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The EORTC quality of life questionnaire predicts early and long-term incontinence in patients treated with robotic assisted radical prostatectomy: Analysis of a large single center cohort

Cosimo De Nunzio, MD[a,*], Antonio Luigi Pastore, MD[b], Riccardo Lombardo, MD[a], Fabiana Cancrini, MD[a], Antonio Carbone, MD[b], Andrea Fuschi, MD[b], Lorenzo Dutto, MD[c], Andrea Tubaro, MD[a], Joern Heinrich Witt, MD[c]

[a] *Department of Urology, "Sant'Andrea" Hospital, "La Sapienza" University, Rome, Italy*
[b] *Department of Urology, Ospedale di Latina, Latina, Italy*
[c] *St Antonius Hospital Gronau, Department of Urology, Pediatric Urology and Urological Oncology, Prostate Cancer Northwest, Gronau, Germany*

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ABSTRACT

Objectives: The aim of our study is to evaluate the role of preoperative quality of life (QL) as a possible risk factor for post robotic assisted radical prostatectomy (RARP) urinary incontinence. The secondary aim is to evaluate the possible effect of preoperative QL on post RARP lower urinary tract symptoms (LUTS) and erectile dysfunction (ED).

Methods and materials: Between 2012 and 2017, all patients undergoing RARP for prostate cancer were enrolled. Patient's demographic, clinical, and histological characteristics were recorded. ED, LUTS, urinary incontinence, and QL were evaluated at baseline and postoperatively at 3, 6, and 12 months. Incontinence was evaluated with the International Consultation on Incontinence Questionnaire − Urinary Incontinence Short Form questionnaire and QL with the EORTC QLQ-C30 global health score (QLQ-GHS). Multivariate logistic regression analysis was used to evaluate the risk of postoperative incontinence, moderate/severe incontinence, LUTS, and moderate/severe ED.

Results: Overall 4,603 patients were enrolled. Incontinence rates at 3, 6, and 12 months were respectively 17%, 10%, and 8%. On multivariate analysis, QL was an independent predictor of early incontinence (QLQ-GHS:0.71, CI:0.59−0.86; P= 0.001), severe incontinence (QLQ-GHS:0.65, CI:0.49−0.97; P= 0.006), and LUTS (QLQ-GHS:0.48, CI:0.41−0.57; P= 0.001). Single center design may be considered a limitation.

Conclusions: In our study a comprehensive evaluation of preoperative patient's QL, assessed by the EORTC QLQ-C30 questionnaire, can predict the early and long-term moderate/severe incontinence risk in RARP treated patients. Further studies should confirm our results.
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Keywords: Prostate cancer; Incontinence; Quality of life; Robotic radical prostatectomy; EORTC QL30

1. Introduction

Prostate cancer (CaP) has been the most common non-cutaneous malignancy in men since 1984. In 2012, 1.1 million of new cases were estimated worldwide, representing 15% of all diagnosed cancers. Again, 1.6 million were reported in 2015 mainly in developed countries [1]. Radical prostatectomy (RP) represents one of the possible therapeutic options for these patients [2]. Although the primary goal of RP is to achieve cancer control and cure, patient's satisfaction and quality of life (QL) can be negatively affected by either the presence of urinary incontinence (UI), erectile dysfunction (ED), or both of them [3,4]. So far, several authors have highlighted the importance of evaluating both oncological and functional outcomes in

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*Corresponding author. Tel: +39-0633777716; fax: +39-0633775059.
E-mail address: cosimodenunzio@virgilio.it (C. De Nunzio).

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patients treated with radical retropubic prostatectomy [2,5]. Regarding the risk of early and late incontinence, the improving knowledge of anatomical prostatic landmarks and the resultant improvement in surgical techniques have significantly reduced the risk of postoperative incontinence. The estimated 12-month urinary recovery rate ranges between 84% and 97% [2]. In particular, the risk of urinary incontinence after robotic assisted radical prostatectomy (RARP) is influenced by several factors including preoperative patient characteristics, surgeon experience, and surgical techniques. More specifically, as reported by Ficarra et al. in a recent meta-analysis, 12-month urinary incontinence rates ranged from 4% to 31% using a no pad definition and from 8% to 11% if continence definition included also patients who used a safety pad. Recent data have also supported the possible impact of depression and QL on functional outcomes in prostatic surgery [6,7]. As well, it is important to evaluate disease-specific QL outcomes with validated cancer-specific patient-reported outcome measures with at least 1 year of follow-up after primary treatment for clinically localized CaP [8]. Although in the past years several questionnaires have been proposed and validated, the Quality of Life Questionnaire Core module with 30 items (provided by the European Organization for Research and Treatment of Cancer: EORTC QLQ-C30) is generally considered one of the most frequently used. In particular, in CaP patients the EORTC QLQ-C30 has been used to evaluate the impact of RP on postoperative patient's QL. No study has yet evaluated the possible effect of preoperative patient's QL on RARP functional outcomes [9].

The primary aim of our study was to evaluate the role of preoperative QL as a possible risk factor for post RARP early and late urinary incontinence. The secondary aim was to evaluate the possible effect of preoperative QL on post RARP lower urinary tract symptoms (LUTS) and ED.

