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*Article*

# A 5-Year Follow-Up of Patient-Reported Outcome Measures Following External Beam Radiotherapy or Radical Prostatectomy in Localised Prostate Cancer

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**Abstract: Background/Objectives**: Late toxicity following radiotherapy is common and compromises patient quality of life. However, the impact of toxicity on patient-reported outcome measures (PROMs) five years after prostate external beam radiotherapy (EBRT) is poorly characterised. We describe PROMs using the Expanded Prostate Cancer Index Composite (EPIC-26) five years post-EBRT compared against radical prostatectomy (RP). **Methods**: A prospective cohort of patients with localised prostate cancer treated from 2000 to 2020 captured by a state-level cancer registry was analysed. Multivariable mixed-effects linear modelling was performed to compare differences between EPIC-26 domains over time between ERBT and RP patients. The percentage of patients recording a decline in EPIC-26 domains compared with baseline which exceeded the minimal clinically important difference (MCID) was calculated and compared between groups. Additionally, subgroup analysis was performed on patients treated using contemporary techniques. **Results**: There were 1720 patients (EBRT n = 1441 vs. RP n = 279) with evaluable EPIC-26 PROMS. Patients in the EBRT group had a higher median age (74 vs. 66, $p < 0.001$) and National comprehensive Cancer Network (NCCN) high-risk disease (61% vs. 24%, $p < 0.001$). Bowel domain scores were worse after EBRT compared to RP (beta −0.46, 95% CI −1.20–−0.28, $p < 0.001$), with a greater proportion of patients reporting a change in symptoms that exceeded the MICD at 12 months (22 vs. 11%, $p = 0.009$). Moderate/big bowel bother scores were significantly higher in the EBRT cohort at baseline and all follow-up periods compared to RP (beta −8.27, 95% CI −10.21–−6.34, $p < 0.001$). Pad use (i.e., ≥1) per day was significantly lower amongst the EBRT group (beta 16.56, 95% CI 14.35–18.76, $p < 0.001$). Despite contemporary techniques, EBRT was associated with worse bowel domain scores at 12 (75 vs. 80, $p < 0.05$) and 60 months (75 vs. 80, $p < 0.05$) compared to RP; however, EBRT was associated with less pad use at 12 (4% vs. 34%, $p < 0.001$), 24 (10% vs. 33%, $p < 0.001$) and 60 months (13% vs. 33%, $p = 0.15$) than RP. **Conclusions**: There are significant differences in PROMs after local curative treatment for prostate cancer which persist to five years post-treatment, despite contemporary techniques. Understanding the associated toxicity patterns helps inform shared decision-making during pre-treatment counselling.



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**Keywords:** prostate cancer; radiotherapy; radical prostatectomy; patient-reported outcome measures; EPIC-26; quality of life

## 1. Introduction

Patients with localised prostate cancer who undergo either primary external beam radiotherapy (EBRT) or radical prostatectomy (RP) often suffer treatment-related adverse effects which impair patient quality of life. A growing population of men is at risk of developing these adverse effects because of the increasing incidence of the disease, the ageing population, and prolonged survival following treatment [1]. The importance of patient-reported outcome measures (PROMs) has been demonstrated by multiple studies which show their superior accuracy in determining the incidence of treatment-related adverse events compared to clinician-reported outcomes [2,3]. However, there is a lack of high-quality population-level studies which compare PROMs following EBRT or RP in patients with localised prostate cancer [4]. There are very few studies that have included five-year follow-up outcomes [1,5]. In addition, there are few population-based comparative studies [1,6,7], most of which lack a validated PROM instrument [1,6] or contain heterogeneous radiotherapy treatments (e.g., adjuvant/salvage treatment, combination EBRT + Brachytherapy) [5,6].

Hence, the primary aim of this study is to describe five-year PROMs post primary curative intent EBRT alone for localised prostate cancer and to compare outcomes against patients treated with radical prostatectomy. The secondary aims are to describe and compare baseline characteristics between the groups and to perform subgroup analysis on a cohort of patients treated using contemporary techniques.

## 2. Methods

### 2.1. Study Population

We analysed a state population-level cohort of patients with non-metastatic prostate cancer who underwent radical prostatectomy (open radical retropubic prostatectomy [ORRP] or robotic-assisted laparoscopic prostatectomy [RALP]) or EBRT in South Australia between 1 January 1998 and 31 January 2019, as prospectively captured by the South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCCOC) registry. The SA-PCOCC registry prospectively recruits >90% of patients diagnosed with prostate cancer in South Australia. Patients were invited to complete the Expanded Prostate Cancer Index Composite (EPIC-26) quality of life questionnaire via a paper-based survey at diagnosis and 3, 6, 12, 24 and 60 months post-diagnosis. Men treated with salvage or adjuvant radiotherapy were excluded because these treatments can lead to additional toxicity. Men with concurrent bladder cancer (ICD-10-AM code 'C67') were also excluded.

### 2.2. Study Variable and Outcome

EPIC-26 function domain scores and bother symptoms were reported separately [8]. EPIC-26 domain scores were determined for urinary continence, urinary irritation/obstruction, bowel, sexual and hormonal function and presented as a 0–100 score. Higher domain scores indicate better function [9–11]. Minimum clinically important difference (MCID) presents the amount of change that results in a clinically discernible difference to patients. MCID was defined as 12 points for sexual function [7,12], 6 for urinary incontinence [7,12], 5 for urinary irritative symptoms [7,12], 4 for bowel function [12], and 4 for hormonal function [7,12]. The proportions of patients who reported a decline in each domain which exceeds the

MCID was determined and compared between treatment groups at each follow-up interval. The bother items were dichotomised into moderate/big bother and small/very small/no bother, consistent with cut-off points reported elsewhere [11,13–15]. We report specific items from the urinary and sexual domains because of their relevance in daily clinical practice for both patients and their physicians [5]. Urinary continence pad usage was dichotomised into 'no pads per day' and '≥1 pad per day' [11,16].

