Impact of Surgical Approach on Patient-Reported Outcomes after Radical Prostatectomy: A Propensity Score-Weighted Analysis from a Multicenter, Prospective, Observational Study (The Pros-IT CNR Study)

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Patient-reported outcome measures · Prostate cancer · Quality of life · Radical prostatectomy · Sexual function · Urinary function

Abstract
Background: To report health-related quality of life outcomes as assessed by validated patient-reported outcome measures (PROMs) after radical prostatectomy (RP).

Methods: This study analyzed patients treated with RP within The PROState cancer monitoring in Italy, from the National Research Council (Pros-IT CNR). Italian versions of Short-Form Heath Survey and university of California los Angeles-prostate cancer index questionnaires were administered. PROMs were physical composite scores, mental composite scores and urinary, bowel, sexual functions and bothers

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(UF/B, BF/B, SF/B). Baseline unbalances were controlled with propensity scores and stabilized inverse weights; differences in PROMs between different RP approaches were estimated by mixed models. ***Results:*** Of 541 patients treated with RP, 115 (21%) received open RP (ORP), 90 (17%) laparoscopic RP (LRP) and 336 (61%) robot-assisted RP (RARP). At head-to-head comparisons, RARP showed higher 12-month UF vs. LRP (interaction treatment * time $p = 0.03$) and 6-month SF vs. ORP ($p < 0.001$). At 12-month from surgery, 67, 73 and 79% of patients used no pad for urinary loss in ORP, LRP and RARP respectively (no differences for each comparison). Conversely, 16, 27 and 40% of patients declared erections firm enough for sexual intercourse in ORP, LRP and RARP respectively (only significant difference for ORP vs. RARP, $p = 0.0004$). ***Conclusions:*** Different RP approaches lead to significant variations in urinary and sexual PROMs, with a general trend in favour of RARP. However, their clinical significance seems limited.

Introduction

Both European and North-American guidelines [1, 2] recommend radical prostatectomy (RP) as a standard management option for clinically localized prostate cancer (PCa), along with radiation therapy and active surveillance. However, no specific recommendations are given regarding the surgical approach, if open RP (ORP), laparoscopic RP (LRP) or robot-assisted RP (RARP).

Comprehensive meta-analyses [3–5] of retrospective institutional series, as well as the only available randomized controlled trail [6, 7], did not provide definitive data on the superiority of one surgical approach over the others. On the whole, these studies have been criticized because of arbitrary outcome definitions, lack of validated outcome measures, short follow-up time, disparities in surgeon's experience and inclusion of series from single surgeons or high volume institutions [8].

Considering such limitations, an increasing interest has risen towards prospective population-based studies with rigorous assessment of outcomes. Such studies are potentially able to account for selection bias and provide more reproducible results [9]. Up to now, 6 population-based projects [10–15] assessed the impact of surgical approach on perceptions of urinary, bowel, and sexual function and of general health-related quality of life (HRQoL) by validated patient-reported outcome measures (PROMs). However, these studies are not devoid of flaws, since they relied on long time span, generally including the learning phase of minimally invasive approaches.

In the present study, we compared HRQoL outcomes measured by PROMs after ORP, LRP or RARP in a contemporary Italian cohort of patients prospectively recruited within a short time span during the PCa monitoring in ITaly project from the National Research Council (Pros-IT CNR) [16, 17].

Materials and Methods

Study Design and Population

The Pros-IT CNR project is a prospective observational longitudinal study that monitors through validated tools an Italian cohort of 1,705 men diagnosed with PCa from September 2014 to September 2015 [16, 17]. The decision on treatments and surgical approach was made on patients and tumour's characteristics following current guidelines, institutional policy and physicians' preferences. The approval of the Ethics Committee of coordinating centre (Sant'Anna Hospital, Como, Italy; register number 45/2014) and local committees was obtained and all participants signed an informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki.

The present study is a retrospective analysis of the prospectively maintained Pros-IT database, focused on the patients treated with ORP, LRP or RARP as primary exclusive treatment. Patients treated with radiation treatment within 12 months from surgery, as well as those who received neoadjuvant or adjuvant androgen deprivation were excluded.

Assessment of HRQoL Outcomes

HRQoL outcomes were assessed by validated questionnaires delivered, self-administered and returned during in-hospital visits, at diagnosis and then at 6 and 12 months after surgery. Physical composite scores (PCS) and mental composite scores (MCS) were evaluated by the Italian versions of the Short-Form Heath Survey [18]. Urinary, bowel and sexual functions and bothers (UF/B, BF/B, SF/B, respectively) were evaluated by the University of California Los Angeles-prostate cancer index (Italian UCLA-PCI) [19]. Scores of both questionnaires ranged from 0 to 100, with higher scores indicating better outcomes.