2. Materials and methods

2.1. Patient selection

After obtaining the institutional review board approval, a retrospective analysis of a prospectively maintained database of men who underwent RARP in one center between January 2012 and December 2017 was carried out. All patients signed a dedicated informed consent and the study was conducted in accordance with the principles of the declaration of Helsinki. All patients with biopsy confirmed CaP, in a tertiary referral center within 3 months before surgery, were included in the analysis. Patients who received neoadjuvant hormonal therapies or did not have complete data were excluded from the study. RARP was performed by an experienced surgeon (J.W.) and when a nerve sparing approach was performed it was recorded as a dichotomized variable (yes or no). Extended lymph node dissection was carried out according to the European Association of Urology guidelines [10].

2.2. Data collected

Evaluated variables included age, body mass index, calculated as weight in kilograms divided by height in squared meters (kg/m^2), preoperative prostate-specific antigen, prostate volume assessed by transrectal ultrasound, pathological stage, bioptic and pathological prognostic grade group (PGG) system, surgical margin status and lymph node status. PGG were assigned according to the new 2014 ISUP described by Epstein et al. [11]. High-grade cancer is defined as: PGG system >2.

Patient-reported outcomes were assessed using standardized self-administrated questionnaires at baseline, 3, 6, 12 months after treatment in our outpatient clinic. In particular, patients completed the International Prostatic Symptom score (IPSS), the International Index on erectile dysfunction short form (IIEF) and the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form questionnaire (ICIQ-UI Short Form). UI was defined as ICIQ-UI short form question 3 (Q3) ≥4. Moderate/severe incontinence was defined as ICIQ-UI short form question 4 (Q4) ≥4. Moderate-severe LUTS were defined as an IPSS ≥ 8 and moderate/severe ED as an IIEF short form <11. Erectile function (EF) was considered without the use of postoperative phosphodiesterase inhibitors.

The EORTC QLQ-C30 (version 3.0) was used to evaluate QL at baseline and postoperatively. The EORTC QLQ-C30 is a validated questionnaire for QL in cancer patients, used to measure QL and general health status in a score called Global Health status (QLQ-GHS), allowing values in a range from 0 to 100. High scores represent a high QL. In addition, 5 functioning scales (physical, role, cognitive, emotional, and social) and 3 symptom scales (fatigue, pain, and nausea/vomiting) are included. The 2 items of the QLQ-GHS (QLQ-29 and QLQ-30) scales use a modified 7-point linear analogue scale while all other items are scored on a 4-point categorical scale ranging from 1 "not at all" to 4 "very much." All scales and single items are linearly transformed to a 0 to 100 scale. A high QLQ-30 symptom score represents a large amount of symptoms and a lower QLQ-GHS indicates a poor QL [12–15].

2.3. Statistical analysis

Statistical analysis was performed using the SPSS 24.0 software. Differences between groups for continuous variables were tested with the Kruskal-Wallis one-way analysis and for quantitative variables with the chi-square test. The statistically significant variables in univariate analysis were included in a multiple logistic regression model to evaluate the risk of early and severe postoperative UI, postoperative ED, and postoperative LUTS. The variables considered valid for the model were those with a significant result at the univariate analysis, excluding the ones that could determine a multicollinearity effect (i.e., QLQ-GHS vs QLQ-30). In the same way, as well, predictors of positive outcome defined as:

continence, no symptoms, and good erectile function were analyzed in a multivariable binary logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the parameters in each model. An alpha value of 5% was considered as threshold for significance.

3. Results

Overall, 4,603 patients were enrolled. General characteristics of the cohort are listed in Table 1.

3.1. Incontinence outcomes

Overall 37/4603 (0.8%) patients were incontinent before surgery and 771/4603 (17%) 3 months after surgery (Fig. 1). Incontinent patients presented a lower preoperative QL when compared to continent patients defined by the QLQ-GHS (Table 2). The mean difference in QLQ-GHS was 6% between both groups, considered clinically significant [16].

Moderate/severe incontinence was reported by 271/4603 (6%) of the patients at 3 months. Moderate/severe incontinent patients presented a lower preoperative QL when compared to mildly/not incontinent patients (Table 2). The mean difference in QLQ-GHS between both groups, considered clinically significant, was 6%.

On multivariate analysis older age, higher preoperative IPSS scores, lower QLQ-GHS scores and performing a no-nerve sparing procedure were independent predictors of incontinence and moderate/severe incontinence. More specifically the risk of incontinence is decreased by 29% in patients with good-excellent QLQ-GHS when compared to patients with poor QLQ-GHS (OR: 0.71 95%CI: 0.58 −0.90; *P*= 0,001) (Table 3). The latest results were confirmed at 6 and 12 months (Supplementary Tables S1−4)

Table 1
General characteristics of the overall population.

