (years)	69.1 (4.8)	69.6 (4.6)	0.470	69.1 (0.5)	69.1 (1.2)	0.975
Smoking status (%)						
Never smoked	29 (33.7)	25 (24.3)	< 0.001	29 (33.7)	13 (25.4)	0.614
Current smoker	18 (20.9)	63 (61.2)		18 (20.9)	11 (20.7)	
Ex-smoker	39 (45.3)	15 (14.6)		39 (45.3)	28 (53.9)	
Prostate volume (cc)	43.2 (22.8)	39.5 (14.1)	0.226	43.2 (2.5)	41.5 (2.2)	0.370
Gleason total	5.3 (1.1)	6.1 (0.3)	< 0.001	5.3 (0.1)	6.1 (0.0)	< 0.001
6 or less (%)	88 (95.7)	93 (87.7)	0.084	88 (95.7)	50 (94.8)	0.794
7 or more (%)	4 (4.3)	13 (12.3)		4 (4.3)	3 (5.2)	
Prostate-specific antigen (ng/mL)	6.7 (1.7)	6.2 (1.8)	0.069	6.7 (0.2)	6.3 (0.3)	0.337
T stage (%)						
T1c	72 (78.3)	88 (83)	0.505	72 (78.3)	39 (74.6)	0.735
T2a	20 (21.7)	18 (17)		20 (21.7)	13 (25.4)	
Risk group (%)						
Low	88 (95.7)	92 (86.8)	0.056	88 (95.7)	49 (93.5)	0.531
Intermediate	4 (4.3)	14 (13.2)		4 (4.3)	3 (6.5)	
Comorbidity (%)	76 (88.4)	80 (75.5)	0.037	76 (88.4)	43 (81.2)	0.388
Urological history (%)	20 (21.7)	37 (34.9)	0.060	20 (21.7)	13 (24.2)	0.803
Bowel history (%)	22 (23.9)	16 (15.1)	0.164	22 (23.9)	9 (17.2)	0.526

SD in the unweighted columns and SE in the weighted columns. IMRT: Intensity-modulated radiotherapy; 3D-CRT: Three-dimensional conformal radiotherapy.

cohorts are indicated in bold in the tables.

Figure 1 exhibits the results of the EPIC urinary domain, showing means or percentages weighted by propensity scores and *P* values, comparing trends of both cohorts. No statistically significant difference in urinary incontinence was found (Figure 1A). Incontinence and pad use were rare and remained stable over time (Figure 1B). IMRT patients reported worse obstructive/irritative symptoms ($P = 0.002$; Figure 1C), with higher rates of burning/pain at 12 months, but with a statistically lower frequency of symptoms from 48 months onward in the IMRT cohort (Figure 1D).

Figure 2A and B reveal a progressive decline in sexual function score and an increase over time in the proportion of men reporting erections not firm enough for intercourse in both cohorts. Figure 2C shows an initial mild deterioration in the EPIC bowel domain in both cohorts, followed by some improvement. Figure 2D shows a very small proportion of men reporting problems with losing control of stools in both cohorts. Figure 2E and F reveal a better evolution of rectal bleeding problem and frequency in the IMRT cohort, which was statistically significant in the latter ($P = 0.021$), specially from the month 24.

Figure 3 shows a decline in both cohorts in the SF-36v2 physical component score, but more stability in the SF-36v2 mental component score over time.

Table 2 summarizes GEE models. Statistically significant differences within-cohort over time, and in changes between-cohorts (using 3D-CRT as the reference category), were marked. Urinary continence and physical health declined over five years, with no significant differences between cohorts. IMRT patients had worse pre-treatment irritative/obstructive scores, but showed a greater improvement from month 36 to month 60 compared to 3D-CRT patients after their initial worsening. Bowel scores improved more with IMRT at 24 months and 48 months. Sexual decline was greater in IMRT after month 36. Finally, unlike the decline in physical health, the mental health remained stable, with greater improvement from month 6 onward in the IMRT cohort.