### *2.3. Statistical Analysis*

Descriptive statistics were used to compare differences in patient demographic characteristics between the treatment groups as well as between patients with and without PROMS data. Differences between continuous variables were compared using Wilcoxon rank-sum tests, and differences between categorical variables were compared using Fisher's exact tests or chi-squared tests, depending on sample size at each follow-up interval. The proportions of patients in each treatment group who reached the MCID in deterioration of EPIC-26 domain scores were described and compared at each follow-up interval. Mixed-effects linear regression was performed for each outcome to compare overall differences between the curves [16]. To accurately measure the association between treatment groups and domain score over time, the models were adjusted for age at diagnosis, comorbidity, National comprehensive Cancer Network (NCCN) disease risk and baseline EPIC domain score. The correlation of treatment with each adverse event outcome score was presented as a beta coefficient estimate with a 95% confidence interval and a *p*-value [17]. Statistical significance was set at $p < 0.05$.

Propensity score matching was attempted but was unsuccessful due to inadequate sample sizes remaining at 60 months after matching. Subgroup analysis was performed on a cohort of patients treated from 2010 onwards, which indicates the transition towards contemporary techniques with the evolution of intensity-modulated radiotherapy and image-guided radiotherapy as well as the adoption of robotic laparoscopic-assisted prostatectomy in South Australia (Supplementary Table S1). Additional intra-group comparisons (EBRT before 2010 vs. EBRT after 2010 (Supplementary Table S2), RP before 2010 vs. RP after 2010 [Supplementary Table S3]). Whilst treatment data, including the type of surgery (open retropubic and RALP), was available to the investigators, this has not been included in the subgroup analysis due to the risk of attribution disclosure. The STROBE checklist was followed in reporting this observational study.

## 3. Results

Of the 3279 eligible patients, 1103 patients (n = 824 RP, n = 279 EBRT) had evaluable PROMS data. (Figure 1) Table 1 summarises and compares the demographic patient characteristics of patients treated by RP and EBRT. Patients treated by EBRT had a higher median (IQR) age (74 [69–77] vs. 66 [62–70], $p < 0.001$) and were more likely to have high NCCN risk disease (n = 167 [61%] vs. n = 190 [24%], $p < 0.001$) and to receive androgen deprivation therapy (ADT) (n = 105 [38%] vs. n = 13 [2%], $p < 0.001$). Patients treated with EBRT had shorter median (IQR) length in follow-up (4 [3, 6] vs. 5 [3, 8], $p < 0.001$).

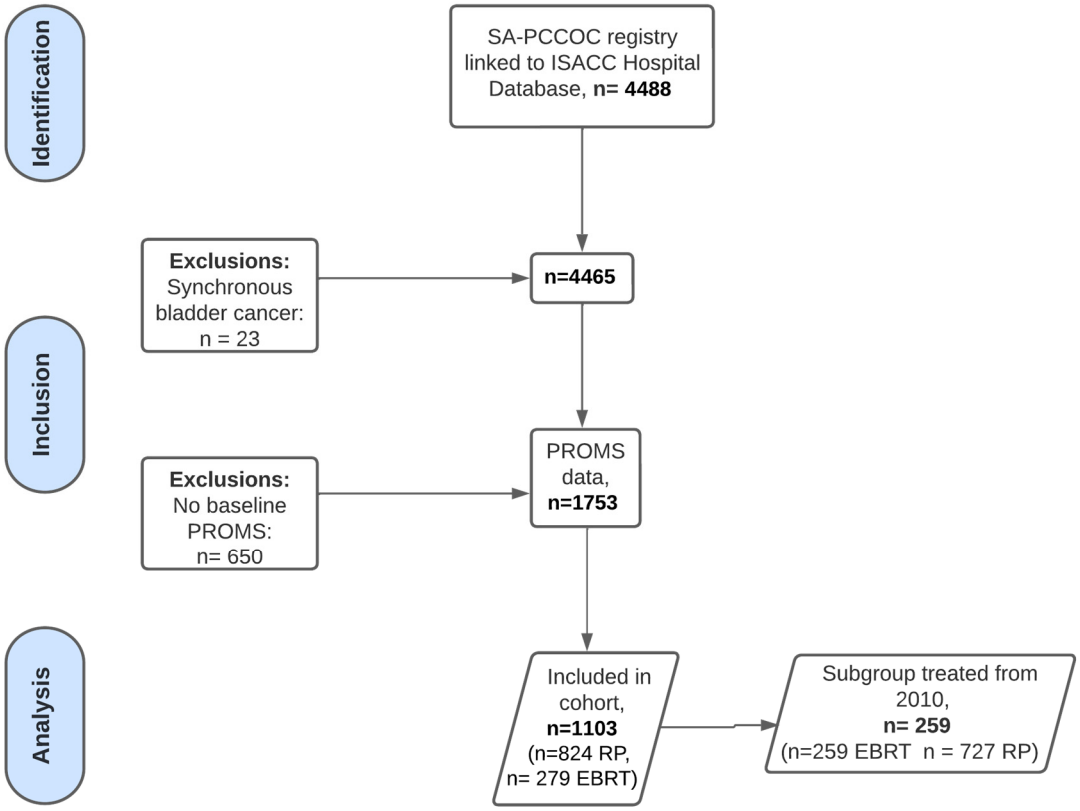


**Figure 1.** Flow chart of patient selection process.

**Table 1.** (**a**) Comparison of demographic characteristics of included patients with evaluable PROMS. (**b**) Comparison of demographic characteristics of included patients with evaluable PROMS pre- and post-2010.