	Mean ± SD; median (IQR)
Age (y)	64.5 ± 7.0; 65 (60/70)
TRUS volume (ml)	43.2 ± 20.8;39 (30/51)
BMI (kg/m^2)	27.0 ± 3.5; 26.5 (24.6/28.9)
PSA (ng/ml)	10.6 ± 12.9; 7.4 (5,5/11)
IPSS score	8.1 ± 6.5; 7 (3/12)
IIEF score	14.1 ± 9.2; 16 (4/24)
ICIQ score	1.05 ± 2.2; 1 (0/3)
QLQ score	37.1 ± 9.0; 34 (31/41)
ASA score	
1	1052/4603 (23%)
2	3070/4603 (67%)
3	479/4603 (10%)
4	2/4603 (<1%)
Operative time	149 ± 40; 143 (120/178)
Grade group sec. Epstein	%
1	1542/4603 (33%)
2	1358/4603 (30%)
3	925/4603(20%)
4	212/4603 (5%)
5	566/4603 (12%)
pStage ≥3a	1749/4603 (38%)
Surgical margins	485/4603 (11%)
Nerve sparing	4372/4603 (95%)
eLND	4217/4604 (91,6%)
N+	337/4217 (8%)

ASA = American Society of Anesthesiologists score; BMI = body mass index; EORTC-QLQ = Quality of life Score; ICIQ = International Consultation on Incontinence Questionnaire − Urinary Incontinence Short Form questionnaire; IIEF = International Index on Erectile dysfunction short form (IIEF); IPSS = International Prostatic Symptom score; TRUS = transrectal ultrasound.

3.2. LUTS after surgery

Overall 2,025/4,603 (44%) patients were asymptomatic or mild symptomatic (IPSS ≥ 8) before surgery and 1,197/4,603 (26%) patients were symptomatic (IPSS ≥ 8) 3 months after surgery (Fig. 1). Symptomatic patients presented a lower preoperative QL (QLQ-GHS) when compared to nonsymptomatic ones (Table 4). The mean difference in QLQ-GHS between both groups was 8%.

On multivariate analysis older age, lower IIEF scores, lower QLQ-GHS score and performing a no-nerve sparing procedure were independent predictors of postoperative LUTS. More specifically the risk postoperative LUTS is decreased by 53% in patients with good-excellent QLQ-GHS when compared to patients with poor QLQ-GHS (OR: 0.47 95%CI: 0.39−0.58; *P*= 0.001) (Table 5). The latest results were confirmed at 6 and 12 months (S5−8).

In a subanalysis of patients with no/mild symptoms preoperatively. Poor QLQ-GHS is a predictor of postoperative urinary incontinence (multivariate OR: 0.74; 95%CI 0.54 −0.91; *P*= 0.003). Poor QLQ-GHS was still a predictor of postoperative LUTS. More specifically the risk postoperative LUTS is decreased by 26% in patients with good-excellent QLQ-GHS when compared to patients with poor QLQ-GHS (OR: 0.64 95%CI: 0.39−0.58; *P*= 0.001). However, in this group of patients poor QLQ-GHS is not a predictor of ED (multivariate OR: 0.95 95%CI 0.71−1.29 *P*= 0.785).

3.3. ED after surgery

Overall 1,979/4,603 (43%) patients presented moderate/severe ED before surgery and 3867/4603 (84%) patients presented moderate/severe ED 3 months after surgery (Fig. 1). Patients with ED presented a lower preoperative QL when compared to patients with mild/no ED (Table 4). The mean difference in QLQ-GHS between both groups, which can be considered clinically significant, was 5%.

On multivariate analysis older age, pathological stage ≥T3a, lower QLQ-GHS scores and performing a no-nerve sparing procedure were independent predictors of postoperative ED (Table 5). More specifically the risk of postoperative ED decreased of 39% in patients with good-excellent QLQ-GHS when compared to patients with poor QLQ-GHS (OR: 0.61 95%CI: 0.48−0.80; *P*= 0.001). The latest

