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Prostate-Specific Symptom Burden and Global Quality of Life After Dose-Escalated Moderately Hypofractionated Radiotherapy for Prostate Cancer: A Single-Center Cross-Sectional Study

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Simple Summary

Radiotherapy for prostate cancer can control disease effectively, but urinary, bowel, sexual, and hormone-related symptoms may affect daily life after treatment. We assessed 57 men treated at one center with high-dose external-beam radiotherapy using 2.25–2.30 Gy per fraction who completed EORTC quality-of-life questionnaires once after treatment. Greater urinary and bowel symptom burden was consistently linked to lower overall quality of life in univariable and rank-based analyses, but no symptom domain showed an independent association after robust multivariable adjustment. Mean rectal and bladder doses were not clearly associated with quality-of-life outcomes. Because the exact time between radiotherapy and questionnaire completion was unavailable and pretreatment questionnaires were not available, the study cannot establish treatment-related changes over time. The findings support combining general and prostate-specific patient-reported measures in follow-up and highlight the need for prospective longitudinal studies.

Abstract

Background: Patient-reported outcomes complement clinician-reported toxicity after prostate radiotherapy, but real-world data linking prostate-specific symptoms to global health-related quality of life (HRQoL) remain limited. We evaluated a historical high-dose external-beam radiotherapy regimen using 2.25–2.30 Gy fractions. **Methods:** This single-center cross-sectional study included 57 patients treated between 2010 and 2024. HRQoL was assessed once after radiotherapy with the EORTC QLQ-C30 and QLQ-PR25; the exact interval from radiotherapy completion to questionnaire completion and pretreatment PROs were unavailable. Associations with global HRQoL were examined using linear regression with HC3 heteroscedasticity-robust inference and Spearman correlations. **Results:** Mean global HRQoL was 65 ± 22. Robust univariable associations were observed for urinary symptoms (β = −0.46, 95% CI −0.89 to −0.03; $p = 0.038$) and bowel symptoms (β = −0.53, 95% CI −1.00 to −0.05; $p = 0.031$). Spearman correlations were −0.434 ($p = 0.001$) and −0.361 ($p = 0.007$), respectively. In the multivariable HC3 model ($n = 53$), neither urinary (β = −0.36, 95% CI −0.83 to 0.11; $p = 0.128$) nor bowel symptoms (β = −0.26, 95% CI −0.76 to 0.23; $p = 0.287$) showed an independent statistically significant association. Exploratory mean-dose models showed no clear association with global HRQoL or the corresponding

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urinary or bowel symptom domains. **Conclusions:** Urinary and bowel symptom burden showed consistent inverse associations with global HRQoL in univariable and rank-based analyses, but robust multivariable models did not confirm independent effects. The cross-sectional design, absence of baseline PROs, unknown assessment timing, and modest sample size preclude causal attribution to radiotherapy.

Keywords: prostate cancer; health-related quality of life; patient-reported outcomes; external-beam radiotherapy; EORTC QLQ-PR25; robust regression

1. Introduction

Prostate cancer is one of the most common malignancies in men, with approximately 1.47 million new cases and 397,000 related deaths worldwide in 2022 [1]. In Europe, it remains the most frequently diagnosed male malignancy when non-melanoma skin cancer is excluded [2]. Because many patients with localized disease have long life expectancy, treatment evaluation should include functional outcomes and HRQoL in addition to oncological control.

External-beam radiotherapy is an established curative option for localized and locally advanced prostate cancer [2]. Randomized trials such as PROFIT and CHHiP established shorter moderate-hypofractionation regimens, and the HYDRA individual-patient-data meta-analysis further supports biologically isodose schedules such as 60 Gy in 20 fractions [3–5]. The 2026 ASTRO clinical practice guideline now recommends moderate hypofractionation over conventional fractionation for localized prostate cancer across risk groups and identifies 60–62 Gy in 20 fractions and 70 Gy in 28 fractions among the recommended schedules [6]. Patient-reported outcomes from CHHiP demonstrated the importance of longitudinal baseline and post-treatment assessment when comparing fractionation schedules [7].

Patient-reported outcomes capture treatment effects that may be incompletely represented by clinician-reported toxicity. Prospective longitudinal EORTC data show that global HRQoL can deteriorate transiently during radiotherapy and subsequently recover, while urinary or bowel symptoms may follow different trajectories [8]. The recent long-term patient-reported analysis of the randomized PROFIT trial likewise found no significant differences in urinary, bowel, sexual, hormonal, or general HRQoL between 60 Gy in 20 fractions and conventional fractionation, with assessments anchored to the baseline and prespecified follow-up time points [9]. A contemporary population-based Australian cohort of 3647 patients treated between 2016 and 2023 similarly reported no statistically or clinically significant differences in 12-month urinary or bowel quality-of-life outcomes between hypofractionated and conventionally fractionated radiotherapy [10]. Long-term comparative studies further demonstrate distinct urinary, bowel, sexual, and hormonal profiles across prostate cancer management strategies [11–14]. The EORTC QLQ-C30 and prostate-specific QLQ-PR25 provide validated complementary measures for these domains [15–17].

The present cohort is clinically distinct from contemporary 60 Gy in 20 fractions practice. Most patients received 75.9 Gy in 33 fractions of 2.30 Gy, a historical high-dose IMRT/IGRT concept related to the Würzburg program [18–21]. Although 2.25–2.30 Gy fractions are below the fraction sizes now commonly used for moderate hypofractionation, this cohort remains relevant as a real-world survivorship sample treated with dose-escalated, highly conformal radiotherapy. Its added value is the linkage of validated general and prostate-specific EORTC outcomes with routine clinical, target-volume, and organ

mean-dose data within a single institutional treatment concept, rather than comparison of competing fractionation regimens.