| (a) Characteristic | Overall, N = 1103 [1] | Treatment Modality RP, N = 824 [1] | EBRT, N = 279 [1] | *p*-Value [2] |
|---|---|---|---|---|
| Age at Diagnosis | 68 (63, 72) [1] | 66 (62, 70) [1] | 74 (69, 77) [1] | <0.001 [2] |
| Charlson Score | 0 (0, 1) | 0 (0, 1) | 1 (0, 2) | <0.001 [3] |
| NCCN Risk Category | | | | <0.001 [3] |
| High | 357 (33%) | 190 (24%) | 167 (61%) | |
| Intermediate | 482 (45%) | 407 (51%) | 75 (27%) | |
| Low | 232 (22%) | 201 (25%) | 31 (11%) | |
| (Missing) | 32 (2.9%) | 26 (3.2%) | 6 (2.2%) | |
| initial prostate-specific antigen | 7 (5, 10) | 7 (5, 9) | 10 (7, 15) | <0.001 [3] |
| (Missing) | 89 (8%) | 67 (8.1%) | 22 (7.8%) | |
| iPSA Level | | | | <0.001 [3] |
| 1. <4 | 90 (9%) | 77 (10%) | 13 (5%) | |
| 2. 4–10 | 660 (65%) | 544 (72%) | 116 (45%) | |
| 3. >10 | 264 (26%) | 136 (18%) | 128 (50%) | |
| (Missing) | 89 (8.1%) | 67 (8.1%) | 22 (7.9%) | |
| Gleason Grade | | | | <0.001 [3] |
| 1. <7 | 311 (28%) | 264 (32%) | 47 (17%) | |
| 2. 3 + 4 | 366 (34%) | 305 (37%) | 61 (22%) | |
| 3. 4 + 3 | 196 (18%) | 136 (17%) | 60 (22%) | |
| 4. >7 | 219 (20%) | 109 (13%) | 110 (40%) | |
| (Missing) | 11 (0.1%) | 10 (1.2%) | 1 (0.4%) | |
| ADT | 118 (11%) | 13 (2%) | 105 (38%) | <0.001 [3] |

**Table 1.** *Cont.*

| (a) Characteristic | Overall, N = 1103 [1] | Treatment Modality RP, N = 824 [1] | EBRT, N = 279 [1] | *p*-Value [2] |
|---|---|---|---|---|
| Operation Type | | | | |
| Open | 115 (14%) | 115 (14%) | 0 (NA%) | |
| RALP | 703 (86%) | 703 (86%) | 0 (NA%) | |
| (Missing) | 285 (25.8%) | 6 (0.7%) | 279 (NA%) | |
| Dose Gy | 78 (74, 78) [1] | NA (NA, NA) | 78 (74, 78) [1] | |
| (Missing) | 832 (75.4%) | 824 (NA%) | 8 (2.9%) | |
| Fractions | 39 (37, 39) [1] | NA (NA, NA) | 39 (37, 39) [1] | |
| (Missing) | 832 (74.6%) | 824 (NA%) | 8 (2.9%) | |
| Treatment Date | | | | <0.001 [3] |
| 1. <2010 | 108 (10%) | 97 (12%) | 11 (4%) | |
| 2. ≥2010 | 995 (90%) | 727 (88%) | 268 (96%) | |
| Follow-Up Years | 5 (3, 7) [1] | 5 (3, 8) [1] | 4 (3, 6) [1] | <0.001 [2] |

| (b) | Unmatched Cohort with Evaluable Baseline and 60-month PROMs | | | |
|---|---|---|---|---|
| **Characteristic** | **Overall (N = 264)** | **<2010 (N = 17)** | **>=2010 (N = 247)** | ***p*-value** |
| Treatment Modality | | | | 0.14 |
| RP | 226 (86%) | 17 (100%) | 209 (85%) | |
| EBRT | 38 (14%) | 0 (0%) | 38 (15%) | |
| Operation Type | | | | 0.54 |
| Open | 48 (21%) | 2 (12%) | 46 (22%) | |
| RALP | 178 (79%) | 15 (88%) | 163 (78%) | |
| (Missing) | 38 | 0 | 38 | |
| Dose Gy | | | | |
| Median (IQR) | 77 (74, 78) | NA (NA, NA) | 77 (74, 78) | |
| (Missing) | 226 | 17 | 209 | |
| Fractions | | | | |
| Median (IQR) | 38 (37, 39) | NA (NA, NA) | 38 (37, 39) | |
| (Missing) | 226 | 17 | 209 | |
| ADT | 19 (7%) | 0 (0%) | 19 (8%) | 0.62 |

[1] n (%); median (IQR); [2] Wilcoxon rank sum test; [3] Pearson's chi-squared test.

Patients who completed PROMs appeared to be significantly different from those who did not complete PROMs. Supplementary Table S1 summarises and compares the demographic characteristics of patients who did and did not complete PROMS. Patients who completed PROMS had fewer GU admissions (157 [9%] vs. 439 [16%], $p < 0.001$) and gastrointestinal (GI) admissions (64 [4%] vs. 247 [9%], $p < 0.001$).

Table 2 and Figure 2 compare EPIC-26 Domain Function Scores between RP and EBRT cohorts at baseline and follow-up intervals. Similarly, Table 3 and Figure 3 compare moderate/big bother scores between groups. Patients managed with ERBT had higher EPIC-26 domain function scores for bowel (13 [5%] vs. 8 [16%], $p = 0.012$) and urinary bother (26 [10%] vs. 11 [21%], $p = 0.025$) in the initial 24 months. However, patients who underwent RP had higher rates of pad use per day compared to ERBT after 12 months (146 [34%] vs. 3 [4%], $p < 0.001$) and at 60 months for follow-up (72 [33%] vs. 5 [13%], $p = 0.015$). Table 4 summarises and compares the proportion of patients with a MCID in EPIC-26 domain scores at follow-up intervals between treatment groups. Patients who had ERBT were more likely to experience MCID bowel changes than RP patients at 12 months (41 [9%] vs. 20 [26%], $p < 0.001$) and 60 months (35 [15%] vs. 13 [34%], $p = 0.006$). Additionally, patients managed with ERBT were more likely to have reached the MCID in urinary irritative (35 [15%] vs. 11 [29%], $p = 0.43$) and urinary incontinence domain scores (57 [25%] vs. 4 [11%], $p = 0.047$) at 60 months.