Statistical Analyses

Statistical analyses relied on the following analytical steps. First, a comparison of preoperative baseline characteristics by standardized differences, without imputation of missing values, was performed. Second, propensity scores weighting was used to minimize baseline differences, since it was found to work better when small sample sizes were considered [20]. Propensity scores were estimated by logistic regression models with the type of RP as dependent variable and pre-treatment characteristics, which exceeded 10% of difference at univariate analyses as independent variables [21]. Stabilized inverse weights equal to (1/propensity

scoreLRP) and (1/propensity scoreRARP) were assigned to LRP and RARP patients, respectively, and weight of (1/1-[propensity scoreLRP + propensity scoreRARP]) to ORP patients, with weights stabilized for the observed frequencies in each group [22]. Third, mixed models were defined on weighted data to estimate the differences in HRQoL outcomes according to treatment type, time and treatment * time interaction, adjusting for baseline score. Compound symmetry covariance structure and Tukey adjustment for multiple comparisons were applied. Finally, in sensitivity analysis, propensity score trimming was considered to evaluate the population between the 2.5th centile or >97.5th of the propensity score distribution [23].

All analyses were 2-sided, and $p < 0.05$ was considered significant. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

Baseline Features before and after Propensity Score Weighting

From September 2014 to September 2015, 1,705 patients were enrolled in the Pros-IT CNR project. Data on treatments was available for 1,542 patients (90%) and were referred up to 12 months after diagnosis (Fig. 1). No baseline differences were recorded between the cohort whit available and not available information about treatment. This study focused on 541 RP patients, of whom 115 (21%) received ORP, 90 (17%) LRP and 336 (61%) RARP, after a median time of 83 days from the diagnosis (interquartile range 54–120; ORP vs. LRP vs. RARP, 79 vs. 82 vs. 85 days, $p = 0.21$). The rate of patients treated at high-volume centres (>50 procedures/year) was 74, 54 and 92% in ORP, LRP and RARP groups, respectively ($p < 0.0001$). The completion rate of UCLA-PCI and Short-Form Heath Survey questionnaires was 98.2 and 98.7% at baseline, 93.7 and 92.0% at 6 months, 94.2 and 96.1% at 12 months respectively.

Standardized preoperative differences in the unweighted sample exceeded 10% for 14/18 covariates – age, education, diabetes, comorbidities, family history of PCa, bioptic Gleason score and several HRQoL variables. After propensity score weighing, preoperative baseline differences were balanced (Table 1). Preoperative urinary- and bowel-domains were still close to the upper limit of 100, while PCS, MCS and sexual-domains were largely below.

After propensity score weighing, both nerve sparing and lymph-node dissection remained unbalanced. Nerve sparing was significantly more represented in RARP patients (75, 43 and 39% for RARP, LRP and ORP; $p < 0.0001$). Conversely, lymph-node dissection was significantly more represented in ORP patients (78.2, 40.3 and 33.7% for ORP, LRP and RARP; $p < 0.0001$).

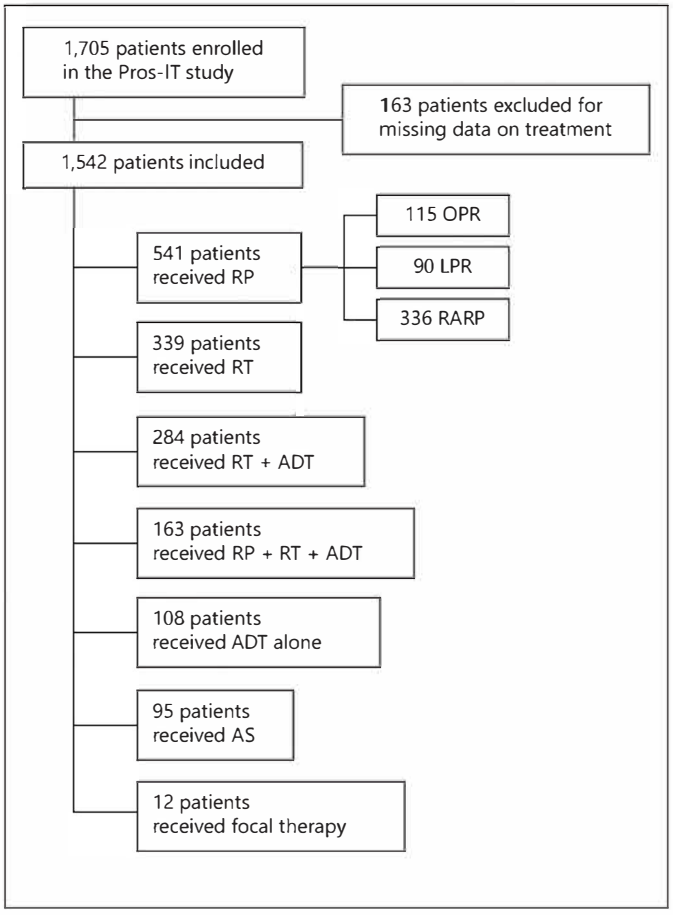

Fig. 1. Flowchart of patients included in this study, identified within the PCa monitoring in Italy project from the National Research Council (Pros-IT CNR) from September 2014 to September 2015. RP, radical prostatectomy; RARP, robot-assisted RP; RT, radiation therapy; AS, active surveillance.

