Impact of Preoperative LUTS on Health-related Quality of Life Following Radical Prostatectomy: A Propensity Score Matched Longitudinal Study

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OBJECTIVE To assess the impact of preoperative lower urinary tract symptoms (LUTS) on long-term health-related quality of life (HRQOL) up to 10 years after radical prostatectomy (RP) for prostate cancer (PC).

METHODS Within our prospective institutional database of 6487 patients treated with RP for PC (2008-2020), 2727 patients with preoperative LUTS (IPSS score of ≥8) were identified. A 1:1 propensity-score matched analysis of 3056 men (n = 1528 LUTS, n = 1528 no LUTS) was conducted. Primary endpoint was HRQOL (based on EORTC QLQ-C30 and PR25). Linear regression models tested the effect of preoperative LUTS on the net change in general HRQOL ($P < .05$).

RESULTS Median follow-up was 48 months. Preoperative mean global health status (GHS) score (67.4 vs 75.7) was significantly lower in the LUTS cohort ($P < .001$). Post-RP the difference in general HRQOL between the LUTS cohort and the no-LUTS cohort became smaller (65.7 vs 67.8), however, remaining statistically significant ($P = .037$). In long-term follow-up, general HRQOL was comparable between both subcohorts (P-range 0.716-0.876). Multivariable linear regression analysis revealed increased preoperative IPSS as an independent predictor for increased perioperative improvement of IPSS ($P < .001$)

CONCLUSION For patients undergoing RP, preoperative LUTS were associated with a postoperative improvement of HRQOL outcomes. In long-term follow-up, HRQOL was comparable to patients without preoperative LUTS. Hence, RP is an efficient option to treat PC as well as LUTS in those patients. UROLOGY 192: 52–58, 2024.

Radical prostatectomy (RP) is a standard curative treatment option for organ-confined as well as locally advanced prostate cancer (PC).[1] Since lower urinary tract symptoms (LUTS) as well as PC are common in elderly men,[2,3] many patients who undergo RP suffer from concomitant LUTS, mostly due to benign prostate hyperplasia (BPH). Originally, male LUTS was thought to be merely related to benign prostatic obstruction (BPO). Since RP reduces BPO, the common opinion would be that RP automatically relieves LUTS. However, this rather simplistic causal relationship between prostatic overgrowth, progressive urethral obstruction, and concomitant LUTS, has been challenged.[4] Furthermore, there is evidence showing de novo development of LUTS following RP.[5,6] Several previous studies have assessed the effect of LUTS prior RP on functional outcome, reporting controversial results which are predominantly based on data from historic cohorts with limited follow-up[7-9] With growing awareness for the importance of patient-reported outcome measures (PROMs), it could be shown that LUTS as well as RP have a pronounced impact on HRQOL.[10,11] Current literature, however, lacks evidence on the impact of LUTS prior RP on long-term HRQOL.

Driven by this paucity of data, we conducted the first propensity-score matched analysis of a large contemporary cohort of patients who underwent RP for prostate cancer with or without severe LUTS prior surgery. Hereby, we tested the hypothesis that RP leads to

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improved HRQOL in patients who suffered from LUTS prior surgery.

PATIENTS AND METHODS

Patient Population, Study Design and Data Assessment

After approval by a local institutional ethics committee (#20–1022), 6487 patients from a prospective institutional database who underwent RP for PC between January 2008 and December 2020 were identified. Surgical techniques in our department have been described before.[12] 5489 patients met the inclusion criteria for the current study which encompassed: surgery performed by high-volume surgeons with more than 200 previous RP. Exclusion criteria were preoperative imaging indicative for metastatic disease (n = 95), neoadjuvant treatment prior RP (n = 87), and patients with incomplete data or lost to follow-up (n = 620).

Patients were stratified by preoperative LUTS assessed by the validated International Prostate Symptom Score (IPSS)-questionnaire.[13] As per well-established cut-off values, LUTS in need of treatment were defined as an IPSS of ≥8.[3]

Propensity-score matching (PS-matching) limited to eligible patients with complete follow-up was created applying the following matching variables: age, BMI, pT-stage, Gleason grade, positive surgical margin rate, and robotic-assisted-RPs (RALP). PS-matching was conducted in a 1:1 manner, applying nearest neighbor matching with a matching tolerance of 0.0001, resulting in a matched cohort of 3056 patients (n = 1528 patients with IPSS≥ 8 [LUTS], n = 1528 patients with IPSS < 8 [no LUTS]). A flow chart illustrating the patient selection is provided in Supplementary Figure 1.