**Table 2.** Comparison of EPIC-26 domain scores amongst patients with evaluable PROMS.

| | Baseline | | | | 12 Months | | | | 24 Months | | | | 60 Months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Overall, N = 1103** [1] | **RP, N = 824** [1] | **EBRT, N = 279** [1] | ***p*-Value** [2] | **Overall, N = 516** [1] | **RP, N = 439** [1] | **EBRT, N = 77** [1] | ***p*-Value** [2] | **Overall, N = 311** [1] | **RP, N = 259** [1] | **EBRT, N = 52** [1] | ***p*-Value** [2] | **Overall, N = 264** [1] | **RP, N = 226** [1] | **EBRT, N = 38** [1] | ***p*-Value** [2] |
| Bowel | 81 (7) | 81 (7) | 80 (9) | 0.7 | 80 (8) | 81 (6) | 73 (14) | <0.001 | 79 (8) | 80 (7) | 76 (12) | 0.002 | 78 (10) | 79 (9) | 73 (15) | 0.004 |
| (Missing) | 68 | 46 | 22 | | 21 | 18 | 3 | | 12 | 9 | 3 | | 13 | 9 | 4 | |
| Urinary Irritative/Obstructive | 84 (16) | 86 (15) | 80 (17) | <0.001 | 91 (11) | 92 (10) | 82 (16) | <0.001 | 90 (12) | 91 (12) | 84 (14) | <0.001 | 90 (13) | 90 (13) | 89 (12) | 0.49 |
| (Missing) | 93 | 54 | 39 | | 37 | 25 | 12 | | 18 | 11 | 7 | | 25 | 21 | 4 | |
| Urinary Incontinence | 89 (18) | 89 (18) | 87 (17) | 0.005 | 74 (23) | 73 (23) | 83 (20) | <0.001 | 75 (23) | 74 (24) | 81 (22) | 0.016 | 74 (25) | 72 (26) | 84 (17) | 0.012 |
| (Missing) | 87 | 52 | 35 | | 37 | 26 | 11 | | 28 | 24 | 4 | | 21 | 18 | 3 | |
| Hormonal | 90 (13) | 91 (12) | 86 (15) | <0.001 | 88 (14) | 90 (12) | 78 (19) | <0.001 | 89 (15) | 90 (13) | 80 (23) | 0.022 | 88 (15) | 89 (15) | 85 (17) | 0.22 |
| (Missing) | 141 | 86 | 55 | | 44 | 34 | 10 | | 32 | 23 | 9 | | 27 | 22 | 5 | |
| Sexual | 58 (30) | 62 (29) | 41 (27) | <0.001 | 33 (27) | 34 (27) | 24 (19) | 0.057 | 36 (30) | 38 (30) | 22 (16) | 0.071 | 37 (28) | 39 (29) | 21 (12) | 0.043 |
| (Missing) | 299 | 175 | 124 | | 178 | 137 | 41 | | 106 | 79 | 27 | | 99 | 78 | 21 | |

[1] Mean (SD); [2] Wilcoxon rank sum test.

**Table 3.** Comparison of EPIC-26 bother scores amongst patients with evaluable PROMS.

| | Baseline | | | | 12 Months | | | | 24 Months | | | | 60 Months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Overall, N = 1103** [1] | **RP, N = 824** [1] | **EBRT, N = 279** [1] | ***p*-Value** [2] | **Overall, N = 516** [1] | **RP, N = 439** [1] | **EBRT, N = 77** [1] | ***p*-Value** [3] | **Overall, N = 311** [1] | **RP, N = 259** [1] | **EBRT, N = 52** [1] | ***p*-Value** [3] | **Overall, N = 264** [1] | **RP, N = 226** [1] | **EBRT, N = 38** [1] | ***p*-Value** [3] |
| Bowel Bother | 64/1086 (6%) | 38/813 (5%) | 26/273 (10%) | 0.003 | 29/511 (6%) | 17/435 (4%) | 12/76 (16%) | <0.001 | 21/307 (7%) | 13/256 (5%) | 8/51 (16%) | 0.012 | 18/263 (7%) | 13/225 (6%) | 5/38 (13%) | 0.2 |
| (Missing) | 17 | 11 | 6 | | 5 | 4 | 1 | | 4 | 3 | 1 | | 1 | 1 | 0 | |
| Urinary Bother | 147/1074 (14%) | 92/806 (11%) | 55/268 (21%) | <0.001 | 54/505 (11%) | 43/428 (10%) | 11/77 (14%) | 0.3 | 37/309 (12%) | 26/257 (10%) | 11/52 (21%) | 0.025 | 29/262 (11%) | 28/224 (12%) | 1/38 (3%) | 0.092 |
| (Missing) | 29 | 18 | 11 | | 11 | 11 | 0 | | 2 | 2 | 0 | | 2 | 2 | 0 | |
| Pads per day | 63/1069 (6%) | 51/804 (6%) | 12/265 (5%) | 0.3 | 149/500 (30%) | 146/425 (34%) | 3/75 (4%) | <0.001 | 84/292 (29%) | 79/241 (33%) | 5/51 (10%) | <0.001 | 77/258 (30%) | 72/220 (33%) | 5/38 (13%) | 0.015 |
| (Missing) | 34 | 20 | 14 | | 16 | 14 | 2 | | 19 | 18 | 1 | | 6 | 6 | 0 | |
| Sexual Bother | 211/904 (23%) | 156/710 (22%) | 55/194 (28%) | 0.063 | 179/405 (44%) | 156/351 (44%) | 23/54 (43%) | 0.8 | 107/249 (43%) | 94/216 (44%) | 13/33 (39%) | 0.7 | 79/210 (38%) | 71/182 (39%) | 8/28 (29%) | 0.3 |
| (Missing) | 199 | 114 | 85 | | 111 | 88 | 23 | | 62 | 43 | 19 | | 54 | 44 | 10 | |
| Haematuria Bother | 16/1029 (2%) | 10/782 (1%) | 6/247 (2%) | 0.2 | 1/487 (0%) | 1/420 (0%) | 0/67 (0%) | >0.9 | 1/298 (0%) | 1/251 (0%) | 0/47 (0%) | >0.9 | 3/243 (1%) | 3/207 (1%) | 0/36 (0%) | >0.9 |
| (Missing) | 74 | 42 | 32 | | 29 | 19 | 10 | | 13 | 8 | 5 | | 21 | 19 | 2 | |

[1] n/N (%); [2] Pearson's chi-squared test; [3] Pearson's chi-squared test.