Physical and Mental Status

At 6 months, the PCS decreased, to return closer to baseline at 12 months. A more marked 6-month decline was recorded for LRP (difference with baseline $p < 0.001$), followed by a more moderate recovery with respect to ORP and RARP. Both ORP and RARP showed a less pronounced decline and better recovery, almost complete for RARP (Table 2). No statistically significant differences among RP approaches were recorded ($p = 0.0940$ for the interaction treatment * time; Fig. 2).

The MCS steadily increased with respect to the baseline (difference between time points $p < 0.05$ for each

Table 1. Preoperative baseline characteristics of the cohort after propensity score weighting. Numbers indicate percentages for categorical variables, median and interquartile range or mean and SD for continuous variables; *p* values based on chi-square test or generalized linear models

	ORP	LRP	RARP	*p* value
Age, years	65.1±8.4	65.1±8.9	64.6±4.9	0.6888
Education > lower secondary school	45.1	47.5	43.3	0.7280
BMI ≥30 kg/m^2	10.7	11.2	11.6	0.9679
Current smoker	17.1	13.5	14.1	0.1009
Diabetes mellitus	11.0	11.1	10.7	0.9925
Moderate/severe co-morbidities ≥3	9.1	6.4	9.7	0.4511
Family history prostate cancer	23.5	24.0	21.3	0.8168
T stage				0.9950
T1	59.3	61.7	60.1	
T2	38.5	36.2	37.7	
T3 or T4	2.2	2.2	2.2	
Biopsy gleason score				0.9866
≤6	49.9	54.1	51.4	
3 + 4	26.0	23.4	25.2	
4 + 3	14.3	11.8	13.3	
≥8	9.8	10.7	10.5	
PSA, ng/mL	6.0 (4.5–7.8)	6.0 (5.3–7.1)	6.4 (5.0–9.2)	
SF-12 PCS	53.6±8.1	53.5±8.1	53.3±4.4	0.9305
SF-12 MCS	49.3±12.6	49.5±13.1	49.0±6.8	0.9060
UCLA PCI UF	95.6±17.3	95.5±23.4	95.2±9.3	0.9685
UCLA PCI UB	93.9±21.2	92.8±27.9	92.1±15.5	0.6745
UCLA PCI BF	95.1±14.0	96.5±12.2	95.9±7.8	0.4251
UCLA PCI BB	96.6±17.9	96.3±19.2	95.8±9.5	0.8362
UCLA PCI SF	62.9±36.4	62.0±38.6	61.9±20.6	0.9348
UCLA PCI SB	69.7±40.3	67.4±52.2	68.0±24.7	0.8176

ORP, open radical prostatectomy; LRP, laparoscopic radical prostatectomy, RARP, robot-assisted radical prostatectomy; BMI, body mass index; PCS, physical component score; MCS, mental component score; UCLA PCI, university of California Los Angeles-prostate cancer index; UF, urinary function; UB, urinary bother; BF, bowel function; BB, bowel bother; SF, sexual function; SB, sexual bother; IQR, interquartile range.

techniques; Table 2) without significant differences among RP approaches (p = 0.2033 for the interaction treatment * time; Fig. 2).

Urinary Function and Bother

The UF and UB scores had a significant decline at 6 months ($p < 0.001$ for all the approaches) followed by a gradual increase at 12 months, though far from complete restoration ($p < 0.01$ for all the comparisons between time points; Table 2). The magnitude of reduction in UF and UB was significantly lower for RARP vs. LRP at 12 months (p = 0.03) and for LPR vs. ORP at 6 months ($p < 0.001$), respectively (Table 3). A significant in between-group difference for both UF and UB was detected (p = 0.0002 and p = 0.03 for the interaction treatment * time, respectively; Fig. 2).

Referring to item "did you use pads for urinary loss?" of the UCLA-PCI questionnaire, the rate of cases with no need of pads was 63, 64 and 61% at 6 months (p = 0.84) and 67, 73 and 79% at 12 months for ORP, LRP and RARP, respectively (ORP vs. LRP p = 0.7628 at 6 months and p = 0.2707 at 12 months; ORP vs. RARP p = 0.7762 at 6 months and p = 0.0120 at 12 months; LRP vs. RARP p = 0.55762 at 6 months and p = 0.1617 at 12 months).