Outcomes

Primary endpoint was HRQOL based on validated questionnaires. Assessment of HRQOL was performed using a validated translation of the standardized European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its prostate-specific QLQ-PR25 add-on.[14,15] The QLQ-C30 incorporates 15 single- and multi-item scales: 5 functional scales (higher scores reflecting better functioning), 9 symptom scales (higher scores higher scores reflecting more symptoms) and a global health status (GHS) scale representing general HRQOL (higher scores reflecting better general HRQOL).[14] According to established cut-off values, "good general HRQOL" was defined as a GHS of ≥70.[16] The QLQ-PR25 incorporates 6 scales with higher scores reflecting either more symptoms or higher levels of functioning.[15] LUTS were assessed by the IPSS. The IPSS incorporates 7 symptom questions and 1 QoL question with higher scores reflecting either more symptoms or better QoL.[13] Urinary continence was assessed by the International Consultation of Urinary Incontinence questionnaire in its short-form (ICIQ-SF) and daily pad usage. The ICIQ-SF comprised 5 items, with higher scores reflecting more urinary incontinence.[17]. Continence recovery was defined by use of up to 1 (dry) security pad per 24 hours. Erectile function was assessed with the simplified International Index on Erectile Function (IIEF-5) questionnaire. The IIEF-5 comprised 5 items, with higher scores reflecting better erectile functioning.[18] According to institutional standards, questionnaires were handed out to patients 1 to 3 days prior RP.

Secondary endpoints encompassed functional outcome parameters, biochemical recurrence-free survival (BRFS), defined as the time from RP to biochemical recurrence defined as PSA ≥0.2 ng/mL following current guidelines,[19] and metastasis-free survival (MFS) based on conventional or PET-based imaging and calculated from date of the RP. Patients were censored at last follow-up including imaging or death.

Follow-up

Follow-up of eligible patients was performed at 3 months after surgery (postop), followed by annual intervals thereafter up to 10 years after surgery. Hereby, validated questionnaires were sent via mail to eligible patients. In addition, oncological outcome information was retrieved directly from patients, referring urologists and primary physicians.

Statistical Analysis

All statistical analysis was performed using MedCalc Statistical Software version 20.011 (MedCalc Software, Ostend, Belgium). To test for normal distribution of variables, Shapiro-Wilk test was performed. For descriptive statistics, median and means were used to present continuous variables and percentages or absolute numbers to present non-continuous variables. Chi-square test and Mann-Whitney U test were applied for univariate analyses of categorical variables and continuous variables, respectively. Multivariable linear regression was used to identify factors which independently predict perioperative improvement of HRQOL. Survival and continence recovery probabilities were estimated applying Kaplan-Meier method and compared using log-rank test. A P-value of < .05 was considered statistically significant.

RESULTS

Perioperative Patient Characteristics

Patient characteristics of the unmatched and matched cohorts are displayed in Table 1. Applying PS-matching, a well-balanced cohort of 3056 patients was generated (n = 1528 [LUTS], n = 1528 [no LUTS]). Median follow-up was 48 months. In the matched cohort median prostate volume (PV) was statistically significantly higher in the LUTS subcohort (48 vs 52cc, P < .001). Furthermore, preoperative alpha-blocker-therapy was

Table 1. Baseline characteristics of the unmatched and matched cohorts included in the current study