Table 3 shows linear regression results for the 106 IMRT patients exploring the association between the image-guided techniques applied and the outcomes at 12 months after treatment. PTV margins ≤ 5 mm with CBCT were associated with less deterioration in EPIC incontinence scores ($P = 0.048$), whereas ≥ 3 Gy/fraction ($P = 0.030$) and EQD2 > 78 Gy ($P = 0.006$) predicted greater urinary deterioration in the EPIC irritative/obstructive symptoms score at 12 months.

Table 2 Weighted expanded prostate cancer index composite and short form-36 health survey results over time from Generalized Estimating Equation repeated-measures models, adjusted by Gleason score, means (95%CI)

	EPIC urinary incontinence	EPIC urinary irritative/obstructive	EPIC bowel summary	EPIC sexual summary	SF-36 physical component summary	SF-36 mental component summary
Cohort treated with three-dimensional conformal radiotherapy						
Pre-treatment	95.1 (92.9-97.4)	95.9 (93.9-98.2)	98.9 (97.5-100.3)	51.9 (47.2-56.3)	51.4 (50.3-52.6)	55.2 (54.2-56.1)
3 months	91.8 (88.6-95.0) ^a	89.0 (86.0-92.2) ^a	95.3 (92.8-97.8) ^a	44.4 (39.4-49.2) ^a	51.7 (50.7-52.8)	54.7 (53.6-56.0)
6 months	93.8 (91.0-97.0)	93.7 (91.7-96.1)	96.0 (93.9-98.0) ^a	49.6 (44.4-54.7)	51.0 (50.1-51.9)	55.8 (54.9-57.0)
12 months	93.3 (90.9-95.9)	95.8 (94.3-97.4)	94.8 (92.5-97.4) ^a	47.4 (42.4-52.9)	50.3 (49.2-51.3) ^a	56.2 (55.0-57.4) ^a
24 months	92.5 (89.9-95.5)	94.0 (92.2-95.9)	93.7 (91.1-96.4) ^a	41.8 (36.1-47.0) ^a	48.9 (47.7-50.1) ^a	56.1 (55.0-57.3)
36 months	89.3 (86.0-92.5) ^a	89.2 (86.2-92.4) ^a	92.5 (89.4-96.0) ^a	42.1 (36.6-47.6) ^a	46.2 (44.8-47.6) ^a	54.3 (52.9-55.9)
48 months	90.8 (87.4-94.3) ^a	87.3 (83.8-91.2) ^a	93.4 (90.8-96.4) ^a	34.2 (28.9-39.7) ^a	46.0 (44.6-47.5) ^a	52.2 (50.4-54.0) ^a
60 months	88.6 (84.5-92.6) ^a	87.9 (84.4-91.5) ^a	94.4 (92.3-96.9) ^a	30.7 (26.1-35.2) ^a	44.9 (43.3-46.6) ^a	53.3 (51.6-55.2) ^a
Cohort treated with intensity-modulated radiotherapy						
Pre-treatment	92.1 (88.3-95.8)	89.9 (86.3-93.6)	97.9 (96.9-99.0)	62.8 (56.6-70.2)	49.1 (47.0-51.4)	50.8 (48.4-53.3)
3 months	87.3 (82.4-93.2)	82.6 (76.7-88.9)	95.2 (93.1-97.1) ^a	49.6 (42.4-57.1) ^a	47.3 (45.4-49.3)	53.9 (51.4-56.6) ^a
6 months	85.0 (79.7-90.5) ^a	88.7 (83.6-94.5)	95.7 (93.0-98.5)	53.2 (46.4-60.1) ^a	46.3 (44.5-48.4) ^a	54.9 (53.2-56.7) ^{a,b}
12 months	89.1 (84.2-94.5)	85.9 (81.4-91.0)	95.0 (93.0-97.1) ^a	49.7 (43.5-56.4) ^a	46.9 (45.1-48.6) ^a	54.4 (52.7-56.3) ^a
24 months	91.2 (86.4-96.3)	90.0 (86.2-94.1)	97.6 (96.2-99.1) ^b	44.4 (38.1-50.5) ^a	47.0 (45.3-49.0) ^a	55.2 (53.7-56.9) ^{a,b}
36 months	89.5 (84.6-94.3)	91.5 (88.5-94.6) ^b	95.4 (93.1-97.4) ^a	39.4 (33.1-45.4) ^b	45.8 (44.1-47.7) ^a	54.4 (52.5-56.5) ^{a,b}
48 months	88.0 (82.2-94.5)	93.5 (89.7-96.5) ^b	99.0 (96.7-101.7) ^b	33.9 (27.7-40.1) ^b	43.1 (41.1-45.4) ^a	56.2 (54.2-58.3) ^{a,b}
60 months	89.3 (84.0-94.8)	90.0 (86.5-93.4) ^b	94.1 (91.1-97.9)	33.3 (25.0-40.5) ^a	41.9 (39.9-44.2) ^a	51.6 (48.9-54.8)