Bowel Function and Bother

After being stable at 6 months, BF significantly declined at 12 months ($p < 0.001$ for all the comparisons between time points). Conversely, no significant changes in BB were observed (Table 2). The interaction treatment * time curves did not show significant differences (p = 0.147 and p = 0.266 for BF and BB, respectively; Fig. 2), while a difference between OPR and LPR was found at the head-to-head comparison at 6 months ($p < 0.001$; Table 3).

Table 2. Comparison of variation over time of propensity-weighed UCLA-PCI and SF-12 scores, within each radical prostatectomy approach (open, laparoscopic or robot-assisted). Numbers indicate mean difference and 95% CI *p* indicates post hoc *p* value from mixed-model repeated measures analyses with Tukey adjustment)

	ORP	*p* value	LRP	*p* value	RARP	*p* value
SF-12 PCS						
Baseline vs. 6 months	1.34 (−0.35 to 3.03)	0.2526	2.9 (1.11 to 4.69)	<0.0001	1.01 (−0.64 to 2.67)	0.6157
Baseline vs. 12 months	1 (−0.79 to 2.79)	0.7229	1.65 (−0.24 to 3.54)	0.1437	0.02 (−1.65 to 1.7)	1.0000
SF-12 MCS						
Baseline vs. 6 months	−4.41 (−6.54 to −2.28)	<0.0001	−2.26 (−4.51 to 0)	0.0492	−3.08 (−5.17 to −1)	0.0002
Baseline vs. 12 months	−6.52 (−8.77 to −4.27)	<0.0001	−4.65 (−7.02 to −2.28)	<0.0001	−5.65 (−7.8 to −3.5)	<0.0001
UCLA PCI UF						
Baseline vs. 6 months	22.49 (15.86 to 29.11)	<0.0001	32.03 (25.04 to 39.03)	<0.0001	23.09 (16.6 to 29.61)	<0.0001
Baseline vs. 12 months	19.24 (12.16 to 26.32)	<0.0001	25.07 (17.81 to 32.34)	<0.0001	12.35 (5.73 to 18.97)	<0.0001
UCLA PCI UB						
Baseline vs. 6 months	15.76 (7.86 to 23.67)	<0.0001	31.55 (23.2 to 39.89)	<0.0001	18.82 (11.04 to 26.6)	<0.0001
Baseline vs. 12 months	16.33 (7.9 to 24.76)	<0.0001	19.85 (11.18 to 28.51)	<0.0001	8.73 (0.81 to 16.64)	0.0184
UCLA PCI BF						
Baseline vs. 6 months	−1.61 (−4.84 to 1.62)	0.8319	1.35 (−2.05 to 4.75)	0.9486	0.15 (−3.02 to 3.31)	1.0000
Baseline vs. 12 months	5.99 (2.58 to 9.4)	<0.0001	9.67 (6.15 to 13.2)	<0.0001	7.46 (4.25 to 10.67)	<0.0001
UCLA PCI BB						
Baseline vs. 6 months	0.56 (−3.43 to 4.55)	1.0000	3.78 (−0.44 to 8.01)	0.122	0.2 (−3.71 to 4.11)	1.0000
Baseline vs. 12 months	−1.01 (−5.23 to 3.21)	0.9981	1.93 (−2.43 to 6.29)	0.9074	−0.81 (−4.79 to 3.16)	0.9994
UCLA PCI SF						
Baseline vs. 6 months	44.13 (37.23 to 51.03)	<0.0001	38.7 (31.46 to 45.94)	<0.0001	30.05 (23.31 to 36.8)	<0.0001
Baseline vs. 12 months	32.23 (24.99 to 39.47)	<0.0001	33.33 (25.83 to 40.82)	<0.0001	23.5 (16.65 to 30.35)	<0.0001
UCLA PCI SB						
Baseline vs. 6 months	21.23 (11.71 to 30.74)	<0.0001	31.95 (21.97 to 41.93)	<0.0001	24.47 (15.2 to 33.8)	<0.0001
Baseline vs. 12 months	15.99 (6.01 to 25.97)	<0.0001	23.26 (12.93 to 33.6)	<0.0001	17.63 (8.18 to 27.08)	<0.0001

ORP, open radical prostatectomy; LRP, laparoscopic radical prostatectomy; RARP, robot-assisted radical prostatectomy; PCS, physical component score; MCS, mental component score; UCLA PCI, university of California Los Angeles-prostate cancer index; UF, urinary function; UB, urinary bother; BF, bowel function; BB, bowel bother; SF, sexual function; SB, sexual bother.