	Unmatched Cohort			Matched Cohort		
	LUTS	no LUTS	*P*	LUTS	no LUTS	*P*
No. of patients	2727	2762		1528	1528	
IPSS pre-OP	14 [10,20]	3 [2,5]	**< .001**	14 [10,21]	3 [2,5]	**< .001**
Age, y [median,IQR]#	67 [61,72]	65 [59,71]	**< .001**	66 [61,71]	66 [61,71]	1.000
BMI kg/m2 [median,IQR]#	26.3 [24.3,28.7]	26.3 [24.5,28.7]	.773	26.3 [24.4,28.7]	26.5 [24.6,28.7]	.252
PSA preop. ng/ml [median,IQR]	8.1 [5.5,13.6]	7.7 [5.4,12.1]	**.002**	7.4 [5.3,11.5]	7.4 [5.3,11.2]	.439
Prostate volume ml [median,IQR]	56 [44,73]	49 [40,60]	**< .001**	48 [40,58]	52 [42,63.1]	**< .001**
Gleason score [n (%)]#						
6	575 (21.1)	409 (14.8)	**< .001**	283 (18.5)	283 (18.5)	1.000
7a	906 (33.2)	1121 (40.6)		652 (42.7)	652 (42.7)	
7b	524 (19.2)	591 (21.4)		306 (20.0)	306 (20.0)	
8	275 (10.1)	307 (11.1)		120 (7.9)	120 (7.9)	
9	401 (14.7)	312 (11.3)		161 (10.5)	161 (10.5)	
10	46 (1.7)	22 (0.8)		6 (0.4)	6 (0.4)	
pT stage [n (%)]#						
pT2a	166 (6.1)	238 (8.6)	**< .001**	76 (5)	76 (5)	1.000
pT2b	55 (2.0)	58 (2.1)		8 (0.5)	8 (0.5)	
pT2c	1508 (55.3)	1375 (49.8)		955 (62.5)	955 (62.5)	
pT3a	575 (21.1)	503 (18.2)		264 (17.3)	264 (17.3)	
pT3b	423 (15.5)	588 (21.3)		225 (14.7)	225 (14.7)	
Positiv surgical margin [n (%)]#	403 (14.8)	309 (11.2)	**< .001**	188 (12.3)	188 (12.3)	1.000
Lymph node involvement [n (%)]	303 (11.1)	207 (7.5)	**< .001**	124 (8.1)	99 (6.5)	.095
Nerve sparing [n (%)]	2007 (73.6)	2119 (76.7)	**.007**	1195 (78.2)	1214 (79.5)	.590
Operative time min [median,IQR]	78 [64,152]	81 [65,165]	**.003**	75 [61,154]	76 [63,146]	.965
Estimated blood loss ml [median,IQR]	200 [100,300]	200 [100,300]	.383	200 [100,300]	200 [100,300]	.167
Roboter assisted RP [n (%)]#	675 (24.8)	851 (30.8)	**< .001**	383 (25.1)	383 (25.1)	1.000
preop alpha-blocker therapy [n (%)]						
yes	265 (9.7)	98 (3.6)	**< .001**	163 (10.7)	38 (2.5)	**< .001**
no	1219 (44.7)	1583 (57.3)		621 (40.6)	756 (49.5)	
no information	1243 (45.6)	1081 (39.1)		744 (48.7)	734 (48.0)	
# propensity score matched variables						

BMI, body-mass index; IPSS, International prostate symptom score; IQR, interquartile range; PSA, prostate-specific antigen; RALP, robot-assisted laparoscopic radical prostatectomy; RP, radical prostatectomy.
Bold values indicate $P < .05$.

significantly more frequent within the LUTS subcohort ($P < .001$). All other baseline parameters were well balanced between both subcohorts (*P*-range: .095-1.000) (Table 1).

LUTS and HRQOL

Detailed preoperative and longitudinal postoperative results on general HRQOL and QLQ-C30 subscales are outlined in Figure 1 and Supplementary Table 1. In

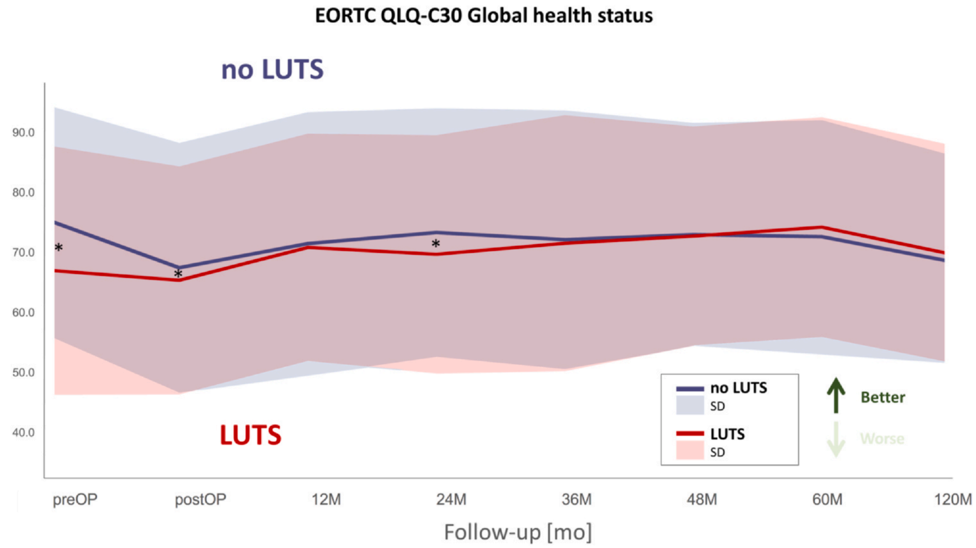

Figure 1. Longitudinal assessment of the mean EORTC QLQ-C30 Global Health Status for patients with or without preoperative LUTS undergoing radical prostatectomy [* $P < .05$]. EORTC, European Organization for Research and Treatment of Cancer; QLQ, quality of life questionnaire. (Color version available online.)