The primary hypothesis was that greater urinary, bowel, and hormonal treatment-related symptom burden would be associated with lower QLQ-C30 global HRQoL. Secondary objectives were to describe the broader QLQ-C30/QLQ-PR25 profile and documented acute and late toxicities, and to explore associations with clinical factors, pelvic irradiation, target volumes, and available rectal and bladder mean doses.

2. Methods

2.1. Study Design, Setting, and Participants

This single-center cross-sectional observational study combined a one-time post-treatment assessment of patient-reported outcomes with retrospective extraction of clinical, tumor, treatment, dosimetric, and toxicity data. Eligible participants had histologically confirmed prostate cancer, had undergone definitive external-beam radiotherapy at the Department of Radiation Oncology, University Hospital Halle (Saale), Germany, and had an evaluable study questionnaire record. Clinical and questionnaire data were linked using a unique study identifier.

The analysis source files contained 60 clinical records and 61 questionnaire records. During data-quality reconciliation, three clinical records and four questionnaire records were not retained, leaving 57 concordant identifiers in both sources (Figure 1). The available analysis files do not preserve a more granular reason category for each source-record exclusion. The denominator of all patients originally invited to complete the questionnaire was not available; therefore, a formal questionnaire response rate cannot be calculated.

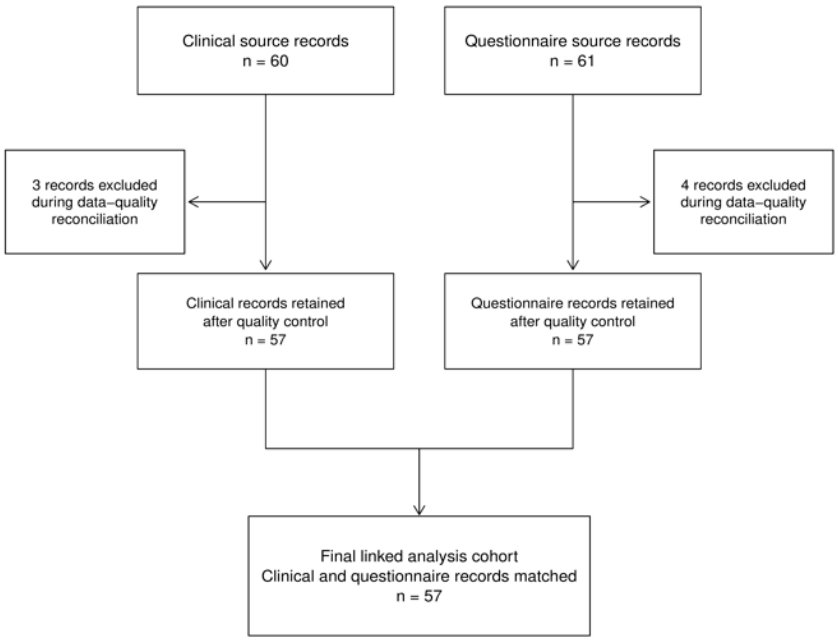


Figure 1. Study cohort assembly. Clinical and questionnaire source files were reconciled independently and linked by study identifier. The source-record counts do not represent the denominator of all patients originally invited to participate; therefore, a formal questionnaire response rate could not be calculated.

Radiotherapy was delivered between 11 January 2010 and 22 August 2024. The final analytic dataset contains radiotherapy start and end dates but no questionnaire-completion date. Consequently, neither the exact nor an approximate interval from radiotherapy

completion to PRO assessment could be reconstructed. No pretreatment EORTC QLQ-C30/QLQ-PR25 assessment was available. The analysis should therefore be interpreted as a cross-sectional post-treatment snapshot rather than a longitudinal assessment of treatment-related change.

Clinical data were obtained from ORBIS (Dedalus HealthCare GmbH, Bonn, Germany; version not consistently recoverable across the study period; https://www.dedalus.com/; accessed 20 November 2026), radiotherapy data from MOSAIQ (Elekta AB, Stockholm, Sweden; version not consistently recoverable across the study period; https://www.elekta.com/; accessed 20 November 2026), and imaging/treatment-planning information from Centricity PACS (GE HealthCare, Chicago, IL, USA; version not consistently recoverable across the study period; https://www.gehealthcare.com/; accessed 20 November 2026). Implausible or non-interpretable entries, including question marks, incomplete date strings, spreadsheet-error codes, and empty character strings, were treated as missing. The report follows the STROBE guidance for cross-sectional studies.

Historical radiotherapy delivery predated the present research protocol and was not a study intervention. Retrospective extraction and linkage of historical treatment data were conducted under ethics approval reference 2024-003. Protocol version 2, dated 6 May 2025, received a favorable ethics assessment on 27 May 2025. Written informed consent was obtained before study participation.

2.2. Clinical Variables

Extracted variables included age at radiotherapy, prostate-specific antigen (PSA) at diagnosis, Gleason score, TNM classification, staging examinations, and androgen deprivation therapy (ADT). Gleason scores were summarized as 6, 7a (3 + 4), 7b (4 + 3), 8, or 9. Tumor and nodal categories were reduced to T1, T2, T3, or Tx and N0, N1, or Nx. Metastatic status was categorized as documented M0, documented M1, or unknown/not documented. No M1 case was present in the final cohort. Castration-resistant disease was not separately coded and could not be reliably reconstructed.

ADT was analyzed as a binary covariate in the primary model. Treatment type could be described as GnRH analogue only, antiandrogen only, or combined treatment. Raw variables for ADT start and duration existed, but the category definitions and treatment status at the time of questionnaire completion were not sufficiently documented to permit clinically reliable timing or duration classification. Comorbidity burden and prior urological procedures were not available as structured variables and therefore could not be included.