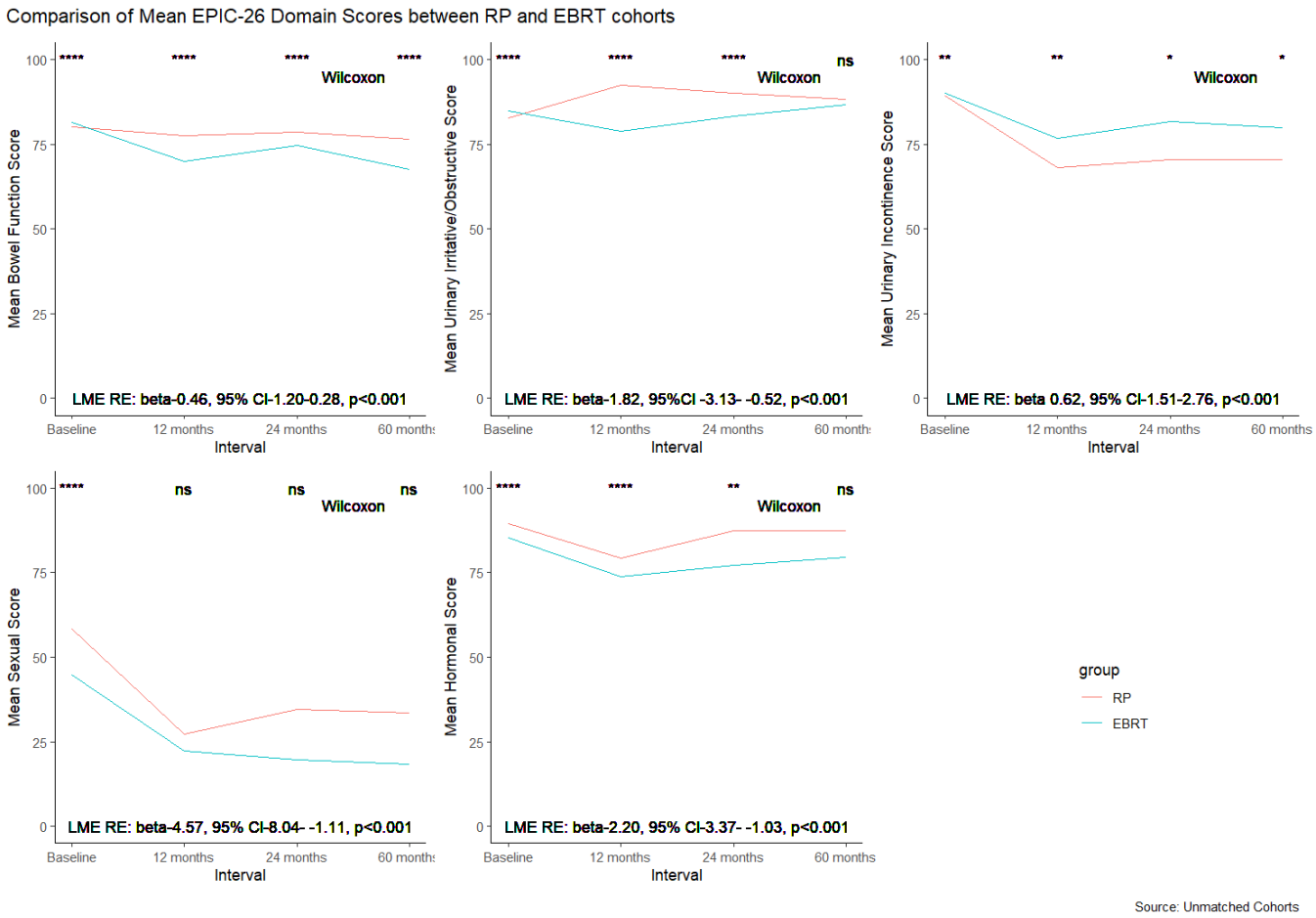


**Figure 2.** Comparison of mean EPIC-26 domain scores between EBRT and RP cohorts. Linear mixed-effects model with random effects (LME RE) of ERBT (blue) vs. RP (red) over each EPIC-26 domain at set treatment intervals (0, 12, 24, and 60 months). ns: Not significant, $p \geq 0.05$; *: Statistically significant, $0.01 \leq p < 0.05$; **: Highly significant, $0.001 \leq p < 0.01$; ****: Extremely significant, $p < 0.0001$.

Subgroup analysis determined significant differences between the groups despite contemporary techniques. (Supplementary Table S2) Mean bowel domain scores were worse after EBRT at 12 (75 vs. 80, $p < 0.05$) and 60 months (75 vs. 80, $p < 0.05$), including a higher proportion of patients with MCID at 12 months (21% vs. 10%, $p = 0.008$). (Figure 2, Supplementary Table S3).