^a $P < 0.05$ in the comparison of the mean score between pre-treatment and post-treatment.^b $P < 0.05$ in the comparison of the mean score change since pre-treatment between patients treated with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy (reference group).

EPIC: Expanded prostate cancer index composite; SF-36: Short form-36 health survey.

DISCUSSION

Our findings demonstrate how PROMs support technology evaluation in radiation oncology, providing a patient-centred perspective on the clinical impact of technical advances. By systematically applying PROMs across two technological generations of radiotherapy, this study illustrates their potential as a structured framework for evaluating technological changes. Implementation characteristics within IMRT also influenced outcomes, underscoring the role of procedural consistency. Importantly, these differences in PROMs reflect meaningful variations in daily functioning and quality of life, beyond what conventional clinical endpoints capture.

PROMs have shown value across medical specialties. The systematic review by Balitsky *et al*[18] linked their use to improve overall survival and enhance quality of life across diverse clinical settings. They have been integrated into technology assessment frameworks in cardiology[19], orthopaedics[20], and ophthalmology[21], complementing clinical endpoints by capturing patient-perceived benefits. Their integration into radiotherapy evaluation remains limited, underscoring the relevance of our study. Furthermore, PROMs have demonstrated providing support to guide earlier toxicity management, shared decision-making, and treatment adaptation, reinforcing their clinical utility beyond research [22].

Traditional endpoints such as biochemical control or physician-reported toxicity often fail to capture the full clinical effect of technological innovations. PROMs allow detection of treatment-related physical and psychosocial changes[23]. In our analysis, PROMs provided additional insight into the temporal evolution of symptoms that toxicity grading alone would not have revealed, highlighting nuanced yet clinically relevant functional differences between techniques. Overall, both approaches produced only modest and transient declines in quality of life, confirming the low side effects of contemporary radiotherapy. The PROMs used (EPIC-26 and SF-36) are valid, reliable, reproducible and responsive instruments [15,24], reinforcing their ability to detect subtle implementation-related effects not captured by toxicity endpoints.

Table 3 Linear regression of image-guided radiation therapy characteristics and patient-reported outcomes in intensity-modulated radiotherapy cohort ($n = 106$), n (%)/mean (SD or SE)