2.3. Radiotherapy Planning and Delivery

The institutional concept was related to the high-dose IMRT/IGRT program reported from Würzburg [18–21]. The larger clinical target volume included the prostate and proximal seminal vesicles with an approximately 10-mm expansion reduced posteriorly to 7 mm; the high-dose target comprised the prostate and seminal-vesicle base with an approximately 5-mm margin while avoiding rectal overlap. Pelvic lymphatic pathways were included when clinically indicated. Target definition and treatment delivery were adapted to the individual clinical situation and treatment era.

Definitive radiotherapy was delivered in 32 or 33 fractions: 72.0 Gy in 32 fractions of 2.25 Gy (n = 1), 73.6 Gy in 32 fractions of 2.30 Gy (n = 6), or 75.9 Gy in 33 fractions of 2.30 Gy (n = 50). Equivalent doses in 2-Gy fractions were calculated as $EQD2 = D \times (d + \alpha/\beta)/(2 + \alpha/\beta)$ using $\alpha/\beta = 1.5$ Gy for prostate cancer, yielding approximately 77.1, 79.9, and 82.4 Gy, respectively. Pelvic lymphatic irradiation was delivered in 19 patients. IMRT was

documented for all patients; VMAT, IGRT, and fiducial localization were used according to treatment era and clinical indication.

The specific treatment-planning system version, dose-calculation algorithm, and uniform organ-at-risk constraint set were not stored as structured variables and could not be consistently reconstructed across the 2010–2024 treatment period. Available volumetric and dosimetric variables included primary PTV, a PTV including pelvic lymphatics when pelvic irradiation was performed, the stored high-dose/boost PTV structure, and mean doses to rectum and bladder. The pelvic PTV was structurally not applicable to the 38 patients treated to the prostate alone (without elective pelvic lymphatic irradiation) and was therefore not treated as ordinary missing data. The cohort was defined by definitive irradiation of the intact prostate; postoperative prostate-bed irradiation was not part of this analysis. A stored boost PTV represented a planning structure and did not necessarily imply documented delivery of a separate boost. Detailed historical D2/D50/D98-type DVH parameters were incomplete and showed internal inconsistencies in retrospective quality control; inferential dosimetric analyses were therefore restricted to organ mean doses and selected target volumes.

2.4. Patient-Reported Outcomes

HRQoL was assessed with the EORTC QLQ-C30 version 3.0 and the prostate-specific EORTC QLQ-PR25 [15–17]. The QLQ-C30 provides a global health status/quality-of-life scale, five functioning scales, three multi-item symptom scales, and six single-item symptom measures. The QLQ-PR25 assesses urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, sexual activity, and sexual functioning, with a conditional incontinence-aid item.

Questionnaires were scored according to EORTC procedures and transformed to 0–100 scales. Multi-item scales were calculated when at least half of the constituent items were valid. The incontinence-aid item was evaluated only in patients to whom it was applicable, and sexual functioning was calculated only for sexually active patients. Higher QLQ-C30 global/functioning scores indicate better HRQoL; higher QLQ-C30 symptom and QLQ-PR25 urinary, bowel, hormonal, and incontinence-aid scores indicate greater symptom burden. Scale-specific evaluable sample sizes are reported.

2.5. Retrospectively Documented Toxicity

Routine clinical records contained separate source indicators for acute and late treatment-related symptoms. Acute and late toxicity were classified according to the original categories in the clinical source records; no additional uniform post-radiotherapy time threshold (such as 90 days) was imposed retrospectively. The archived indicators did not permit independent verification of a consistent temporal cut-off across all records. Documented GU/GI symptoms included dysuria, pollakiuria, urinary incontinence, cystitis, diarrhea, and proctitis; nocturia was available for acute toxicity, while hematuria, urethral stricture, rectal bleeding, and erectile dysfunction were additionally available among late indicators. Standardized CTCAE or RTOG severity grades were not consistently reconstructible. Toxicity was therefore reported as binary documented presence/absence, separately for acute and late periods, using the number of evaluable records as the denominator. These variables should not be interpreted as graded toxicity endpoints.

2.6. Statistical Analysis

Continuous variables were summarized using medians, interquartile ranges, and ranges; PRO scores were additionally summarized using means and standard deviations. Categorical variables were reported as counts and percentages. Missing data were

handled by available-case descriptive analysis and complete-case regression; no imputation was performed.

The primary hypothesis was evaluated using linear regression with QLQ-C30 global HRQoL as the outcome. Separate univariable models were fitted for QLQ-PR25 domains. The main multivariable model included urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, age, and ADT. Because the Breusch–Pagan test indicated heteroscedasticity in this model (p = 0.012), HC3 heteroscedasticity-consistent standard errors and 95% confidence intervals were used for primary inference. Conventional model-based OLS standard errors were retained as a sensitivity analysis. Spearman rank correlations provided a nonparametric sensitivity analysis.

Model assessment included variance inflation factors (VIFs), residual inspection, the Shapiro–Wilk test, Ramsey RESET test, externally studentized residuals, leverage, Cook's distance, DFBETAs, and leave-one-out refitting. No observation was excluded from the primary model solely because of influence diagnostics.

The redesigned exploratory dosimetric model used all patients with available organ mean doses and included rectum mean dose, bladder mean dose, and pelvic irradiation as a binary indicator for global HRQoL. Domain-oriented exploratory models assessed urinary symptoms in relation to bladder mean dose and pelvic irradiation and bowel symptoms in relation to rectum mean dose and pelvic irradiation. Pelvic PTV was not entered into an all-patient model because it was structurally applicable only to the 19 patients receiving pelvic irradiation. Selected target-volume analyses were performed separately.

The counterintuitive exploratory association between pelvic irradiation and hormonal treatment-related symptoms was examined using a parsimonious model including pelvic irradiation and ADT, an ADT-by-pelvic-irradiation interaction model, and a sensitivity analysis among ADT-treated patients using the available raw ADT-duration category. Because the clinical meaning of the raw duration codes could not be verified, those categories were not assigned clinical labels. Secondary and exploratory analyses were not adjusted for multiplicity and were interpreted as hypothesis-generating.