Sexual Function and Bother

For all the surgical approaches a marked reduction in SF and SB was recorded at 6 months, followed by a slight restoration at 12 months with final values considerably below the baseline (all $p < 0.001$; Table 2). RARP showed a decrease in SF. Its magnitude was 10 points lower than other approaches, but the only comparisons reaching statistical significance were 6-months SF for RARP vs. ORP ($p < 0.001$), and 6-months SB for ORP vs. LRP ($p = 0.016$; Table 3). A significant interaction treatment * time was found for SF ($p < 0.0001$), not for SB ($p = 0.1797$; Fig. 2), also after adjusting models for nerve sparing ($p = 0.0005$ and $p = 0.4810$ for SF and SB respectively).

Among patients with preoperative normal erections, the rate declaring erections firm enough for sexual intercourse was higher for RARP, both after 6 months (14, 28 and 30% in ORP, LRP and RARP groups, respectively; $p = 0.0143$ for ORP vs. LRP, $p = 0.0043$ for ORP vs. RARP; $p = 0.7043$ for LRP vs. RARP) and 12 months (16, 27 and 40%, $p = 0.0822$ for ORP vs. LRP, $p = 0.0004$ for ORP vs. RARP; $p = 0.0667$ for LRP vs. RARP).

Fig. 2. Estimated mean for quality-of-life scores (Short-Form Heath Survey and UCLA-PCI), by treatment over time (bars represent 95% CI *p* value from propensity-score weighted mixed models repeated measures analyses for the interaction treatment time). RARP, robot-assisted radical prostatectomy; ORP, open radical prostatectomy; LRP, laparoscopic radical prostatectomy; SF, sexual function; PCS, physical component score; MCS, mental component score; UCLA PCI, University of California los Angeles-prostate cancer index.

(*For figure see next page.*)