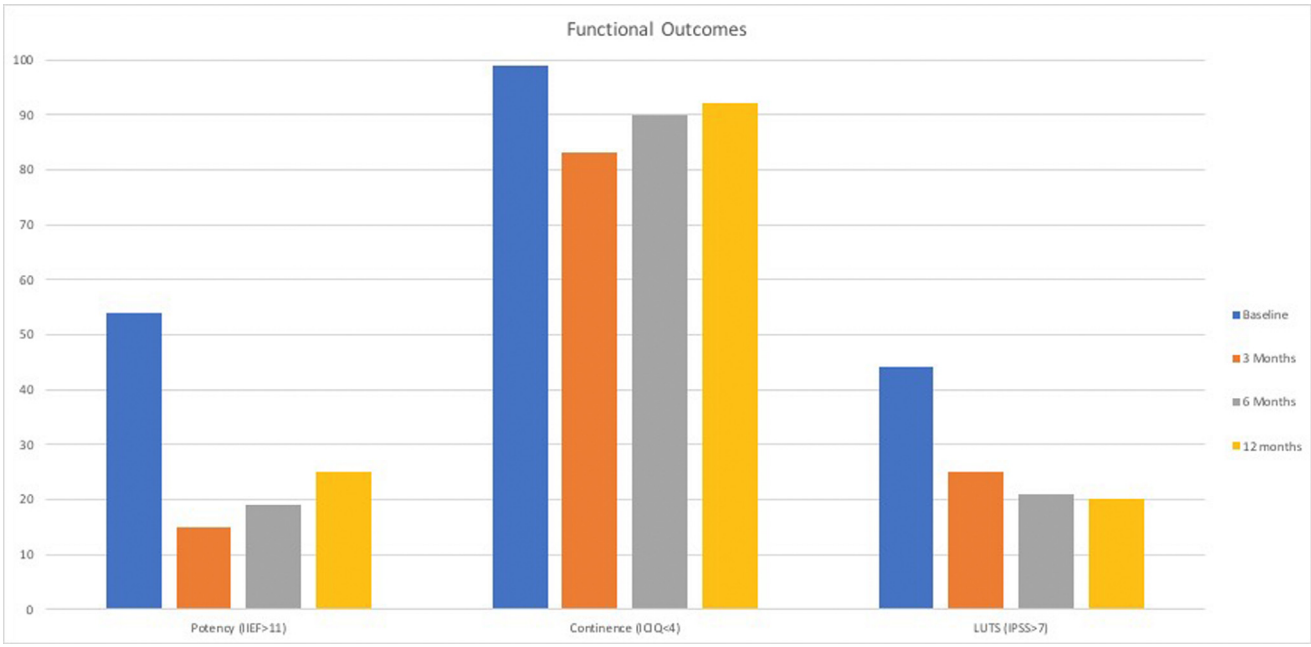

Fig. 1. Continence, potency, and LUTS changes after RARP.

Table 2
Three months incontinence and moderate/severe incontinence according to baseline patients' characteristics.

	3 months incontinence characteristics					
	No incontinence	Incontinence	*P*	No/mild incontinence	Moderate/ severe incontinence	*P*
Patients	3825/4603 (83%)	771/4603 (17%)		4332/4603 (94%)	271/4603 (6%)	
Age (y)	64.3 ± 7.1; 65 (60/70)	66.0 ± 64; 67 (62/71)	0.001	64.4 ± 7.0; 65 (60/70)	67.2 ± 6.1; 67 (63/72)	0.001
TRUS volume (ml)	43.1 ± 20.5;39 (30/51)	44.1 ± 22.6;39 (29/52)	0.491	43.3 ± 20.7;39 (30/51)	44.1 ± 22.6;39 (29/52)	0.537
BMI (kg/m^2)	27 ± 3; 27 (25/29)	27 ± 4; 27 (25/29)	0.196	27 ± 4; 27 (25/29)	26 ± 3; 26 (24/29)	0.141
PSA (ng/ml)	10.6 ± 13.0; 7.4 (5,4/11)	10.8 ± 12.1; 7.6 (5,6/11)	0.284	10.6 ± 13.0; 7.4 (5,4/11)	10.5 ± 11.5; 7.6 (5,3/11)	0.946
IPSS score	7.8 ± 6.2; 6 (3/11)	9.6 ± 6.9; 8 (4/13)	0.001	8.0 ± 6.3; 7 (3/11)	9.8 ± 6.9; 9 (4/13)	0.001
IIEF score	14.3 ± 9.1; 17 (5/24)	12.9 ± 9.0; 13 (4/23)	0.001	14.3 ± 9.1; 17 (5/24)	11.1 ± 8.7; 9 (3/20)	0.001
QLQ-30	36.7 ± 8.8; 34 (31/41)	38.5 ± 9.8; 36 (31/42)	0.001	36.9 ± 8.9; 34 (31/40)	38.5 ± 10.2; 35 (31/43)	0.048
QLQ-GHS	76 ± 20; 84 (67/84)	70 ± 21; 75 (58/83)	0.001	75 ± 24; 84 (66/84)	69 ± 23; 75 (50/84)	0.001
ASA score ≥3	377/3825 (10%)	104/771 (13%)	0.004	440/4332 (10%)	41/271 (14%)	0.050
Operative time (min)	149 ± 40; 143 (120/175)	151 ± 38; 150 (120/180)	0.030	149 ± 40; 140 (120/177)	149 ± 36; 150 (120/174)	0.384
Grade group ≥3	1382/4603 (36%)	321/771 (41%)	0.030	1602/4332 (37%)	111/271 (41%)	0.212
pStage ≥3a	1448/3825 (38%)	301/771 (39%)	0.537	1655/4332 (38%)	94/271(34%)	0.176
Surgical margins	390/3825 (10%)	95/771 (12%)	0.087	453/4332 (10%)	32/271 (12%)	0.842
Nerve sparing	3663/3825 (96%)	709/771 (92%)	0.001	4125/4332 (95%)	247/271 (91%)	0.001

BMI = body mass index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom score; pStage = pathological stage; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

results were confirmed at 6 and 12 months (Supplementary Tables, S5−8).

In a subanalysis of patients with normal erectile function and nerve sparing procedure preoperative QL was a statistically significant predictor of postoperative incontinence (multivariate OR: 0.75; 95%CI 0.55−0.98; *P*= 0.030) as well as for postop LUTS (multivariate OR: 0.52; 95%CI 0.41−0.66; *P*= 0.001). However, preoperative QL was not a predictor of postoperative ED (OR: 1.04, 95%CI: 0.82 −1.33, *P*= 0.702).

Overall, age (OR: 0.93 95%CI: 0.92−0.94), nerve sparing procedure(OR: 3.33 95%CI: 1.69−6.55) and preoperative QL (OR: 1.37 95%CI: 1.09−1.71) were predictors of a positive outcome defined as continence, no symptoms, and good erectile function.

4. Discussion

QL outcomes of competitive treatments for localised CaP are considered an important endpoint in CaP treatment.

Table 3
Univariate and multivariate logistic regression analysis for the risk of incontinence and moderate/severe incontinence.