Analyses were performed in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). HC3 covariance estimation used the sandwich package version 3.0-1 and lmtest version 0.9-40; data manipulation and graphics used dplyr version 1.1.4 and ggplot2 version 3.5.2. Analyses were run within the RStudio version 2026.08.0+187 (Posit Software, PBC, Boston, MA, USA).

2.7. Use of Generative Artificial Intelligence in Manuscript Preparation

OpenAI ChatGPT (current model used for the final manuscript revision and proofing: GPT-5.6 Sol; OpenAI, San Francisco, CA, USA; https://chatgpt.com/; accessed 20 November 2026) was used to assist with language editing, manuscript restructuring, preparation and checking of R analysis code, and journal-specific formatting. All statistical analyses were executed by the authors in R version 4.1.0 using the final study dataset, and all outputs were reviewed against the source data and clinical context. No generative AI system was used to create or modify raw study data. The authors critically reviewed and edited all AI-assisted material and take full responsibility for the final manuscript.

3. Results

3.1. Cohort Assembly and Clinical Characteristics

After data-quality reconciliation, 57 concordant clinical and questionnaire records constituted the final cohort (Figure 1). Median age at radiotherapy was 69 years (IQR 65–75; range 59–83), and median PSA at diagnosis was 9 ng/mL (IQR 6–16; range 3–343).

Twenty-five patients (44%) had Gleason score 6 or 7a and 32 (56%) had Gleason score 7b–9. T1 disease was recorded in 46 patients (81%), N1 disease in six (11%), and documented M0 status in 52 (91%); the remaining five had unknown/not documented M status. All six N1 cases were documented M0, and no M1 case was present. The patient with the maximum PSA (342.8 ng/mL) had T2cN0M0 disease with documented CT, bone scan, and MRI staging. Thus, the apparently discordant distribution reflects different dimensions of clinical stage, histologic grade, nodal status, and PSA rather than a single internally inconsistent staging variable.

ADT was administered to 22 patients (39%): 12 received a GnRH analogue without a documented antiandrogen, five an antiandrogen without a documented GnRH analogue, and five both. Nineteen patients (33%) received elective pelvic lymphatic irradiation (Table 1).

Table 1. Baseline clinical characteristics of the study cohort.

Characteristic	N = 57
Age at radiotherapy, years	69 [65, 75] (59–83)
PSA at diagnosis, ng/mL	9 [6, 16] (3–343)
Gleason score 6	9 (16%)
Gleason score 7a (3 + 4)	16 (28%)
Gleason score 7b (4 + 3)	18 (32%)
Gleason score 8	11 (19%)
Gleason score 9	3 (5.3%)
T1/T2/T3/Tx	46 (81%)/9 (16%)/1 (1.8%)/1 (1.8%)
N0/N1/Nx or unknown	45 (79%)/6 (11%)/6 (11%)
M0/unknown or not documented	52 (91%)/5 (8.8%)
Androgen deprivation therapy, yes	22 (39%)
GnRH analogue only	12 (21%)
Antiandrogen only	5 (8.8%)
GnRH analogue + antiandrogen	5 (8.8%)
Pelvic lymphatic irradiation, yes	19 (33%)

Data are median [IQR] (range) or *n* (%). Percentages use N = 57. M status was classified as M0 only when documented; otherwise it was reported as unknown/not documented. PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

3.2. Radiotherapy Characteristics

Radiotherapy was delivered from January 2010 through August 2024. Fifty patients (87.7%) received 75.9 Gy in 33 fractions of 2.30 Gy, six (10.5%) received 73.6 Gy in 32 fractions of 2.30 Gy, and one (1.8%) received 72.0 Gy in 32 fractions of 2.25 Gy. Median treatment duration was 47 days (IQR 45–50). IMRT was documented for all patients, VMAT for 40 (70%), fiducial gold markers for 52 (91%), and IGRT clearly for 54 (95%), with two additional uncertain entries. The pelvic PTV was available in all 19 pelvic-irradiation patients and structurally not applicable in all 38 prostate-only patients. Detailed radiotherapy and dosimetric characteristics are summarized in Table 2.

Table 2. Radiotherapy parameters and available dosimetry.

Characteristic	Value	Missing/Unclear, *n*
72.0 Gy in 32 × 2.25 Gy	1 (1.8%)	0
73.6 Gy in 32 × 2.30 Gy	6 (10.5%)	0
75.9 Gy in 33 × 2.30 Gy	50 (87.7%)	0
Pelvic lymphatic irradiation	19 (33%)	0
Boost irradiation documented	49	1 unclear

Image-guided radiotherapy documented	54	2 unclear
IMRT documented	57 (100%)	0
VMAT documented	40 (70%)	0
Fiducial gold markers	52 (91%)	0
Primary PTV, cm^3	253 ± 64; 238 [211, 280]; 172–501	7
PTV including pelvic lymphatics, cm^3	926 ± 422; 892 [591, 1224]; 279–1848	38 (not applicable outside pelvic RT)
Stored high-dose/boost PTV, cm^3	152 ± 72; 128 [111, 170]; 68–467	4
Rectum mean dose, Gy	29 ± 9; 28 [24, 34]; 10–53	3
Bladder mean dose, Gy	24 ± 8; 23 [20, 31]; 4–40	3

Continuous data are mean ± SD; median [IQR]; range. The pelvic PTV was structurally applicable only to pelvic-irradiation patients. A stored high-dose/boost PTV is a planning-structure variable and is not equivalent to documented boost delivery. IMRT and VMAT were not mutually exclusive. PTV, planning target volume.