	EPIC urinary incontinence	P value	EPIC urinary irritative/obstructive	P value	EPIC bowel summary	P value	EPIC sexual summary	P value	SF-36 physical component summary	P value	SF-36 mental component summary	P value
Intercept	-22.4 (28.6)	0.436	34.0 (29.4)	0.250	92.2 (36.8)	0.014	45.8 (45.9)	0.320	17.2 (11.5)	0.139	36.8 (12.7)	0.005
Pre-treatment score	0.6 (0.1)	< 0.001	0.4 (0.1)	< 0.001	0.0 (0.2)	0.952	0.5 (0.1)	< 0.001	0.4 (0.1)	< 0.001	0.3 (0.1)	0.001
CBCI+ planning target volume margins combined												
No CBCT; > 5 mm	Reference		Reference		Reference		Reference		Reference		Reference	
CBCI; 5 mm or less	14.4 (7.2)	0.048	2.6 (7.3)	0.720	-9.9 (6.3)	0.122	0.1 (11.0)	0.989	-3.3 (2.7)	0.217	2.2 (3.3)	0.503
CBCI; > 5 mm	-2.2 (6.0)	0.709	-4.3 (6.2)	0.489	-8.1 (5.3)	0.133	2.2 (9.3)	0.817	-1.7 (2.3)	0.464	-1.1 (2.7)	0.680
Equivalent dose in 2 Gy fractions												
≤ 78	Reference		Reference		Reference		Reference		Reference		Reference	
> 78	-8.4 (5.2)	0.113	-15.2 (5.4)	0.006	-3.2 (4.7)	0.494	-5.8 (8.0)	0.471	-2.4 (2.1)	0.256	0.0 (2.4)	0.993
Dose per fraction												
< 3 Gy/fraction	Reference		Reference		Reference		Reference		Reference		Reference	
≥ 3 Gy/fraction	-13.6 (6.2)	0.030	-11.1 (6.1)	0.075	3.5 (5.2)	0.504	-2.4 (9.0)	0.794	4.0 (2.2)	0.070	-3.1 (2.7)	0.253
Risk												
Low	Reference		Reference		Reference		Reference		Reference		Reference	
Intermediate	-1.2 (5.5)	0.823	3.4 (5.7)	0.550	3.5 (4.9)	0.479	4.4 (8.5)	0.604	3.0 (2.1)	0.148	0.4 (2.5)	0.865
Age	0.8 (0.4)	0.031	0.4 (0.4)	0.334	0.1 (0.3)	0.818	-0.4 (0.6)	0.542	0.1 (0.1)	0.464	0.1 (0.2)	0.752

Equivalent dose in 2 Gy fractions, calculated using the linear-quadratic model to standardize comparisons across different fractionation schedules (α/β prostate: 1.5). CBCT: Cone-beam computed tomography; EPIC: Expanded prostate cancer index composite; SF-36: Short form-36 health survey.

Although IMRT offers better dose conformity, there is still a challenge to translate this advantage into patient-perceived benefit[25,26]. Dose escalation improves biochemical control but may increase toxicity[27-30]; however, non-randomized studies suggest IMRT mitigates this risk[31-33]. In our study, the IMRT cohort (with a higher median EQD2: 77.1 Gy *vs* 74.0 Gy) presented a significant decline in urinary irritative/obstructive symptoms at 12 months, but followed by a more pronounced recovery than in the 3D-CRT cohort. In addition, patients receiving > 78 Gy in the IMRT cohort showed greater worsening at 12 months. Literature supports that IMRT reduces grade 2 genitourinary/ gastrointestinal toxicity at 24 months when high doses are used[7,34]. However, several trials found no significant differences in PROMs at two years, consistently with our findings, where most differences emerged beyond year two[6]. PROMs are partic-