	Risk of incontinence				Risk of moderate/severe incontinence			
	Univariate	*P*	Multivariate	*P*	Univariate	*P*	Multivariate	*P*
Age (y)	1.05 (1.03−1.07)	0.001	1.04 (1.02−1.05)	0.001	1.06 (1.05−1.09)	0.001	1.06 (1.03−1.08)	0.001
TRUS volume >40 ml	1.03 (0.88−1.20)	0.710			0.83 (0.65−1.07)	0.168		
BMI (kg/m^2)	0.99 (0.97−1.01)	0.272			0.97 (0.94−1.01)	0.159		
PSA (ng/ml)	1.01 (0.99-1.01)	0.352			0.99 (0.9−91.01)	0.857		
IPSS score baseline	1.04 (1.03−1.05)	0.001	1.03 (1.02−1.05)	0.001	1.04 (1.02−1.06)	0.001	1.03 (1.02−1.06)	0.001
IIEF score baseline	0.98 (0.98−0.99)	0.001	1.00 (0.99−1.01)	0.655	0.96 (0.95−0.98)	0.001	0.98 (0.97−1.00)	0.046
QLQ-30 baseline	1.18 (1.10−1,26)	0.001			1.15 (1.03−1.29)	0.008		
QLQ-GHS good-excellent Ref: QLQ-GHS poor	0.71 (0.59−0.86)	0.001	0.71 (0.5−80.90)	0.001	0.65 (0.49−0,97)	0.003	0.65 (0.49−0.87)	0.006
ASA score ≥3 Ref ASA score ≤2	1.41 (1.12−1.78)	0.004	1.14 (0.89−1.47)	0.934	1.44 (1.01−2.07)	0.043		
Operativetime (min)	1.01 (0.99−1.00)	0.242			1.00 (0.99−1.01)	0.879		
Biopsy grade group ≥3 Ref biopsy grade group ≤2	1.19 (1.02−1.40)	0.030	1.04 (0.87−1.23)	0.661	1.17 (0.91−1.51)	0.212		
Nerve sparing ref: nonnerve sparing	0.53 (0.40−0.73)	0.001	0.61 (0.44−0.84)	0.003	0.50 (0.32−0.77)	0.002	0.60 (0.38-0.94)	0.027

BMI = body mass index; IIEF = International Index of Erectile function; IPSS = International Prostate Symptom score; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Table 4
Three months LUTS and ED according to baseline patients' characteristics.

	3 months functional characteristics					
	No LUTS (IPSS ≤ 7)	LUTS (IPSS ≥ 8)	*P*	No/mild ED (IIEF ≥ 12)	ED (IIEF ≤ 11)	*P*
Patients	3406/4603 (74%)	1197/4603 (26%)		736/4603 (16%)	3867/4603 (84%)	
Age (y)	64.1 ± 7.0; 65 (59/69)	65.9 ± 6.7; 66 (61/70)	0.010	60.4 ± 7.2; 60 (55/65)	65.2 ± 6.7; 65 (60/70)	0.001
TRUS volume (ml)	43.4 ± 20.8;39 (30/52)	42.8 ± 20.9; 38 (29/51)	0.296	40.3 ± 19.6;36 (28/48)	43.8 ± 21.8;39 (30/52)	0.001
BMI (kg/m^2)	26.9 ± 3,4; 26 (24/29)	27.1 ± 3.7; 27 (25/29)	0.198	26.7 ± 3.4; 26 (24/28)	27.0 ± 3.5; 27 (25/29)	0.028
PSA (ng/ml)	10.4 ± 13.2; 7.3 (5,4/11)	11.2 ± 11.6; 7.6 (5,6/12)	0.024	8.5 ± 11.1; 6.4 (5,8/10)	10.9 ± 13.0; 7.6(5,6/11,4)	0.001
IPSS score	7.2 ± 5.8; 18 (5/24)	11.0 ± 7.0; 9 (6/15)	0.001	8.5 ± 11,1; 6 (4/9)	8.3 ±6.5; 7 (3/12)	0.001
IIEF score	14.7 ± 9.1; 18 (5/24)	12.4 ± 9.0; 11 (3/22)	0.001	20.9 ± 6.1; 24 (20/25)	13.0 ± 9.1; 13 (4/23)	0.001
QLQ-GHS (%)	75 ± 20; 83 (66/83)	67 ± 22; 66 (50/83)	0.001	76 ± 20; 83 (66/83)	72 ± 22; 83 (66/83)	0.001
QLQ-30 (%)	75 ± 21; 83 (66/83)	68 ± 22; 66 (50/83)	0.001	77 ± 20; 83 (66/83)	73 ± 20; 83 (66/83)	0.001
ASA score ≥3	304/3406 (9%)	177/1197 (15%)	0.001	37/736 (5%)	444/3867 (11%)	0.001
Operative time (min)	149 ± 38; 140 (120/170)	150 ± 41; 150 (120/180)	0.013	146 ± 37; 140 (120/171)	150 ± 40; 147 (120/180)	0.003
Grade group ≥3	1231/3406(36%)	472/1197 (39%)	0.010	184/736 (25%)	1519/3867 (39%)	0.001
pStage ≥3a	1273/3406 (37%)	479/1197 (39%)	0.426	191/736(26%)	1558/3867 (39%)	0.001
Nerve sparing	3663/3406 (96%)	709/1197 (92%)	0.001	728/736 (99%)	3644/3867 (94%)	0.001