3.3. Patient-Reported Outcome Scores

All 57 patients had evaluable QLQ-C30 global HRQoL. Mean global HRQoL was 65 ± 22 (median 67, IQR 50–83). Cognitive functioning had the highest mean functioning score (84 ± 19), followed by emotional (77 ± 22) and physical functioning (76 ± 23). The most pronounced QLQ-C30 symptom scores were fatigue (32 ± 28), insomnia (28 ± 34), and dyspnea (26 ± 33) (Table 3).

Table 3. EORTC QLQ-C30 scores.

Scale	*n*	Mean ± SD	Median [IQR]	Range
Global HRQoL	57	65 ± 22	67 [50, 83]	0–100
Physical functioning	57	76 ± 23	80 [60, 93]	13–100
Role functioning	57	72 ± 28	67 [50, 100]	0–100
Emotional functioning	57	77 ± 22	83 [58, 92]	0–100
Cognitive functioning	57	84 ± 19	83 [67, 100]	33–100
Social functioning	57	73 ± 31	83 [67, 100]	0–100
Fatigue	57	32 ± 28	33 [11, 56]	0–100
Nausea and vomiting	57	6 ± 17	0 [0, 0]	0–100
Pain	57	17 ± 27	0 [0, 33]	0–100
Dyspnea	57	26 ± 33	0 [0, 67]	0–100
Insomnia	57	28 ± 34	0 [0, 67]	0–100
Appetite loss	57	10 ± 24	0 [0, 0]	0–100
Constipation	57	14 ± 27	0 [0, 33]	0–100
Diarrhea	57	11 ± 23	0 [0, 0]	0–100
Financial difficulties	57	11 ± 22	0 [0, 0]	0–100

Scores range from 0 to 100. Higher global HRQoL/functioning scores indicate better outcomes; higher symptom scores indicate greater burden. EORTC, European Organisation for Research and Treatment of Cancer; IQR, interquartile range; SD, standard deviation.

QLQ-PR25 evaluable sample sizes differed by scale. Mean scores were 35 ± 21 for urinary symptoms ($n = 54$), 10 ± 15 for bowel symptoms ($n = 54$), and 20 ± 17 for hormonal treatment-related symptoms ($n = 55$). Incontinence-aid problems were evaluable in 17 patients; sexual functioning, a conditional scale, was evaluable in 15 (Table 4).

Table 4. EORTC QLQ-PR25 scores.

Scale	*n*	Mean ± SD	Median [IQR]	Range
Urinary symptoms	54	35 ± 21	33 [18, 50]	0–92
Incontinence-aid problems	17	35 ± 38	33 [0, 67]	0–100

Bowel symptoms	54	10 ± 15	0 [0, 17]	0–67
Hormonal treatment-related symptoms	55	20 ± 17	17 [6, 31]	0–67
Sexual activity	55	25 ± 28	17 [0, 50]	0–100
Sexual functioning	15	47 ± 21	42 [42, 54]	0–92

Higher urinary, bowel, hormonal treatment-related, and incontinence-aid scores indicate greater symptom burden/bother; higher sexual activity and sexual functioning scores indicate higher functioning. Scale-specific *n* reflects missingness and conditional applicability.

3.4. Retrospectively Documented Acute and Late Toxicity

At least one acute symptom was documented in 53 of 56 evaluable records (94.6%), most commonly nocturia (32/56, 57.1%), dysuria (27/56, 48.2%), pollakiuria (25/56, 44.6%), and diarrhea (17/56, 30.4%). At least one late symptom was documented in 12 of 52 evaluable records (23.1%). Because severity grades were unavailable, these frequencies represent documented symptoms, not grade ≥2 toxicity (Table 5).

Table 5. Retrospectively documented acute and late treatment-related symptoms.

Symptom	Acute, *n*/N (%)	Late, *n*/N (%)
Any documented toxicity	53/56 (94.6%)	12/52 (23.1%)
Dysuria	27/56 (48.2%)	2/52 (3.8%)
Pollakiuria	25/56 (44.6%)	2/52 (3.8%)
Nocturia	32/56 (57.1%)	—
Urinary incontinence	3/55 (5.5%)	3/52 (5.8%)
Cystitis	4/56 (7.1%)	0/52 (0%)
Diarrhea	17/56 (30.4%)	1/52 (1.9%)
Proctitis	8/56 (14.3%)	0/52 (0%)
Hematuria	—	1/52 (1.9%)
Urethral stricture	—	1/52 (1.9%)
Rectal bleeding	—	0/52 (0%)
Erectile dysfunction	—	2/51 (3.9%)

Percentages use evaluable observations for each source indicator. Acute and late periods were assigned according to the original clinical-record categories; no uniform post-treatment time threshold was applied retrospectively. Standardized CTCAE/RTOG grades were not consistently available; therefore, these are binary documented symptoms.