The subgroup analysis revealed significant associations between EBRT and EPIC-26 scores, adjusting for confounders including age, comorbidities (Charlson score), NCCN risk, baseline EPIC-26 score, and interval. Notably, EBRT showed significant effects on various domain scores: bowel ($\beta = -0.46$, 95% CI: $-0.28$ to $-1.20$, $p < 0.001$), urinary irritative/obstructive ($\beta = -1.82$, 95% CI: $-0.52$ to $-3.13$, $p < 0.001$), urinary incontinence ($\beta = 0.62$, 95% CI: $-1.51$ to $-2.76$, $p < 0.001$), sexual ($\beta = -4.67$, 95% CI: $-1.11$ to $-8.04$, $p < 0.001$), hormonal ($\beta = -2.20$, 95% CI: $-1.03$ to $-3.37$, $p < 0.001$), moderate/big bother bowel ($\beta = -8.27$, 95% CI: $-6.34$ to $-10.21$, $p < 0.001$), moderate/big bother urinary ($\beta = -4.75$, 95% CI: $-2.24$ to $-7.26$, $p < 0.001$), moderate/big bother sexual ($\beta = 0.97$, 95% CI: $-0.88$ to 2.81, $p < 0.001$), and pads per day $\geq 1$ ($\beta = 16.56$, 95% CI: 14.35 to 18.76, $p < 0.001$). Age, Charlson score, NCCN, baseline score, and interval also exhibited significant associations with these scores (all $p < 0.001$).

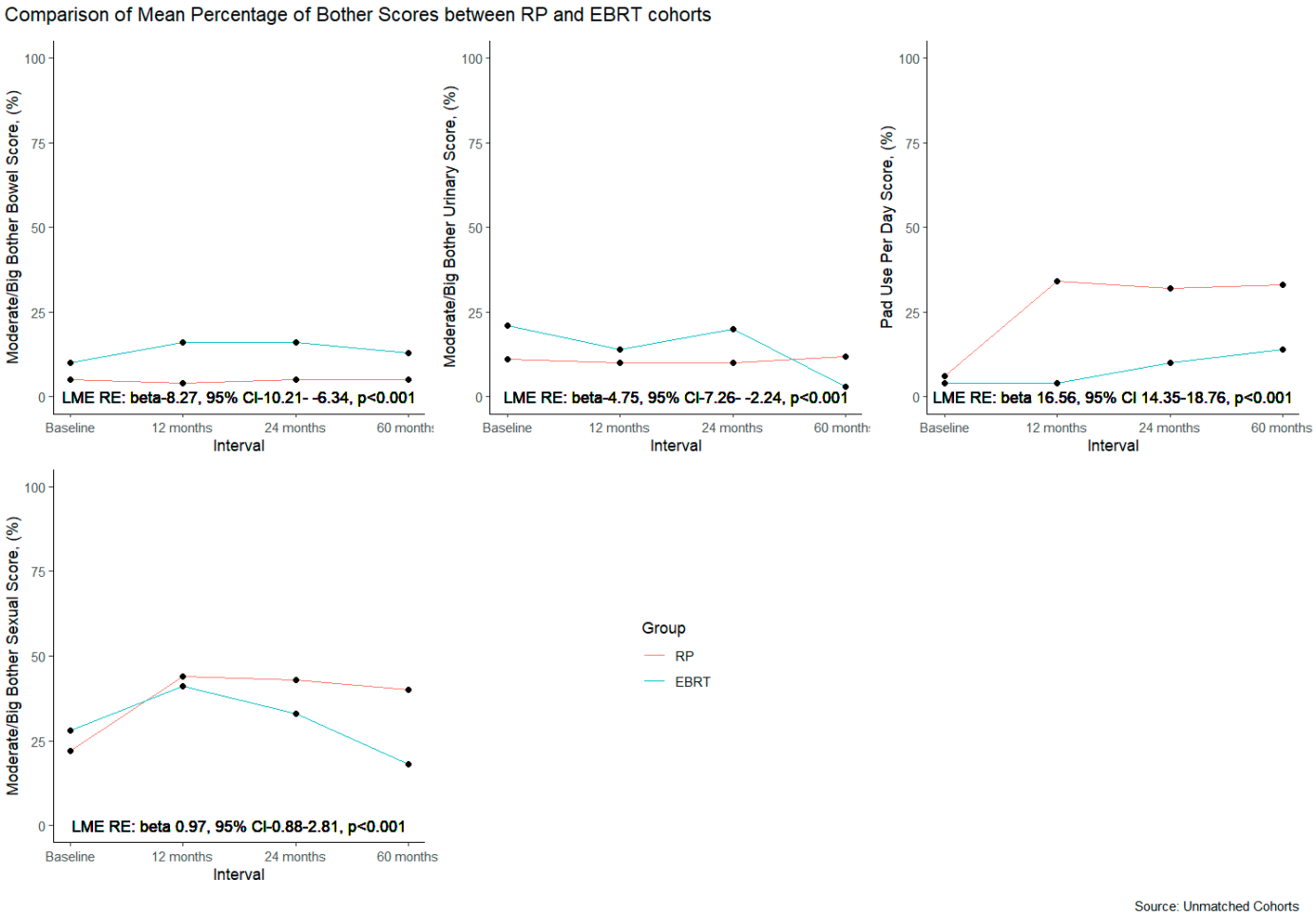


**Figure 3.** Sub-group comparison of mean EPIC-26 moderate/big bother scores between EBRT and RP cohorts. Linear mixed-effects model with random effects (LME RE) of ERBT (blue) vs. RP (red) over each EPIC-26 domain at set treatment intervals (0, 12, 24, and 60 months).