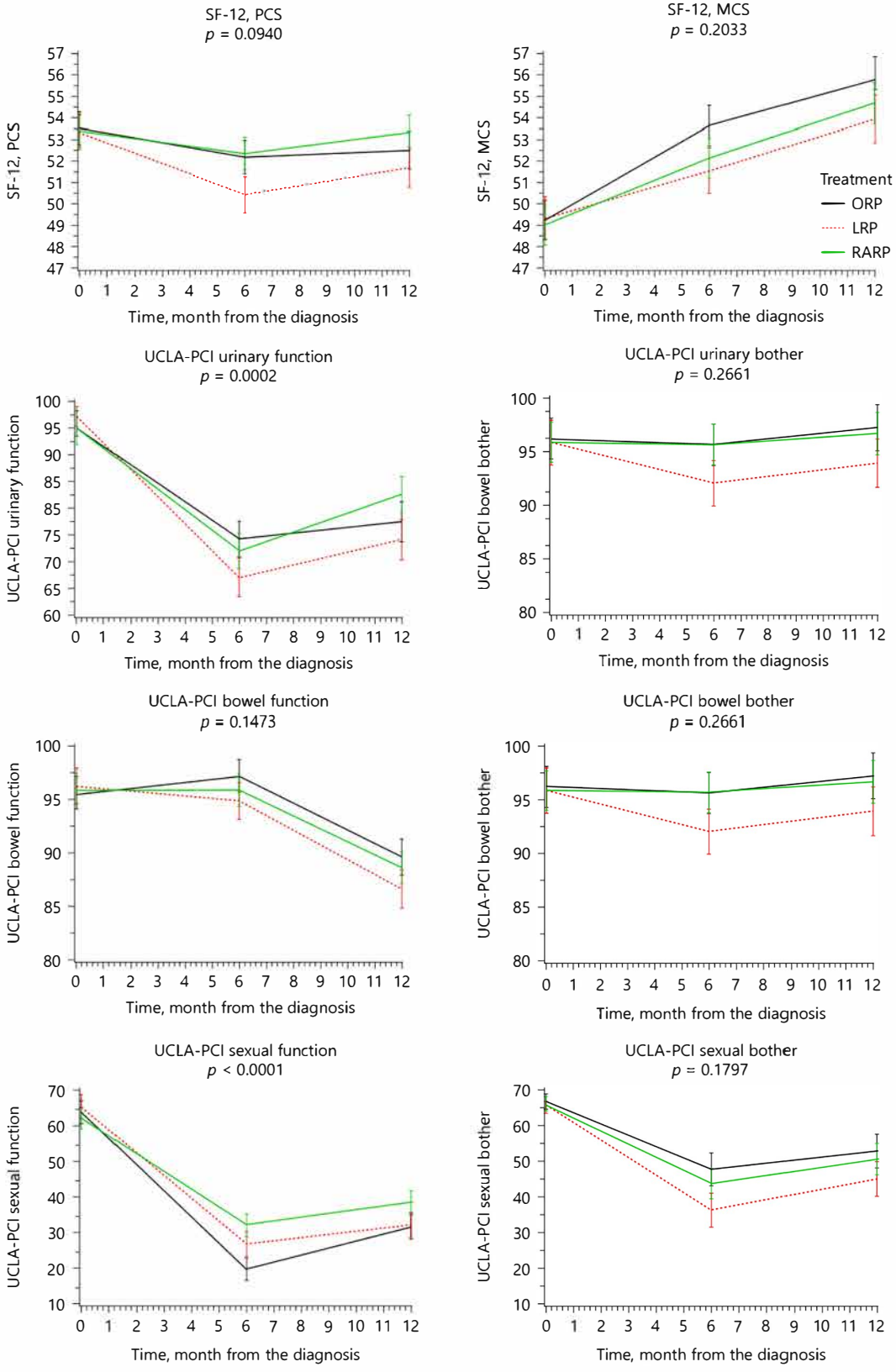

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Table 3. Comparison of variation over time across radical prostatectomy surgical approaches of the propensity-weighed UCLA-PCI and SF-12 scores. Numbers indicate mean difference and 95% CI *p* indicates post hoc *p* value from mixed-model repeated measures analyses with Tukey adjustment

	ORP vs. LRP	*p* value	ORP vs. RARP	*p* value	LRP vs. RARP	*p* value
SF-12 PCS						
Baseline	0.16 (−1.58 to 1.91)	1.0000	0.14 (−1.54 to 1.81)	1.0000	−0.03 (−1.80 to 1.74)	1.0000
6 months	1.71 (−0.11 to 3.53)	0.0863	−0.19 (−1.93 to 1.56)	1.0000	−1.9 (−3.73 to −0.06)	0.0362
12 months	0.80 (−1.21 to 2.81)	0.9476	−0.84 (−2.70 to 1.02)	0.8979	−1.64 (−3.58 to 0.31)	0.1809
SF-12 MCS						
Baseline	−0.10 (−2.23 to 2.03)	1.0000	0.23 (−1.82 to 2.27)	1.0000	0.33 (−1.82 to 2.48)	0.9999
6 months	2.12 (−0.10 to 4.33)	0.0753	1.53 (−0.60 to 3.65)	0.3860	−0.59 (−2.82 to 1.64)	0.9962
12 months	1.82 (−0.62 to 4.27)	0.3335	1.07 (−1.20 to 3.34)	0.8700	−0.75 (−3.12 to 1.61)	0.9869
UCLA PCI UF						
Baseline	−2.31 (−9.93 to 5.32)	0.9906	1.58 (−5.74 to 8.90)	0.9990	3.89 (−3.87 to 11.6)	0.8272
6 months	7.11 (−0.69 to 14.9)	0.1074	2.22 (−5.27 to 9.72)	0.9920	−4.88 (−12.8 to 3.03)	0.6007
12 months	3.39 (−5.01 to 11.8)	0.9436	−5.25 (−13.2 to 2.74)	0.5130	−8.65 (−16.9 to −0.44)	0.0300
UCLA PCI UB						
Baseline	−1.54 (−10.4 to 7.28)	0.9998	2.31 (−6.17 to 10.79)	0.9950	3.85 (−5.11 to 12.81)	0.9202
6 months	14.1 (5.03 to 23.1)	<0.0001	5.43 (−3.27 to 14.13)	0.5860	−8.63 (−17.8 to 0.52)	0.0625
12 months	1.77 (−7.99 to 11.5)	0.9998	−5.22 (−14.51 to 4.07)	0.7170	−6.99 (−16.5 to 2.52)	0.3527
UCLA PCI BF						
Baseline	−0.70 (−4.24 to 2.83)	0.9995	−0.43 (−3.83 to 2.97)	1.0000	0.27 (−3.31 to 3.86)	1.0000
6 months	2.29 (−1.34 to 5.92)	0.5720	1.31 (−2.18 to 4.81)	0.9630	−0.97 (−4.63 to 2.69)	0.9961
12 months	3.02 (−0.88 to 6.92)	0.2796	1.03 (−2.66 to 4.73)	0.9950	−1.99 (−5.79 to 1.81)	0.7910
UCLA PCI BB						
Baseline	0.36 (−4.05 to 4.76)	1.0000	0.34 (−3.89 to 4.57)	1.0000	−0.02 (−4.48 to 4.45)	1.0000
6 months	3.61 (−0.94 to 8.16)	0.2490	−0.04 (−4.39 to 4.31)	1.0000	−3.65 (−8.24 to 0.94)	0.2472
12 months	3.33 (−1.52 to 8.18)	0.4498	0.53 (−4.08 to 5.13)	1.0000	−2.81 (−7.54 to 1.93)	0.6545
UCLA PCI SF						
Baseline	−1.68 (−8.87 to 5.52)	0.9984	1.67 (−5.25 to 8.59)	0.9980	3.35 (−3.94 to 10.63)	0.8866
6 months	−7.12 (−14.5 to 0.29)	0.0706	−12.41 (−19.6 to −5.26)	<0.0001	−5.29 (−12.73 to 2.16)	0.4012
12 months	−0.59 (−8.55 to 7.36)	1.0000	−7.06 (−14.62 to 0.49)	0.0890	−6.47 (−14.22 to 1.28)	0.1896
UCLA PCI SB						
Baseline	0.74 (−9.17 to 10.7)	1.0000	0.63 (−8.89 to 10.15)	1.0000	−0.11 (−10.13 to 9.91)	1.0000
6 months	11.37 (1.17 to 21.6)	0.0161	3.89 (−5.94 to 13.73)	0.9500	−7.48 (−17.72 to 2.77)	0.3625
12 months	7.91 (−3.03 to 18.9)	0.3758	2.3 (−8.1 to 12.7)	0.9990	−5.61 (−16.27 to 5.05)	0.7847