3.5. Primary Associations with Global HRQoL

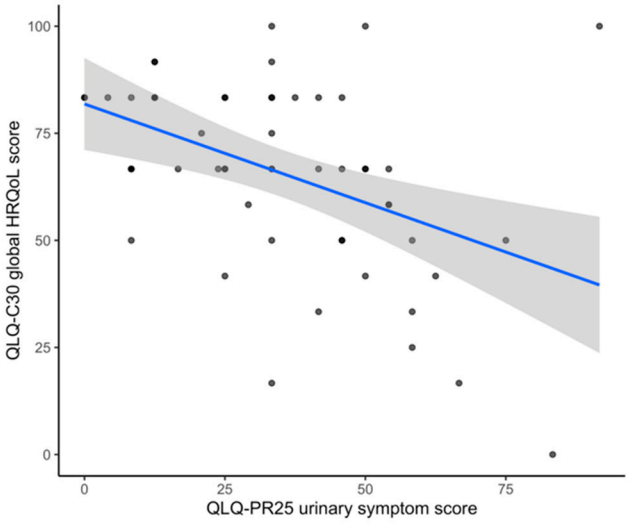
In HC3-robust univariable models, greater urinary symptom burden was associated with lower global HRQoL (β = −0.46, 95% CI −0.89 to −0.03; $p = 0.038$), and greater bowel symptom burden was likewise associated with lower global HRQoL (β = −0.53, 95% CI −1.00 to −0.05; $p = 0.031$). The hormonal treatment-related symptom coefficient was directionally similar but did not reach the 0.05 threshold with HC3 inference (β = −0.43, 95% CI −0.88 to 0.02; $p = 0.064$). Spearman analyses supported inverse correlations for urinary (ϱ = −0.434; $p = 0.001$), bowel (ϱ = −0.361; $p = 0.007$), and hormonal treatment-related symptoms (ϱ = −0.350; $p = 0.009$) (Figure 2; Supplementary Table S1).

In the multivariable HC3 model (complete-case $n = 53$), no individual predictor was statistically significant. Urinary symptoms remained negative (β = −0.36, 95% CI −0.83 to 0.11; $p = 0.128$), as did bowel symptoms (β = −0.26, 95% CI −0.76 to 0.23; $p = 0.287$) and hormonal treatment-related symptoms (β = −0.08, 95% CI −0.61 to 0.44; $p = 0.755$); age and ADT were also not associated with global HRQoL (Table 6; Figure 3). A 10-point higher urinary score corresponded to an estimated 3.6-point lower global HRQoL score in the multivariable model (95% CI −8.3 to 1.1), while a 10-point higher bowel score corresponded to a 2.6-point lower score (95% CI −7.6 to 2.3).

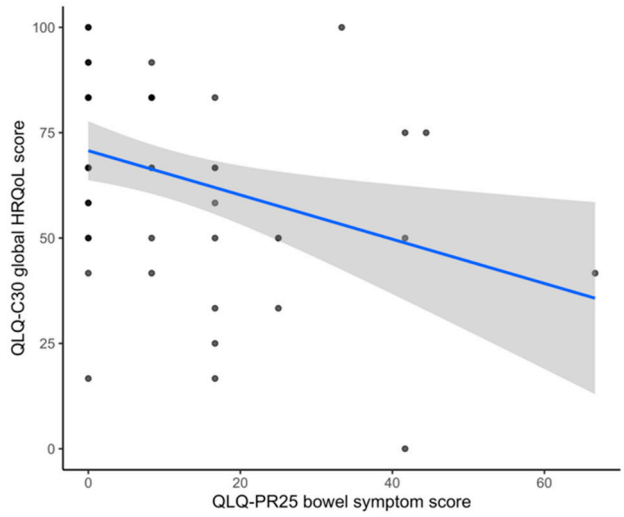
Table 6. HC3-robust univariable and multivariable linear regression analyses for global HRQoL.

Predictor	Univ. β	95% CI	*p*	Multiv. β	95% CI	*p*
Urinary symptoms	−0.46	−0.89 to −0.03	0.038	−0.36	−0.83 to 0.11	0.128
Incontinence-aid problems	0.08	−0.23 to 0.38	0.603	—	—	—
Bowel symptoms	−0.53	−1.00 to −0.05	0.031	−0.26	−0.76 to 0.23	0.287
Hormonal treatment-related symptoms	−0.43	−0.88 to 0.02	0.064	−0.08	−0.61 to 0.44	0.755
Sexual activity	0.18	−0.02 to 0.38	0.081	—	—	—
Sexual functioning	−0.04	−0.57 to 0.49	0.872	—	—	—
Age at radiotherapy, per year	—	—	—	−0.14	−1.28 to 0.99	0.802
ADT, yes vs. no	—	—	—	−0.01	−12.10 to 12.08	0.999

HC3 heteroscedasticity-consistent standard errors were used for primary inference. Univariable *n*: urinary and bowel 54; incontinence-aid 17; hormonal symptoms and sexual activity 55; sexual functioning 15. The multivariable model included urinary, bowel, hormonal treatment-related symptoms, age, and ADT (*n* = 53). Conventional OLS estimates are provided as a sensitivity analysis in Supplementary Table S2.



(**A**)



(**B**)

Figure 2. (**A**) Urinary symptom burden and global HRQoL. Individual QLQ-PR25 urinary symptom scores are plotted against QLQ-C30 global HRQoL (*n* = 54); the line shows the ordinary least-squares fit and shaded 95% confidence band. Primary inferential results used HC3-robust standard errors. (**B**) Bowel symptom burden and global HRQoL. Individual QLQ-PR25 bowel symptom scores are

plotted against QLQ-C30 global HRQoL (n = 54); the line shows the ordinary least-squares fit and shaded 95% confidence band. Primary inferential results used HC3-robust standard errors.