**Table 4.** Patients reporting PROM changes exceeding the MCID compared to baseline.

| | 12 Months | | | | 24 Months | | | | 60 Months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Overall, N = 516** [1] | **RP, N = 439** [1] | **EBRT, N = 77** [1] | ***p*-Value** [2] | **Overall, N = 311** [1] | **RP, N = 259** [1] | **EBRT, N = 52** [1] | ***p*-Value** [2] | **Overall, N = 264** [1] | **RP, N = 226** [1] | **EBRT, N = 38** [1] | ***p*-Value** [3] |
| Hormonal change | 63/516 (12%) | 52/439 (12%) | 11/77 (14%) | 0.5 | 56/311 (18%) | 49/259 (19%) | 7/52 (13%) | 0.35 | 54/264 (20%) | 48/226 (21%) | 6/38 (16%) | 0.44 |
| Bowel Change | 61/516 (12%) | 41/439 (9%) | 20/77 (26%) | <0.001 | 50/311 (16%) | 39/259 (15%) | 11/52 (21%) | 0.27 | 48/264 (18%) | 35/226 (15%) | 13/38 (34%) | 0.006 |
| UO (urinary obstruction) Change | 82/516 (16%) | 65/439 (15%) | 17/77 (22%) | 0.11 | 57/311 (18%) | 46/259 (18%) | 11/52 (21%) | 0.56 | 46/264 (17%) | 35/226 (15%) | 11/38 (29%) | 0.043 |
| UI (urinary incontinence) Change | 105/516 (20%) | 94/439 (21%) | 11/77 (14%) | 0.2 | 73/311 (23%) | 66/259 (25%) | 7/52 (13%) | 0.062 | 61/264 (23%) | 57/226 (25%) | 4/38 (11%) | 0.047 |
| Sexual Change | 40/516 (8%) | 36/439 (8%) | 4/77 (5%) | 0.4 | 44/311 (14%) | 41/259 (16%) | 3/52 (6%) | 0.057 | 32/264 (12%) | 31/226 (14%) | 1/38 (3%) | 0.059 |

[1] n/N (%); [2] Pearson's chi-squared test; [3] Pearson's chi-squared test.

## 4. Discussion

This is the first prospective population-level study to directly compare EPIC-26 scores amongst a cohort of men with clinically localised prostate cancer treated with contemporary techniques over five years of follow-up. Despite the use of contemporary radiotherapy techniques amongst patients with localised prostate cancer, EBRT after 2010 was associated with significantly worse 12- and 60-month bowel domain scores and higher percentages of MCID at 12 months (21% vs. 10%, $p = 0.008$) than RP after 2010. Patients treated with

EBRT after 2010 had lower pad use per day at 12, 24, and 60 months and better urinary incontinence scores at 60 months (87 vs. 89, $p < 0.05$), but there was no statistically significant difference in MCID in either group ($p > 0.05$). However, whilst urinary incontinence scores improved over time in the RP after 2010 group, they progressively deteriorated in the EBRT after 2010 group. Similarly, the proportion of patients requiring daily pads, whilst higher post-RP after 2010 ($p < 0.05$), was increasing over time post-EBRT after 2010 (Supplementary Table S2).

Whilst several other studies compare EPIC-26 scores amongst men with localised prostate cancer treated with primary EBRT or RP [5,7,18–20], these mainly include significantly heterogeneous patient groups [5,18], outdated treatment techniques [18,19] and lack five-year follow-up data [7,20]. Moreover, there are very few population-based comparative studies of QOL outcomes amongst men with localised prostate cancer treated with primary EBRT or RP [1,6,7], of which many include heterogeneous treatment groups (e.g., primary and salvage, EBRT + Brachytherapy) [1,6], non-validated PROM instruments, [1,6] or lack five-year outcomes [7]. Furthermore, of the three RCTs comparing PROMS amongst men with localised prostate cancer treated with primary EBRT or RP [3,4] only 1 included PROMS beyond five years [21] and none include MCID scores to assess PROMS. The phase 3 non-inferiority CCHip Trial compared men treated with normofractionated (74Gy/37# [n = 696]) vs. hypofractionated (60Gy/20# [n = 698], 57Gy/19# [n = 706]) EBRT and limited to 24-month outcome data [3].

Despite bowel domain scores being significantly better at baseline in the EBRT group, bowel scores remained significantly worse until the 60-month follow-up (beta −0.46, 95% CI −1.20–0.28, $p < 0.001$). In addition, a higher proportion of patients with MCID in bowel domain score was identified at 12 months (22 vs. 11%, $p = 0.009$; Table 2; Figure 2) in the EBRT than the RP group. Moreover, the proportion of patients with moderate/big bowel bother scores was significantly higher in the EBRT cohort at baseline and all follow-up periods (beta −8.27, 95% CI −10.21–−6.34, $p < 0.001$; Table 2, Figure 3). Several other studies have similarly demonstrated worse bowel function associated with EBRT compared to radical prostatectomy; however, these mainly involve outdated radiotherapy techniques [4,18,22]. Donovan et al. analysed PROMS from the PROTECT trial (n = 1643) and determined worse bowel function amongst patients with localised prostate cancer six months after treatment with EBRT (3D-CRT, 74Gy/37#) compared to prostatectomy or active surveillance [4]. Other studies support our finding of bowel dysfunction persisting beyond 12 months post-treatment [18,22]. Yagi et al., in a single-institution study involving men with localised prostate cancer without ADT (RRP n = 101 vs. EBRT n = 23), determined that 3-year EPIC-26 bowel function and bother scores were significantly worse after EBRT [22]. Similarly, a conference article by Zhou et al. compared men with localised prostate cancer treated between 1955 and 1999 and found that treatment with RP was associated with better bowel function at 15-year follow-up [18]. However, this study was limited by significant differences between patient groups (age, comorbidity, baseline quality of life), the single-institution design and the use of outdated treatment techniques.

EBRT was associated with less pad use at 12 (4% vs. 34%, $p < 0.001$), 24 (10% vs. 33%, $p < 0.001$) and 60 months (13% vs. 33%, $p = 0.15$) than RP (Table 3). The systematic review by Baker et al. supported our findings that urinary incontinence, whilst initially worse after RP, improves over time but gradually deteriorates following EBRT [23]. A more recent cross-sectional study of men with low-risk prostate cancer (n = 219, RT vs. n = 69, RP vs. n = 120, AS) by Venderbos et al. similarly found that the RT group reported less mean (SD) urinary incontinence (86.5 [20.3] vs. 70.1 [28.8]) and fewer pads per day (8% vs. 38%) [5]. However, this study only involved a heterogeneous RT group (BT, EBRT, BT + EBRT) and a less rigorous one-time QoL questionnaire. Whilst the current study determines a lower

proportion of patients with MCID in urinary incontinence domain score at 60 months in the EBRT than the RP cohort, this is limited by small sample sizes in the former group (4/38 [11%] vs. 57/226 [25%], $p = 0.047$, Table 4).