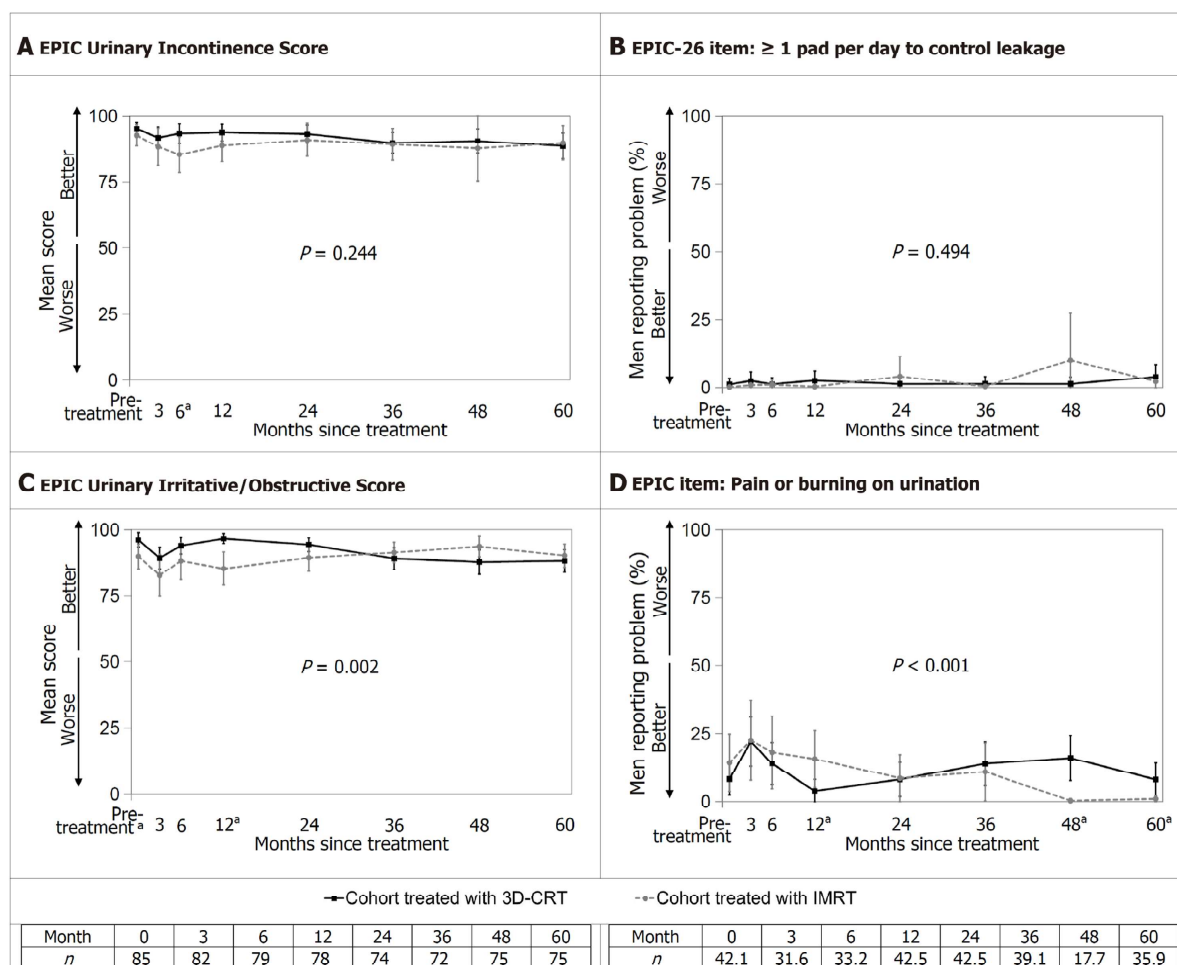


Figure 1 Weighted results of the Urinary domain measured with the expanded prostate cancer index composite. A: Expanded prostate cancer index composite (EPIC)-26 Urinary Incontinence Score; B: EPIC-26 item " ≥ 1 pad per day to control leakage"; C: EPIC-26 Urinary Irritative/Obstructive Score; D: EPIC-26 item "pain or burning on urination". Urinary outcomes over 60 months. Error bars represent 95%CI. The P value for the interaction between treatment and time is shown; ^a $P < 0.05$ for the t-test at that assessment when the treatment-by-time interaction is significant. EPIC: Expanded prostate cancer index composite; IMRT: Intensity-modulated radiotherapy; 3D-CRT: Three-dimensional conformal radiotherapy.

ularly valuable for capturing these recovery trajectories and informing patient counselling.

Chronic gastrointestinal outcomes also favoured IMRT, with improved bowel scores and less frequent rectal bleeding, supporting long-term function preservation[34-36]. Hypofractionation impacted short-term urinary incontinence, but did not alter long-term quality of life in 6 studies[37-42]. No 3D-CRT patients received ≥ 3 Gy per fraction, while 56.6% of IMRT patients did. Those receiving ≥ 3 Gy had significantly worse EPIC urinary incontinence scores at 12 months. These findings highlight the ability of PROMs to capture symptom fluctuations that can guide adjustments in fractionation and supportive care.