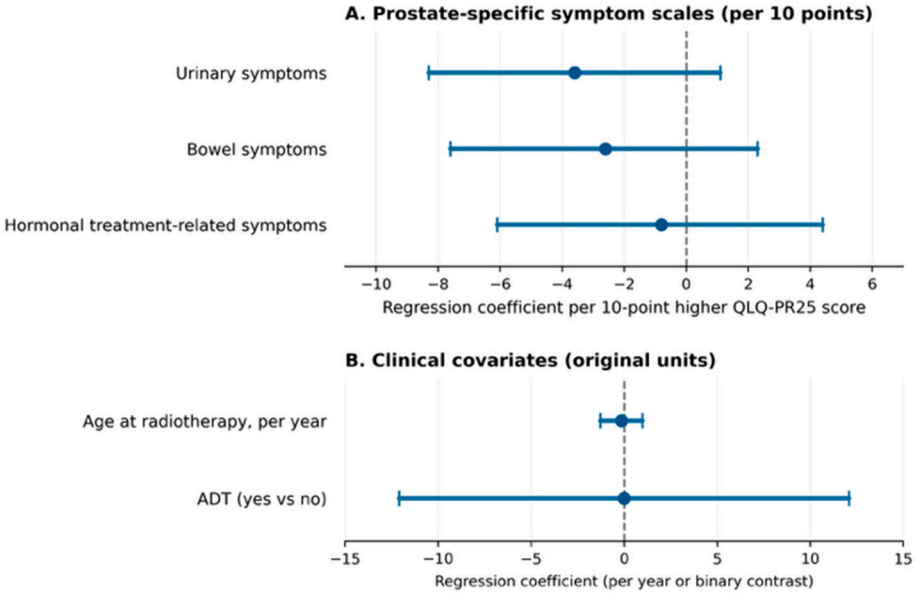


Figure 3. HC3-robust coefficients from the primary multivariable model (n = 53). Points represent regression coefficients and horizontal lines show their 95% HC3 confidence intervals; dashed vertical lines denote no association. Panel (**A**) presents QLQ-PR25 symptom-domain coefficients per 10-point increase on the 0–100 scale. Panel (**B**) displays age per one-year increase and ADT (yes versus no) on a separate axis. The original model and inference are unchanged; only the visual coefficient scaling differs.

3.6. Diagnostics, Sensitivity, and Exploratory Analyses

The Breusch–Pagan test supported heteroscedasticity (p = 0.012), whereas VIFs were low (1.19–1.75), arguing against problematic multicollinearity. Residual normality and functional-form checks did not show strong evidence of violation (Shapiro–Wilk p = 0.209; RESET p = 0.114). Influence diagnostics identified one externally studentized residual above 3, five observations above the Cook's-distance threshold 4/n, and four high-leverage observations. In leave-one-out refitting, urinary coefficients remained negative in all 53 iterations (range −0.532 to −0.267), as did bowel coefficients (range −0.396 to −0.160), but inferential significance was not stable. After the exclusion of three patients with uncertain boost and/or IGRT documentation, the HC3 multivariable model (n = 50) remained non-significant for all predictors (Supplementary Tables S3 and S4).

The redesigned exploratory global-HRQoL dosimetry model included 54 patients. Rectum mean dose (β = 0.30, 95% CI −0.56 to 1.15; p = 0.491), bladder mean dose (β = 0.49, 95% CI −0.14 to 1.12; p = 0.123), and pelvic irradiation (β = 4.72, 95% CI −8.10 to 17.5; p = 0.463) were not statistically significant. Bladder mean dose was not clearly associated with urinary symptoms (β = −0.52; p = 0.144; n = 52), and rectum mean dose was not clearly associated with bowel symptoms (β = −0.10; p = 0.808; n = 52) (Supplementary Table S5). These null findings indicate limited evidence in the available data and should not be interpreted as evidence of absent dose–response relationships.

Pelvic irradiation remained inversely associated with hormonal treatment-related symptoms in an exploratory model adjusted for ADT (β = −17.0, 95% CI −25.7 to −8.37; p < 0.001), while ADT itself was associated with higher hormonal symptom burden (β = 16.9, 95% CI 7.31 to 26.6; p < 0.001). The pelvic-irradiation-by-ADT interaction was not

significant ($p = 0.657$). Among the 21 ADT-treated patients with an available raw duration category, the pelvic irradiation coefficient remained similar in magnitude ($\beta = -17.3$, 95% CI −36.6 to 2.01; $p = 0.076$), but the confidence interval was much wider and statistical significance was lost because of reduced precision in the smaller subgroup, not attenuation of the point estimate. Given the small subgroup, unknown questionnaire timing and ADT status at assessment, unverified duration-code labels, and multiple exploratory comparisons, this counterintuitive association was considered hypothesis-generating only (Supplementary Table S6).

4. Discussion

In this single-center cross-sectional cohort, greater urinary and bowel symptom burden showed the most consistent inverse relationships with global HRQoL. This pattern was supported by HC3-robust univariable models and Spearman correlations. However, once urinary, bowel, and hormonal symptoms, age, and ADT were considered simultaneously, no individual symptom domain showed a statistically significant independent association. The direction of urinary and bowel coefficients remained negative across leave-one-out analyses, but statistical precision was limited. The findings therefore support an association between symptom burden and global HRQoL at the cross-sectional level without demonstrating a causal or independent treatment effect.

The magnitude of the observed associations may be clinically informative even when confidence intervals are emphasized over dichotomous significance testing. In robust univariable analyses, a 10-point higher urinary score corresponded to approximately 4.6 points lower global HRQoL, and a 10-point higher bowel score to approximately 5.3 points lower global HRQoL. In the multivariable model, these estimates attenuated to −3.6 and −2.6 points per 10 symptom-score points and their confidence intervals included no association. These effect sizes are best interpreted as descriptive measures of concurrent symptom–HRQoL relationships rather than longitudinal changes.

Prospective studies demonstrate why assessment timing matters. CHHiP collected baseline and prespecified serial PROs and found similar long-term urinary and bowel outcomes across fractionation schedules [7]. In the longitudinal EORTC study by Maggio et al., several QLQ-C30 domains worsened at radiotherapy completion and generally recovered by six months [8]. The long-term PROFIT PRO analysis assessed outcomes at the baseline and at 24 and 48 months and found no significant differences in urinary, bowel, sexual, hormonal, or general HRQoL between 60 Gy in 20 fractions and conventional fractionation [9]. Similarly, the contemporary population-based Victorian cohort evaluated quality of life at a defined 12-month time point and found no statistically or clinically significant urinary or bowel differences between hypofractionated and conventionally fractionated radiotherapy [10]. In contrast, the present study lacks both baseline PROs and questionnaire dates; consequently, patients treated across 2010–2024 cannot be assigned to comparable post-treatment intervals, and the effects of recovery, aging, survivorship, and ongoing hormonal treatment cannot be disentangled.