summary, the preoperative mean GHS score (67.4 vs 75.7) as well as all functioning subscales were significantly lower in the LUTS-cohort (each $P < .001$). Consistently, symptom subscales were significantly higher in the LUTS-cohort (*P*-range .001-.022). Postoperatively, the difference in general HRQOL between the LUTS cohort and the no-LUTS cohort diminished (65.7 vs 67.8), however, remained statistically significant ($P = .037$) (Supplementary Table 1). Forty-one percentage of patients from the LUTS-cohort experienced perioperative improvement of GHS compared to 25% of patients from the no-LUTS-cohort ($P < .001$). Forty-three percentage of patients from the LUTS-cohort experienced perioperative deterioration of GHS compared to 53% of patients from the no-LUTS-cohort ($P < .001$). In long-term follow-up, general HRQOL was comparable between both subcohorts with no significant difference in mean GHS from 36 months to 120 months after RP (*P*-range .716-.876). Results of longitudinal assessment of symptom subscales and functioning subscales are displayed in Supplementary Table1.

Spearman's rank correlation, revealed a significant positive correlation between preoperative IPSS-score and perioperative improvement of GHS (Delta GHS) (correlation coefficient 0.169, $P < .001$; Fig. 2). Those results held true in long-term follow-up with a significant positive correlation between preoperative IPSS-score and the difference between preoperative GHS and GHS at maximum follow-up (correlation coefficient 0.104, $P = .036$; Supplementary Figure 4).

Multivariable linear regression analysis revealed a higher preoperative IPSS as an independent predictor for increased perioperative improvement of GHS ($P < .001$). Increased preoperative ICIQ was identified as an independent predictor for lower perioperative improvement of GHS ($P < .001$) (Table 2).

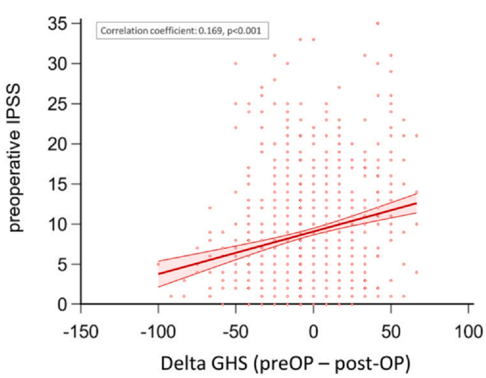

Figure 2. Spearman rank correlation between preoperative international prostate symptom score and perioperative change of the EORTC QLQ-C30 Global Health Status. EORTC, European Organization for Research and Treatment of Cancer; QLQ, quality of life questionnaire. (Color version available online.)

LUTS and Functional Outcome

Functional outcome is summarized in Supplementary Table 2. Preoperatively, 46.1% of patients from the LUTS-cohort and 43.1% from the no-LUTS-cohort reported an IIEF > 18, with mean IIEF5-scores of 13.8 versus 12.3 ($P < .001$). Similarly, mean postoperative IIEF-5 scores did not differ between both cohorts (3.2 vs 3.3, $P = .53$). In mid-term follow-up until 48 months after RP, a trend towards better IIEF-5 scores could be observed, in long-term follow-up (60 months post-RP and 120 months post-RP) no significant difference was observed (*P*-range: .212-.709). Longitudinal assessment of

Table 2. Multivariable linear regression for the perioperative improvement of Health-related quality of life.