We found that mean urinary irritative/obstructive domain scores were similar at baseline but significantly worse in the EBRT group over time (beta = −1.82, 95% CI −3.13–−0.52, $p < 0.001$; Figure 2); however, there was no statistically significant difference in MCID (Table 2). These findings are supported by the single-centre cross-sectional study by Zhou et al. [18], which compared RP and 3DCRT without IGRT (1995–1999) and reported worse EPIC-26 urinary irritative/obstructive domain scores in the EBRT group.

We found that the mean percentage of moderate/big urinary bother was higher amongst the EBRT group at baseline and at the 12- and 24-month follow-up intervals. The mean percentage of moderate/big urinary bother was lower at the 60-month interval following EBRT (beta −4.75, 95% CI −7.26–−2.24, $p < 0.001$; Figure 3); however, this may be due to the low sample sizes remaining at 60 months with evaluable data (n = 363, RP vs. n = 38, EBRT). The impact of EBRT on late patient-reported urinary toxicity far exceeds that reported by the recent ProtecT trial, which reported that urinary voiding and dysuria were similar between groups at 12 months [4]. The differences may be related to the increased mean (SD) age in our study compared to the ProtecT trial (73 [7] vs. 62 [5]) as well as higher proportions of patients with higher-risk disease.

We found that mean sexual domain scores were also lower (i.e., worse) in the EBRT group (beta= −4.57, 95% CI −8.04–−1.11, $p < 0.001$; Figure 2), with significant differences between groups in the proportions who reached the MCID at the 24-month (2 vs. 14%, $p = 0.017$) and 60-month (0 vs. 12%, $p = 0.019$) intervals (Table 2). However, there were no significant differences in sexual bother scores reported during follow-up (Table 3, Figure 3). This many have been due to several factors, including worse baseline sexual function scores in the ERBT group potentially relating to several factors, including more advanced age and likely a more comorbid population compared to RP. Many studies have reported more significant decreases in sexual function following RP compared to EBRT [18,22,24]. These studies include randomised controlled trials [4], population level and prospective multi-institution [19] studies. However, these studies often used outdated techniques [18,19] that did not report EPIC-26 [19], did not include five-year outcome data [5,18,22] or adjusted for significant differences in baseline characteristics between the groups [5,18,19,22]. Yagi et al. supported our finding that sexual function scores in the EBRT group progressively deteriorated over time, whereas the RP group gradually improved over time [22].

Patients treated with EBRT had significantly lower (i.e., worse) median hormonal domain scores at baseline (90 vs. 95, $p < 0.001$) and at all follow-up periods (beta= −2.20, 95% CI −3.37–−1.03, $p < 0.001$); Table 2; Figure 2). However, there were no significant differences in the proportion of patients within each group who reached MCID in hormonal domain scores at each interval ($p > 0.05$). Yagi et al. also found that both groups' EPIC-26 hormonal function and bother scores remained similar [22]. However, neither group received ADT, and the generalisability of the findings is limited by the single institution only [22].

This study has several limitations. Firstly, there were significant differences in the baseline characteristics between groups; however, age, comorbidity, NCCN disease risk and baseline EPIC-26 scores; this is likely representative of the relative safety of treatment modalities, as many of the patients in the ERBT may have been excluded from surgery due to significant comorbidities and increased morbidity and mortality risk. We attempted to adjust for these differences in our multivariable regression. ADT use was not controlled for in the model because concurrent ADT forms part of standard radiotherapy treatment for patients with intermediate and high-risk prostate cancer [25]. Additionally, the number of

patients who also had pelvic lymph node dissection or pelvic radiation was not available, which is a confounder that may have impacted patient EPIC-26 scores. Secondly, the definition of MCID may differ in the literature and between patients. Moreover, the aggregation of data from an observational cohort may fail to accurately describe the adverse events for individuals, such as personalised risk estimates. However, our use of a multivariable mixed-effects linear regression model aims to provide a reasonable estimate of adverse events experienced by individuals over repeated measures. Thirdly, there were low sample sizes remaining at 60 months, particularly amongst the EBRT group (n = 38), which will affect the accuracy of findings. However, the potential bias from missing data and group imbalance has been mitigated by the use of a linear mixed-effects model [16]. Finally, the study relies on the EPIC-26 score, which does not include measures of patient mood, satisfaction or cost analysis [26]. This study demonstrates the ongoing need for recurrent analysis of novel technology and techniques to monitor the toxicity profile and patterns associated with advancements in radical treatment options for localised prostate cancer to ensure updated and informed shared decision-making between patients and their clinicians in the pre-treatment counselling setting.

## 5. Conclusions

There are significant differences in PROMs after local curative treatment for prostate cancer which persist to five years post-treatment, despite contemporary techniques. Understanding the associated toxicity patterns and PROMs helps to advance the shared decision-making process during pre-treatment counselling, improving clinician and patient health literacy and expectations of treatment side effects.

**Supplementary Materials:** The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/siuj6020035/s1: Supplementary Table S1. Comparison of patients with PROMs vs. no PROMS; Supplementary Table S2. Subgroup analysis of patients treatment using contemporary techniques (RP VS EBRT $\geq$ 2010); Supplementary Table S3. Mixed-effects linear regression of relationship between EBRT and EPIC-26 scores with adjustment for age, comorbidity, NCCN risk, and baseline score.

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**Institutional Review Board Statement:** The SA-PCCOC database has been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Database access approval was granted by the SA-PCCOC steering committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee of SALHN HREC (approval date 25 February 2023) approval number 307.14.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The datasets presented in this article are not readily available because they belong to the SA-PCCOC organization. Requests to access the datasets should be directed to SA-PCCOC.

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