Furthermore, the IMRT cohort showed heterogeneity in image-guidance methods (CBCT, kilovoltage with fiducial markers, bone-based). A meta-analysis[43] shows that daily IGRT can reduce acute and late gastrointestinal toxicity, though the optimal strategy remains uncertain. Our IMRT cohort reflects the early stages of adoption of IGRT in Spanish centres, with variable protocols and margin reductions (2-10 mm)[44]. Patients treated with CBCT and ≤ 5 mm PTV margins improved urinary incontinence scores after 12 months, informing practical decisions about image guidance and margin selection.

Although IMRT offers superior dosimetric precision over 3D-CRT, high doses to critical urinary structures (bladder neck, trigone, urethra) limit organ sparing[45]. Inter-fractional organ motion and heterogeneous dose distribution can further affect outcomes[46,47]. However, the lack of detailed dose - volume histogram data for bladder and rectum limits our ability to relate PROM differences to specific dose - response patterns, potentially obscuring mechanistic interpretation of urinary and bowel outcomes.

Sexual function declined more in the IMRT cohort, which is consistent with prior evidence of erectile dysfunction after prostate radiotherapy[48]. IMRT may reduce risk, but dose-response for neurovascular bundles and penile bulb is debated[49,50]. Despite its sexual side effects, IMRT was associated with improved mental health, as in prior studies[51], reflecting how PROMs can capture multidimensional impact on patients beyond the traditional clinical outcomes. Nevertheless, the psychological outcomes may also be influenced by non-technical factors such as generational dif-