Multivariate Linear Regression for Perioperative Improvement of HRQOL				
Variable	B [Regression Coefficient]	Beta [Standardized Regression Coefficient]	SE [Standard Error]	*P* Value
Pre-OP IPSS	0.807	0.218	0.164	***<.001***
Pre-OP ICIQ-SF	-0.836	-0.173	0.213	***<.001***
Pre-OP IIEF-5	0.125	0.035	0.163	.444
Age	-0.037	-0.011	0.160	.817
BMI	0.433	0.063	0.296	.143
Prostate volume	-0.074	-0.061	0.053	.164
Pre-OP PSA	0.022	0.032	0.030	.458
Gleason grade (biopsy)	-0.600	-0.032	0.819	.464
R^2	0.252			
Adjusted R^2	0.201			

BMI, body mass index; ICIQ-SF, International consultation on incontinence questionnaire-short form; IIEF-5, International index of erectile function; IPSS, International prostate symptom score. Bold values indicate statistical significance (p-value < 0.05).

self-reported use of phosphodiesterase-5 inhibitors (PDE5-inhibitors) showed no significant difference between both cohorts (*P*-range: .140-.956).

Preoperative mean ICIQ-SF-scores did not significantly differ between both cohorts (0.5 vs 1.9, *P* = .061). Postoperative mean ICIQ-SF-scores were significantly higher for the LUTS-cohort compared to the no-LUTS cohort (9.6 vs 8, *P* < .001). While a similar significant trend was observed in midterm follow-up to 48 months after RP, no significant difference was found in long-term follow-up (60 months post-RP and 120 months post-RP) (*P*-range: .131-.887) (Supplementary Table 2).

In line, median time to continence recovery was significantly longer for the LUTS cohort, compared to the no-LUTS cohort (6 months vs 5 months, *P* = .015). Long-term continence rates, however, did not significantly differ between both cohorts (95.6 vs 96.6%, *P* = .302 after 60 months; 95.4% vs 96.4%, *P* = .307 after 120 months) (Supplementary Figure 2).

Oncological Outcomes

A significant difference in 5-year BRFS could be observed between both cohorts (72% vs 67%, *P* = .011). Five-year MFS rates, however, were comparable between both cohorts (76% vs 76%, *P* = .562) (Supplementary Figure 3).

DISCUSSION

The impact of RP on male LUTS is not yet fully understood. As men with LUTS and concomitant prostate cancer are considered poor candidates for treatment alternatives such as external beam radiation, which could potentially aggravate bothersome urinary symptoms,[20] the impact of LUTS on the post-RP outcomes is of great interest.

The current study presents unique data from a large propensity-score matched and contemporary cohort on the impact of preoperative severe LUTS on long-term outcome following RP, with focus on HRQOL outcomes based on the validated EORTC QLQ-C30 and QLQ PR25 questionnaire. As long-term survival rates after RP for clinically localized PC are increasing, with 5-year disease-specific survival rates as high as 99%,[21] HRQOL becomes an essential measure to determine clinical benefit of treatment strategies in these patients. Noteworthy, our data showed no significant difference in 5-year-MFS-rates, which was previously confirmed as a surrogate parameter for overall survival.[22]

The current literature provides scarce evidence regarding the impact of preoperative LUTS on functional outcome following RP and is based on small studies with limited follow-up[7-9] Choi et al conducted a small retrospective analysis comparing the functional outcome of patients with different severity of preoperative LUTS, reporting no significant difference in postoperative continence rates.[8] In line with those results, Yamada et al found preoperative LUTS assessed by IPSS not to be associated with impaired continence recovery.[7] Conversely Gordon et al observed significantly lower continence rates for patients with severe LUTS prior RP.[9] Consistent with the aforementioned studies, we found significantly lower continence rates postoperatively and up to 3 years after RP in patients with preoperative LUTS with a significantly longer median time to continence recovery. However, although the difference in time to continence recovery was statistically significant, the clinical relevance is rather low as the median time for both cohorts was low at 5 versus 6 months. Furthermore, in long-term follow-up, continence recovery rates were balanced.

To date, evidence regarding the impact of preoperative bothersome urinary symptoms in prostate cancer patients following RP mainly focuses on the perioperative development of LUTS, assessed by IPSS or AUASS.[23-26] Prabhu et al performed a prospective cohort study of 1788 men undergoing RP for PC and stratified patients by significant baseline LUTS, defined as an AUASS-score of > 7. The author found patients with significant