ORP, open radical prostatectomy; LRP, laparoscopic radical prostatectomy; RARP, robot-assisted radical prostatectomy; PCS, physical component score; MCS, mental component score; UCLA PCI, university of California Los Angeles-prostate cancer index; UF, urinary function; UB, urinary bother; BF, bowel function; BB, bowel bother; SF, sexual function; SB, sexual bother.

Discussion

The present study prospectively collected data from a large, contemporary, nation-based cohort of RPs and provided several noteworthy finding.

First, in Italy, the robotic approach has seen a steadily diffusion and clear trend towards centralization. Indeed, RARP were preponderant in our cohort covering 3 out 5 cases, while the remaining 2 equally shared by LRP and ORP. Institutional case load was significantly unbalanced, since almost all RARP were performed at high volume centres, whereas only 75% of LRP and 50% of ORP. Moreover, a significantly larger proportion of low-risk PCa were treated with RARP in the unweighted cohort. This data may raise concerns whether less strict indications to prostatectomy may exist when the robotic approach is available, due to either more favorable perception of its "toxicity profile" or necessity of reaching the break-even point to balance fixed costs of instrumentations [24, 25]. Such an unbalance represents a selection bias limiting any retrospective study. The statistical plan was directed to account for this bias and allow a more reliable analysis, comparing groups with similar baseline features.

Second, candidates to RP had depressed baseline physical- and mental-related QoL (median value: 53 for PCS and 49 for MCS), similarly to the age-matched Italian co-

Table 4. Summary of findings of previous observational population-based study, as well as of those of the present study, which reported health-related QoL outcomes as assessed by validated PROMs after RP

Author, year	Nation, registry	Time Span	PROMs assessment	RP techniques (number of patients)	UF findings*	SF findings*	BF findings*
Alemozaffar et al. [10], 2015	USA, HPFS	2000–2010	EPIC	ORP (621) vs. RARP (282)	No differences	No differences	NA
Herlemann et al. [11], 2018	USA, CAPSURE	2004–2016	UCLA-PCI, EPIC	ORP (1,137) vs. RARP (755)	Better preservation of UF for RARP	No differences	NA
Haglind et al. [12], 2015	Sweden, LAPPRO trial	2008–2011	IIEF	ORP (778) vs. RARP (1,847)	No differences	Better preservation of SF for RARP	NA
Ong et al. [14], 2016	Australia, Victorian Prostate Cancer registry	2009–2012	EPIC	ORP (1,117) vs. RARP (885)	No differences	No differences	NA
Shin et al. [15], 2018	South Korea	2014–2015	EORTC QLQ-C30, EORTC QLQ-PR25	OPR (41) vs. LRP (63) vs. RARP (105)	No differences	No differences	No differences
Present study	Italy, Pros-IT CNR	2014–2015	SF-12 and UCLA-PCI	OPR (115) vs. LRP (90) vs. RARP (336)	Betterpreservation of UF of RARP vs. LRP	No differences	No differences

* Functional outcomes findings refer to 12-month assessment.

QoL, quality of life; PROMs, patient-reported outcome measures; RP, radical prostatectomy; UF, urinary function; SF, sexual function; BF, bowel function; LAPPRO, Laparoscopic Prostatectomy Robot Open; IIEF, International Index of Erectile Function; OPR, open radical prostatectomy; RARP, robot-assisted radical prostatectomy; NA, not assessed; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; LRP, laparoscopic radical prostatectomy; EPIC, Expanded Prostate Cancer Index Composite; CAPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; UCLA-PCI, University of California, Los Angeles Prostate Cancer Index; HPFS, Health Professionals Follow-up Study; Pros-IT CNR, PROState cancer monitoring in Italy, from the National Research Council; QoL, quality of life.

hort (PCS 49, MCS 50) [26], slightly better than the entire Pros-IT cohort (51 for PCS and 49 for MCS) [17]. After an early decline, particularly evident in the LRP group, PCS returned close to baseline. In particular, RARP group had an almost complete recovery. Conversely, MCS progressively increased over time, irrespectively from the surgical approach. This may reflect the relief from cancer- and hospitalization-related anxiety, as hypothesized in other populations showing that surgery could preserve PCS and improve mental-related QoL [14, 27, 28].