The historical radiotherapy schedule also limits direct generalizability. Most patients received 75.9 Gy in 33 fractions of 2.30 Gy (tumor EQD2 approximately 82.4 Gy for $\alpha/\beta = 1.5$ Gy), whereas contemporary moderate hypofractionation commonly uses approximately 60–62 Gy in 20 fractions or 70 Gy in 28 fractions [3–6]. The present data should therefore be viewed as survivorship information from a dose-escalated IMRT/IGRT concept rather than as direct evidence for current moderate-hypofractionation schedules. Nevertheless, the cohort remains informative because it links EORTC general and prostate-specific PROs to routine treatment data within a highly conformal treatment program [18–21].

The mean global HRQoL score of 65 should not be labeled 'acceptable' in the absence of a pretreatment measurement or a formal comparison with age- and sex-specific German reference values [22]. Rather, it provides a descriptive cross-sectional anchor. A historical EORTC QLQ-C30/PR25 study from our field using 3D-conformal radiotherapy or an HDR boost reported broadly comparable global and urinary symptom levels, although differences in era, selection, dose, and follow-up prevent direct comparison [23]. Long-term treatment-comparison studies likewise show that radiotherapy, surgery, and surveillance have different urinary, bowel, sexual, and hormonal profiles [11–14]. The distinction between acute and late toxicity is also clinically relevant: an individual patient data meta-analysis of six randomized prostate radiotherapy trials found that acute grade 2 or greater genitourinary and gastrointestinal toxicity was associated with both subsequent late toxicity and clinically relevant decrements in corresponding patient-reported urinary and bowel quality of life [24].

The redesigned dosimetric analysis avoids the structural restriction that affected the previous complete-case model. The PTV including pelvic lymphatics was present only for the 19 patients who actually received pelvic irradiation and was not a missing all-patient variable. Mean-dose models could therefore use 52–54 patients. No clear mean-dose association was detected, but organ mean dose is a coarse exposure metric. Prospective data suggest that symptom-specific rectal dose-volume measures may be more informative [25,26], while whole-bladder dose–response relationships are complicated by filling, motion, and substructure exposure [27,28]. The incomplete and occasionally internally inconsistent historical detailed DVH data in this cohort further preclude strong dose-response conclusions.

The exploratory finding of fewer hormonal treatment-related symptoms among patients receiving pelvic irradiation remains biologically counterintuitive. Pelvic-irradiation patients were more likely to receive ADT, and ADT itself was associated with greater hormonal symptom burden. The pelvic-irradiation-by-ADT interaction was not significant. In the analysis restricted to 21 ADT-treated patients with available raw duration categories, the pelvic-irradiation point estimate was essentially unchanged, but the confidence interval widened substantially and the association no longer met the conventional significance threshold. This loss of precision in a small, selected subgroup, together with potential residual confounding, argues against interpreting the finding as a protective effect of pelvic irradiation. Unknown treatment status at PRO assessment, unknown assessment timing, and multiple testing further limit interpretation.

Strengths include the use of validated complementary EORTC instruments, linkage to real-world clinical and radiotherapy records, transparent re-analysis with heteroscedasticity-robust inference, explicit influence diagnostics, and separation of acute and late routine toxicity indicators. Limitations are substantial: small single-center sample size; cross-sectional HRQoL assessment; no pretreatment PROs; unavailable questionnaire completion dates and response-rate denominator; potential selection and survivor bias; unavailable structured comorbidity and prior-urological-procedure data; incomplete ADT timing/duration information; historical changes in planning systems and constraints; binary ungraded toxicity; and incomplete detailed DVH data. No alternative-treatment control group was included, and exploratory analyses were not multiplicity-adjusted.

5. Conclusions

Greater urinary and bowel symptom burden was consistently associated with lower global HRQoL in univariable HC3-robust and rank-based analyses. However, the robust multivariable model did not confirm an independent statistically significant effect for either domain. These findings support combined use of general and prostate-specific patient-reported outcomes in survivorship follow-up, while the cross-sectional design,

absence of baseline PROs, unknown post-treatment assessment timing, and modest sample size preclude conclusions about treatment-related determinants or longitudinal change. Prospective studies with baseline and scheduled follow-up assessments, standardized toxicity grading, and reliable substructure dose-volume data are needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/curroncol33120742/s1, Supplementary File S1: Table S1. HC3-robust univariable analyses and Spearman correlations between QLQ-PR25 domains and global HRQoL; Table S2. Conventional OLS sensitivity analyses for global HRQoL; Table S3. Diagnostics and influence analyses for the primary multivariable model; Table S4. HC3 multivariable sensitivity analysis after exclusion of uncertain boost and/or IGRT entries (complete-case $n = 50$); Table S5. Redesigned exploratory HC3 dosimetry analyses; Table S6. Exploratory analyses of pelvic irradiation, ADT, and hormonal treatment-related symptoms; Table S7. Sexual-functioning subgroup sensitivity analysis ($n = 15$).

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Informed Consent Statement: Informed consent to participate was obtained from all participants before study participation.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable data-protection and ethics requirements.

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Abbreviations

ADT, androgen deprivation therapy; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EQD2, equivalent dose in 2-Gy fractions; GI, gastrointestinal; GU, genitourinary; HRQoL, health-related quality of life; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; PSA, prostate-specific antigen; PTV, planning target volume; QLQ-C30, EORTC Quality of Life Questionnaire Core 30; QLQ-PR25, EORTC prostate cancer-specific quality-of-life module; RT, radiotherapy; SD, standard deviation; TNM, tumor-node-metastasis; VMAT, volumetric-modulated arc therapy.

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