LUTS at baseline to experience significant perioperative improvement of LUTS, while those without baseline LUTS to experience significant perioperative increase of LUTS. Overall, they reported a significant reduction of LUTS from baseline up to 10 years after RP. However, it has to be emphasized that the study included patients treated with open RP only.[24] Ahn et al analyzed 1917 consecutive robotic-assisted RPs and compared baseline preoperative IPSS-scores with postoperative IPSS-scores 12 months after surgery. In line with Prabhu et al the authors reported significant improvement of LUTS after RP for patients with moderate to severe LUTS at baseline, compared to a significant perioperative worsening of LUTS for patients without LUTS prior RARP.[25] In the largest retrospective study assessing the impact of RARP on the symptom burden of LUTS to date, Leyh-Bannurah et al reported on the perioperative change in IPSS-score of 5506 patients undergoing RARP. The authors confirmed significant improvement of LUTS in patients with high IPSS-scores prior RP. For patients with low IPSS prior RP, however, LUTS were mostly remained stable.[23]

With conflicting results on functional outcome and equally favorable oncologic results for both cohorts, the assessment and monitoring of HRQOL, previously considered a soft endpoint, becomes increasingly important. Bearing in mind the impact of RP on HRQOL,[10] PROMs are crucial for guidance of therapy, especially when considering that prostate cancer patients could, to a certain extent, be willing to trade oncologic benefit for improved HRQOL.[27]

Leyh-Bannurah et al as well as Ahn et al also report on QOL outcome following RP, which in both studies, however, was only based on the QOL-question of the IPSS-questionnaire.[23,25] In the knowledge of the importance of adequate and validated HROQL-assessment,[27] we present to the best of our knowledge the first longitudinal HRQOL data with long-term follow-up based on the validated QLQ C30 an QLQ PR 25 which have been shown to be most suitable HRQOL assessment tools in prostate cancer.[27] Moreover, results of previous studies are impaired by a selection bias, since in the majority of studies, the LUTS-cohorts had a significantly higher age,[9,23,25] which was previously confirmed as an independent predictor for impaired functional and HRQOL outcomes.[28,29] In order to overcome this bias, we performed a propensity score matching by known confounders, resulting in a well-balanced cohort, which only differed in prostate volume. Interestingly while the median PV within the unmatched cohort was significantly higher for patients with LUTS, following PS-matching PV was significantly lower for patients with LUTS in the matched cohort. Although there have been conflicting results regarding the impact of PV on severity of LUTS[3] we could previously show larger PV to have no impact on HRQOL following RP.[30] Furthermore, even though the difference in PV is statistically significant, it is debatable whether the difference (48 mL vs 52 mL) is clinically relevant. In the present study, we found patients with LUTS prior to RP to report significantly worse general HRQOL prior to surgery. Interestingly while patients without LUTS prior RP reported significant perioperative deterioration of general HRQOL, mean GHS scores within the LUTS cohort remained stable.

A possible explanation for the difference in perioperative change of GHS might be the development of de novo LUTS after RP, which has been described before[5,6] De novo LUTS following RP may have a more pronounced impact on HRQOL for patients without LUTS prior surgery. Although the difference in HRQOL became smaller after RP, it remained statistically significant in short-term follow-up. Furthermore, the difference met previously defined minimally important differences for the EORTC QLQ-C30 in prostate cancer clinical trials.[31] In long-term follow-up up to 10 years after RP, however, general HRQOL did not significantly differ between both cohorts. Strikingly in multivariable analysis, we identified a higher preoperative IPSS-score as an independent predictor of a more pronounced perioperative improvement in general HRQOL. Those results support the hypothesis that patients with prostate cancer and concomitant bothersome urinary symptoms in particular benefit from RP, assumingly by relief of LUTS.

Our study is not devoid of limitations, mainly inherent to the retrospective study design. However, by performing propensity score-matching including known confounders, we aimed to minimize selection bias, in order to draw valid conclusions. While our study lacks data on overall survival (OS), MFS is an alternate survival endpoint, which has previously been shown to be a valid surrogate for OS.[32] Furthermore, preoperative LUTS was only assessed by IPSS scores, preoperative objective measures such as ultrasound post-void residual volume or maximum urinary flow rates were not available. Finally, the current analysis does not provide further information regarding underlying mechanisms or associations between BPH and PC risk.

In summary, the current study provides further evidence to support the treatment of patients with PC and concomitant LUTS with radical prostatectomy. It contributes to guidance of therapy for those patients, optimal patient selection and consequently improving HRQOL for patients with localized prostate cancer.

Ethical Approval

This study was performed according to the 1964 Helsinki Declaration and was approved by an institutional ethics committee (#20–1022). Informed consent was obtained from all individuals participating in the study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2024.04.020.

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