Third, also variations in urinary- bowel- and sexual-related PROMs were consistent with previous reports [28] showing a steep decline at 6 months followed by incomplete restoration. Significant between-group differences were found for UF, UB and SF indicating that surgical approach could be a determinant of urinary and sexual outcomes. At rough comparisons, an advantage in favour of RARP over LRP for urinary outcomes, as well as over ORP for the sexual ones was evident. However, the magnitude of such differences should be regarded as clinically limited since it rarely reaches 10 points of difference or statistical significance.

When considering specific questions, that is, the number of pad at 12 months and erection stiff for intercourse at 12 months, absolute rates were fairly inferior with respect to previous reports [3–5]. However, these [3–5] generally involved only one or few experienced surgeons, at high-volume institutions. Additionally, the definition of both continence and potency were often arbitrary and lack of standardized definition. Conversely, our data reflect a more "real world" scenario, where both multiple surgeons and centres were involved.

Taken together, these results indicate that a superiority of the robotic approach could be intuited but not substantiated, as in previous similar studies focused on PROMs (Table 4). The American Prospective Health Professional Follow-up Study [10], adopting the Expanded Prostate Cancer Index Composite 26 (EPIC-26), reported no significant differences at 2 years depending on surgical approach in 600 men (ORP 468, RARP 132) recruited between 2000 and 2010. The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) [11] study showed superior urinary function at 12 months for the open approach in a cohort of 1,451 patients (909 ORP, 542 RARP) investigated by the UCLA-PCI (period 2004–2011) and EPIC-26 questionnaires (2011 and 2016). The Swedish Laparoscopic Prostatectomy Robot Open study [12, 13] reported no differences in continence and sexual function for

RARP on 2,265 patients (ORP 778, RARP 1847) treated between 2008 and 2011, assessing functional outcomes by a study-dedicated questionnaire. The analysis of the Australian population from the Victorian PCa registry [14] reported no differences in urinary and sexual functions assessed at 12 months by the EPIC-26 questionnaire through phone interview on 2002 cases (1117 ORP, 885 RARP) treated in the period 2009–2012. Finally, a Korean study [15] at 7 academic centres with high-volume surgeons recruited 258 patients (41 ORP, 63 LRP, 105 RARP) from October 2014 to December 2015 and found a better recovery of sexual functions in the RARP and LRP groups, as measured by the EORTC QLQ-C30 questionnaire.

The overall concordance between these and our results is particularly meaningful considering the heterogeneity of studies in terms of period and time span, inclusion of learning curves, populations and instruments to assess QoL. The design of the Pros-IT CNR study aimed at optimizing the reproducibility of results through several peculiar features: participating institutions had various affiliation and a wide range of case load; the time span was restricted within 12 months to represent the most contemporary scenario; minimally invasive approaches were largely mature and procedures consolidated; given the Italian educational pathway, only expert surgeons were involved and residents excluded [29]; the confounding effect due to adjunctive treatments was controlled by including only exclusive RP.

It was ascertained that no overt advantages attributable to the robotic approach emerged; on the other hand, it should also be remarked that RARP was at least not inferior to counterparts. This finding is noteworthy considering the well-established significant benefits on peri-operative course and the equivalent oncological outcomes [30, 31]. Moreover, it cannot be denied that investigating functional outcomes from the patient's side by PROMs, although unequivocally meaningful, suffer from poor objectivity and reproducibility because they are influenced by individual behavioural profiles and expectations from the procedure [32]. Only instrumental measurements could be more objective to provide a rigorous comparison, but they cannot be applied on large multicentre cohorts. Probably, at the end of the day, it should be simply said that the major reason to debate on the effectiveness of robotics is represented by the costs of this technology and that this controversy is destined to vanish once competitors will come.

Several limitations of our study need to be disclosed. First, the observational design could have made analyses susceptible to confounders and impaired the definition of sample size a priori. Second, the involvement of participating centres on a voluntary basis, with almost half from the North of Italy could have limited the representability of all Italian scenario. Third, lack of data on the factors influenced the patient's choice and individual surgeon's experience. Fourth, lack of data on patient's income and social network influenced HRQoL.

In conclusion, data from the sub-cohort of patients submitted to prostatectomy in the Pros-IT CNR study confirms that the robotic approach tends to be favourable over counterparts in terms of functional outcomes, yet without showing any definite clinical advantages.

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Ethics Statement

All patients involved in this study provided a written informed consent. The study protocol has been approved by committee on human research of all research institutes.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Authors Contribution

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Appendix

§ The Pros-IT CNR Group

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