BMI = body mass index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score ; pStage = pathological stage; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

The EORTC QLQ-C30 questionnaire is considered one of the most used and validated questionnaires [8] to evaluate QL outcomes. In our study, we observed that most of our patients showed a preoperative good to excellent state of health and 15 % of these patients presented a significant decrease in their QL after surgery [12]. Postoperatively the GHS significantly changed at 3, 6, and 12 months. In particular, in patients who experienced postoperative complications: mild to severe urinary incontinence, ED, or urinary symptoms. Our data are in line with the recent evidence from the Protect-Trial, a large randomized controlled trial comparing patient-reported outcomes in men who underwent treatment for localised CaP. They observed that surgery has a negative impact on urinary continence and sexual function. The overall decrease of sexual QL after RP was observed up to 6 years after surgery [6,17]. As expected and in line with previous experiences, there were no clinical significant changes (less than 5 points) in the overall symptom and functional score (QLQ-30) [12]. Although American Society of Anesthesiologists (ASA) score and IIEF were predictors of incontinence on univariate analysis they were not statistically significant on multivariate analysis.

Postoperative UI, urinary symptoms, and ED have a negative effect on the patient's satisfaction and health-related QL after a RARP. In particular, a recent meta-analysis

Table 5
Univariate and multivariate logistic regression analysis for the risk of postoperative LUTS (IPSS ≥ 8) and ED (IIEF ≤ 11).

	Risk of LUTS (IPSS ≥ 8)				Risk of ED (IIEF ≤ 11)			
	Univariate	*P*	Multivariate	*P*	Univariate	P	Multivariate	*P*
Age (y)	1.04 (1.03−1.05)	0.001	1.03 (1.02−1.04)	0.001	1.10 (1.09−1.11)	0.001	1.09 (1.00−1.11)	0.001
TRUS volume >40 ml	0.93 (0.82−1.07)	0.351			1.23 (1.06−1.42)	0.006	1.01 (0.86−1.07)	0.868
BMI (kg/m^2)	1.01 (0.99−1.03)	0.256			1.03 (1.00−1.05)	0.039	1.01 (0.98−1.04)	0.345
PSA (ng/ml)	1.01 (0.99−1.01)	0.096			1.03 (1.01−1.04)	0.001	1.01 (0.99−1.02)	0.102
IPSS score baseline	1.09 (1.08−1.10)	0.001			1.04 (1.02−1.05)	0.001	1.01 (1.02−1.06)	0.510
IIEF score baseline	0.97 (0.96−0.98)	0.001	0.99 (0.98−0.99)	0.018	0.88 (0.87−0.90)	0.001		
QLQ-30 baseline	1.49 (1.41−1.60)	0.001			1.23 (1.12−1.36)	0.001		
QLQ-GHS good-excellent Ref: QLQ-GHS poor	0.48 (0.41−0.57)	0.001	0.47 (0.39−0.58)	0.001	0.62 (0.49−0.79)	0.001	0.61 (0.48-0.80)	0.001
ASA score ≥3 Ref ASA score ≤2	1.78 (1.46−2.18)	0.001	1.25 (0.99−1.57)	0.058	2.21 (1.57−3.13)	0.001	1.24 (0.84−1.83)	0.274
Operative time (min)	1.01 (1.00−1.01)	0.029			1.01 (1.00−1.01)	0.011	1.00 (0.99−1.00)	0.984
Biopsy grade group ≥3 ref biopsy grade group ≤2	1.12 (1.98−1.29)	0.110			1.91 (1.59−2.30)	0.001	1.15 (0.92−1.46)	0.203
Nerve sparing ref: nonnerve sparing	0.53 (0.40−0.73)	0.001	0.70 (0.51−0.96)	0.026	0.93 (0.35−2.52)	0.001	0.20 (0.08−0.57)	0.001

BMI = body mass index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

showed that the 12-month UI rates ranged from 4% to 31% with a mean value of 16% (using a no pad definition). In our study, we have reported a 17% rate of incontinence at 3 months and an 8% rate at 12 months. These results are in line with other studies which evaluated urinary incontinence after CaP surgery [2].

Persistent LUTS are also a common finding after CaP surgery [18]. In our series 25% of patients presented moderate LUTS at 3 months after surgery, especially in older patients. Although in our study voiding and storage LUTS were not evaluated separately, prevalence of LUTS and particularly of storage symptoms are quite common after RARP. According to the available literature storage LUTS may be observed up to 40% of patients after surgery [19]. According to our results, a nerve sparing procedure is associated with a lower postoperative IPSS score. Although the exact pathophysiology of these findings is still unknown, some hypotheses have been proposed in the literature. Periprostatic nerves have been related to the pathogenesis of LUTS and in particular to the storage LUTS. Moreover, Haga et al. evaluated 200 patients undergoing Nerve Sparing RARP and found that these patients had an increase of their maximum voided volume and a decrease in nocturia episodes [20]. Further studies should clarify the exact pathophysiology behind these findings.

In our study 84% of the population presented moderate/severe ED (IIEF < 11) at 3 months and 74% at 12 months. Our results strictly depend on: enrolled population, type of surgery (at 12 months 50% of patients undergoing nerve sparing procedure presented moderate/severe ED), patient's age (55% of moderate/severe ED in patients under 65 years old) and preoperative ED (43% presented a preoperative moderate/severe ED). Our data are completely in line with previous experiences [21,22].