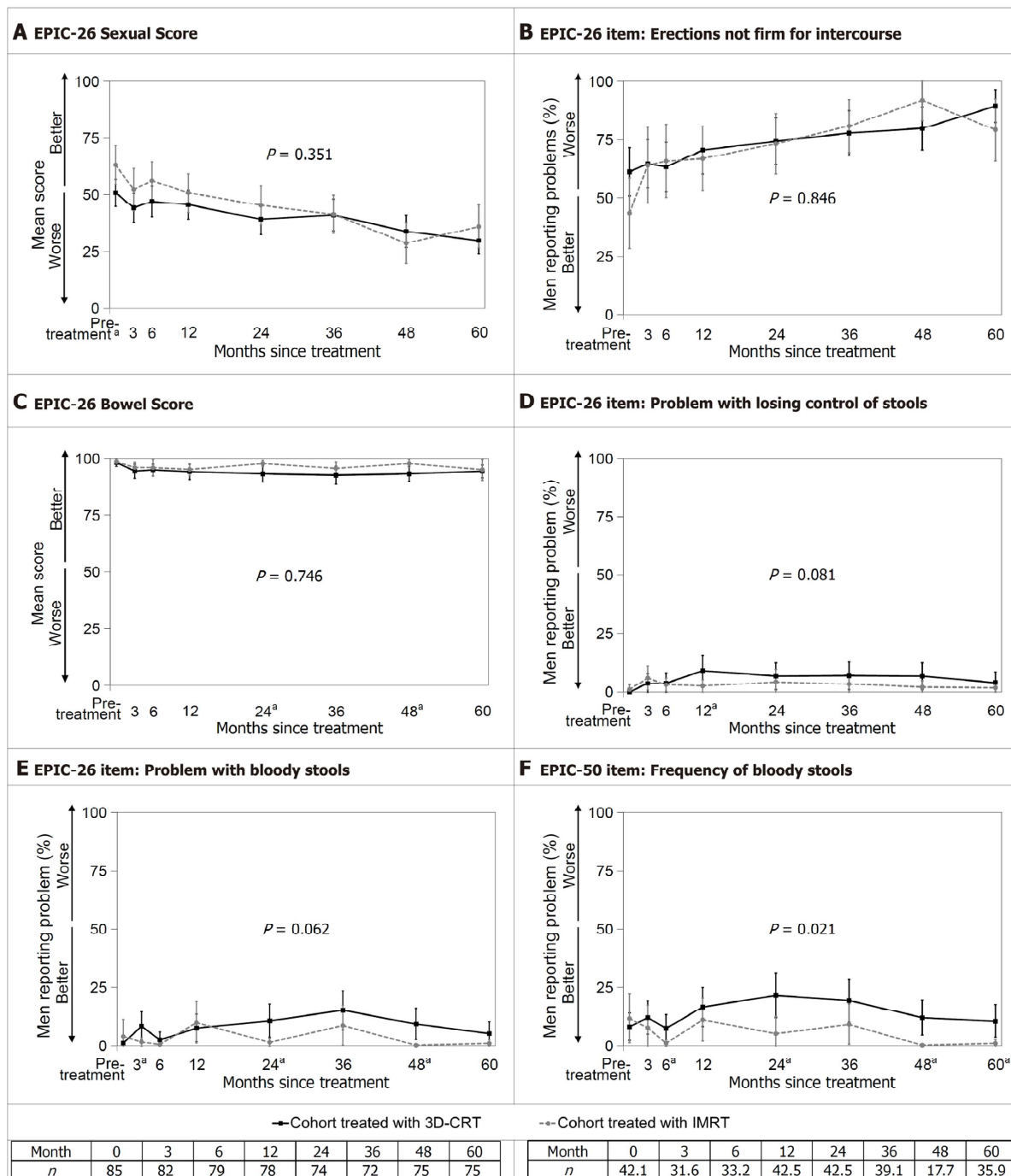


Figure 2 Weighted results of the sexual and bowel domains measured with the expanded prostate cancer index composite. A: Expanded prostate cancer index composite (EPIC)-26 Sexual Score; B: EPIC-26 item "erections not firm for intercourse"; C: EPIC-26 Bowel Score; D: EPIC-26 item "problem with losing control of stools"; E: EPIC-26 item "problem with bloody stools"; F: EPIC-50 item "frequency of bloody stools". Sexual and bowel outcomes over 60 months. Error bars represent 95%CI. The P value for the interaction between treatment and time is shown; $^*P < 0.05$ for the t -test at that assessment when the treatment-by-time interaction is significant. EPIC: Expanded prostate cancer index composite; IMRT: Intensity-modulated radiotherapy; 3D-CRT: Three-dimensional conformal radiotherapy.

erences in reporting, changes in supportive care availability, or expanding rehabilitation resources, which limits causal interpretation.

In summary, IMRT improves dose distribution, but PROM benefits depend on consistent planning, IGRT implementation, and fractionation strategy. Prospective studies with standardized IGRT procedures and detailed dosimetric data are needed to clarify the influence of implementation factors on long-term functional outcomes. PROMs emerge as essential patient-centred tools for evaluating technological innovation and linking technical advances with functional outcomes relevant for patients and clinical decisions.