Patients with either postoperative urinary symptoms, incontinence or ED presented lower preoperative QL. In particular, a lower QLQ-GHS was a risk factor for early and late urinary incontinence (OR: 0.71 95%CI: 0.58−0.90; *P* = 0.001), of LUTS (OR: 0.47 95%CI: 0.39−0.58; *P*= 0.001) and of ED (OR: 0.61 95%CI: 0.48−0.80; *P*= 0.001). However, preoperative QL was not associated with ED in patients with good preoperative EF and undergoing a nerve sparing procedure. A possible explanation of these findings lies on the fact that patients with preoperative ED have poorer QL when compared to patients with preoperative normal EF. Moreover, only 15% of patients with normal EF and Nerve Sparing procedure presented a low preoperative QL. Although no similar data are available in the literature, we have hypothesized that patients with a worst preoperative QL may suffer from physical, emotional, cognitive, and social conditions. These could influence the recovery after surgery and in particular can have an impact on management postoperative complications. Boeri et al. have also recently reported that preoperative depressive symptoms are present in less than 20% of patients treated with radical retropubic prostatectomy. Nevertheless, these increase after surgery with a possible impact on postoperative EF recovery [7].

Our results suggest that patients with poor preoperative QL are at increased risk of postoperative incontinence and LUTS. Our results open new questions on the possible role of psychological support in these patients, which may improve their overall QL and possibly their functional outcomes. Further studies should deeply investigate this interesting insight.

We must acknowledge some important limitations of our study. This is a large single center study with data prospectively collected but retrospectively analyzed. The study

results clearly depend upon the enrolled population. Our cohort features describe a German population that may be different from Southern European, North American, South American, and Asian populations [23]. As well, there might be a selection bias considering that most of our patients presented low-grade CaP (66%), excellent ASA scores (90% ASA score 1–2) and most of them underwent a nerve sparing procedure (95%). Another possible limitation is that we have recorded exclusively total scores of the QLQ-30, as in previous studies on other cancers. So far, the possible impact of every single item on postoperative outcomes cannot be evaluated in our study. Moreover, we lack information regarding the spousal or social support before and after surgery. However, according to the guidelines for interpreting EORTC-QLQ-C30 scores, a mean change in total score of more than 5 points, as observed in our study, may be considered clinically significant (Tables 2–4) [16,24]. Another possible limitation is the that we lack data on single items of the IPSS and the IIEF questionnaires, on the evolution of storage vs. voiding symptoms after surgery and on the number of patients with firm erections for intercourse. As well, we miss data on treatment with 5-phosphodiesterase inhibitor, which is to be considered an important limitation for the evaluation of postoperative EF.

Notwithstanding all these limitations, up to date, this is the largest prospective study in Europe evaluating the association between QL and health-related outcomes (incontinence, urinary symptoms, and ED) in patients with CaP treated with RARP. Our study represents a further contribution in the evaluation of preoperative patient's health status and its possible implications on functional recovery after surgery. We strongly believe, as proposed by several authors [25,26], that the evaluation of preoperative QL and urinary/erectile function should be part of the routine assessment of patients with CaP, especially in patients undergoing radical treatment.

5. Conclusion

The implementation of the EORTC-QLQ-C30 questionnaire in the urological practice represents a further area of research in the next years. The results of our study suggest that most of the patients undergoing RARP present a good QL. However, patients with a lower QLQ-GHS score present a higher risk of postoperative poor functional outcomes including incontinence and LUTS. Further larger and multicentre studies are needed to confirm our results. These should define the role and method for an accurate preoperative QL assessment in patients with CaP undergoing surgery.

Authors contribution

Authorship: Authors have made a substantial contribution to the following:

Cosimo De Nunzio: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Antonio Luigi Pastore: Conception and design of the study, acquisition of data, revising it critically for important intellectual content, final approval of the version to be submitted.

Riccardo Lombardo: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Fabiana Cancrini: Conception and design of the study, acquisition of data, revising it critically for important intellectual content, final approval of the version to be submitted.

Antonio Carbone: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Andrea Fuschi: Conception and design of the study, acquisition of data, revising it critically for important intellectual content, final approval of the version to be submitted.

Lorenzo Dutto: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Andrea Tubaro: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Joern Heinrich Witt: Conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Conflict of interests

All the authors declare no conflict of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.024.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. https://doi.org/10.3322/caac.21442.

[2] Ficarra V, Novara G, Rosen RC, Artibani W, Carroll PR, Costello A, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012;62:405–17. https://doi.org/10.1016/j.eururo.2012.05.045.

[3] Liu F, Wang J, Wu H-L, Wang H, Wang J-X, Zhou R, et al. Leisure time physical activity and risk of prostate cancer: a dose-response meta-analysis. Minerva Urol Nefrol 2017. https://doi.org/10.23736/S0393-2249.17.02874-0.

[4] Cicione A, De Nunzio C, Manno S, Damiano R, Posti A, Lima E, et al. An update on prostate biopsy in the era of magnetic resonance imaging. Minerva Urol Nefrol 2018;70:264–74. https://doi.org/10.23736/S0393-2249.18.03048-5.

[5] Patel VR, Sivaraman A, Coelho RF, Chauhan S, Palmer KJ, Orvieto MA, et al. Pentafecta: a new concept for reporting outcomes of robot-assisted laparoscopic radical prostatectomy. Eur Urol 2011;59:702–7. https://doi.org/10.1016/j.eururo.2011.01.032.

[6] Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016;375:1425–37. https://doi.org/10.1056/NEJMoa1606221.

[7] Boeri L, Capogrosso P, Ventimiglia E, Cazzaniga W, Pederzoli F, Gandaglia G, et al. Depressive symptoms and low sexual desire after radical prostatectomy: early and long-term outcomes in a real-life setting. J Urol 2018;199:474–80. https://doi.org/10.1016/j.juro.2017.08.104.

[8] Lardas M, Liew M, van den Bergh RC, De Santis M, Bellmunt J, Van den Broeck T, et al. Quality of life outcomes after primary treatment for clinically localised prostate cancer: a systematic review. Eur Urol 2017;72:869–85. https://doi.org/10.1016/j.eururo.2017.06.035.

[9] Pompe RS, Tian Z, Preisser F, Tennstedt P, Beyer B, Michl U, et al. Short- and long-term functional outcomes and quality of life after radical prostatectomy: patient-reported outcomes from a tertiary high-volume center. Eur Urol Focus 2017;3:615–20. https://doi.org/10.1016/j.euf.2017.08.001.

[10] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29. https://doi.org/10.1016/j.eururo.2016.08.003.

[11] De Nunzio C, Pastore AL, Lombardo R, Simone G, Leonardo C, Mastroianni R, et al. The new Epstein gleason score classification significantly reduces upgrading in prostate cancer patients. Eur J Surg Oncol 2018. https://doi.org/10.1016/j.ejso.2017.12.003.

[12] Bach P, Döring T, Gesenberg A, Möhring C, Goepel M. Quality of life of patients after retropubic prostatectomy – pre- and postoperative scores of the EORTC QLQ-C30 and QLQ-PR25. Health Qual Life Outcomes 2011;9:93. https://doi.org/10.1186/1477-7525-9-93.

[13] Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. Qual Life Res 1993;2:287–95.

[14] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[15] Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. Eur J Cancer 1995;31A:2260–3.

[16] Cocks K, King MT, Velikova G, de Castro G, Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012;48:1713–21. https://doi.org/10.1016/j.ejca.2012.02.059.

[17] Wallerstedt A, Nyberg T, Carlsson S, Thorsteinsdottir T, Stranne J, Tyritzis SI, et al. Quality of life after open radical prostatectomy compared with robot-assisted radical prostatectomy. Eur Urol Focus 2018. https://doi.org/10.1016/j.euf.2017.12.010.

[18] Prabhu V, Taksler GB, Sivarajan G, Laze J, Makarov DV, Lepor H. Radical prostatectomy improves and prevents age dependent progression of lower urinary tract symptoms. J Urol 2014;191:412–7. https://doi.org/10.1016/j.juro.2013.08.010.

[19] Matsukawa Y, Yoshino Y, Ishida S, Fujita T, Majima T, Funahashi Y, et al. De novo overactive bladder after robot-assisted laparoscopic radical prostatectomy. Neurourol Urodyn 2018;37:2008–14. https://doi.org/10.1002/nau.23556.

[20] Haga N, Hata J, Matsuoka K, Koguchi T, Akaihata H, Kataoka M, et al. The impact of nerve-sparing robot-assisted radical prostatectomy on lower urinary tract function: Prospective assessment of patient-reported outcomes and frequency volume charts. Neurourol Urodyn 2018;37:322–30. https://doi.org/10.1002/nau.23297.

[21] Geiger-Gritsch S, Oberaigner W, Mühlberger N, Siebert U, Ladurner M, Klocker H, et al. Patient-reported urinary incontinence and erectile dysfunction following radical prostatectomy: results from the european prostate centre innsbruck. Urol Int 2015;94:419–27. https://doi.org/10.1159/000369475.

[22] Briganti A, Di Trapani E, Abdollah F, Gallina A, Suardi N, Capitanio U, et al. Choosing the best candidates for penile rehabilitation after bilateral nerve–sparing radical prostatectomy. J Sex Med 2012;9:608–17. https://doi.org/10.1111/j.1743-6109.2011.02580.x.

[23] Antonelli JA, Jones LW, Bañez LL, Thomas J-A, Anderson K, Taylor LA, et al. Exercise and prostate cancer risk in a cohort of veterans undergoing prostate needle biopsy. J Urol 2009;182:2226–31. https://doi.org/10.1016/j.juro.2009.07.028.

[24] Letellier M-E, Dawes D, Mayo N. Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health. Qual Life Res 2015;24:757–68. https://doi.org/10.1007/s11136-014-0791-8.

[25] Salonia A, Zanni G, Gallina A, Saccà A, Sangalli M, Naspro R, et al. Baseline potency in candidates for bilateral nerve-sparing radical retropubic prostatectomy. Eur Urol 2006;50:360–5. https://doi.org/10.1016/j.eururo.2005.12.007.

[26] Novara G, Ficarra V, D'Elia C, Secco S, Cavalleri S, Artibani W. Trifecta outcomes after robot-assisted laparoscopic radical prostatectomy. BJU Int 2011;107:100–4. https://doi.org/10.1111/j.1464-410X.2010.09505.x.