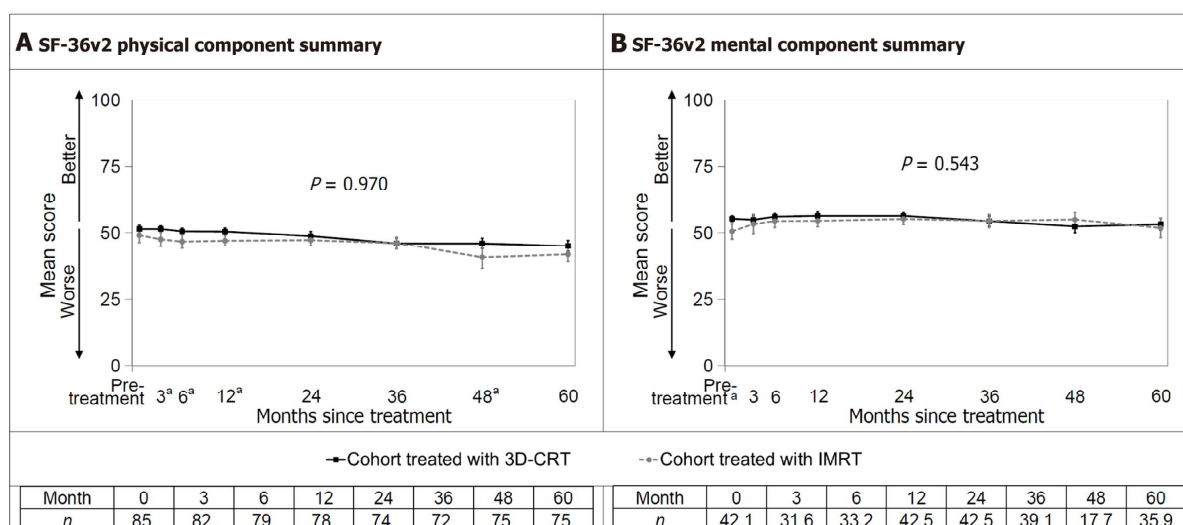


Figure 3 Weighted results of the physical and mental component summaries measured with the short form-36 health survey. A: Short form-36 health survey version 2 physical component summary; B: Short form-36 health survey version 2 mental component summary. Health-related quality of life over 60 months. Error bars represent 95%CI. The P value for the interaction between treatment and time is shown; $^aP < 0.05$ for the t -test at that assessment when the treatment-by-time interaction is significant. SF-36: Short form-36 health survey; IMRT: Intensity-modulated radiotherapy; 3D-CRT: Three-dimensional conformal radiotherapy.

This observational study is limited by its non-randomized design and inclusion of patients from different periods and centres. The two cohorts represent distinct treatment eras (2003-2005 *vs* 2014-2019), during which clinical practice and technology evolved considerably. Therefore, some PROM differences may reflect era-related changes in clinical workflow, supportive care, or toxicity management rather than the radiotherapy technique itself. Differences in cultural norms, health literacy, and expectations of care across generations may also influence PROM reporting, potentially amplifying or attenuating trends. Propensity score weighting and adjustment by Gleason score of the GEE models improved group comparability. However, because the Gleason score strongly influences prognosis and functional trajectories, residual imbalance may still have affected PROM trends, so this limitation should be considered when interpreting the results. Finally, the absence of key dosimetric parameters, such as bladder and rectum dose-volume metrics, limits the strength of the comparison between treatment groups. Without these data, detailed dose-response exploration is restricted and technique-related effects may be partially obscured.

This study is strengthened by the exclusion of patients with androgen deprivation therapy, a potential confounder in assessing radiotherapy's impact on quality of life. Furthermore, the high five-year PROM completion rate (87.2%) – exceeding that of previous studies with shorter follow-up – reinforces their robustness and applicability at long term, highlighting sustained functional outcomes and patient well-being, and supporting their role in clinical practice and technology evaluation.

Our findings highlight two key aspects: First, the radiotherapy technique may influence the timing of quality-of-life changes, particularly when IGRT is combined with hypofractionation and dose escalation. Second, PROMs prove to be sensitive, patient-centred tools for evaluating the clinical impact of new technologies, offering a more integrated view of functional outcomes. Their consistency over time positions them as valuable instruments in health technology assessment, which increasingly incorporates clinical effectiveness, safety, cost-effectiveness, and organizational and ethical dimensions, with potential relevance for decision-making in public healthcare systems. Taken together, these findings highlight the strategic role of PROMs in bridging technical innovation with patient-centred care, offering actionable insights for clinicians, researchers, and policymakers.

CONCLUSION

Both the 3D-CRT and the IMRT cohort maintained good quality of life, with only minor long-term differences. After initial worsening, IMRT patients tended to show greater recovery in urinary and bowel symptoms, but more sexual decline after the second year. Mental health outcomes were slightly better with IMRT. Although IMRT enables dose escalation and offers technical advantages, the optimal IGRT strategy remains unclear. PROMs provide a valuable framework for evaluating radiotherapy technologies, linking technical refinements with patient-centred outcomes and supporting their integration into technology assessment and clinical decision-making.

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