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ORIGINAL ARTICLE

# Health-related quality of life 24 months after prostate cancer diagnosis: an update from the Pros-IT CNR prospective observational study

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## ABSTRACT

BACKGROUND: This study analyzes patient health-related quality of life (QoL) 24-month after prostate cancer (PCa) diagnosis within the PROState cancer monitoring in ITaly from the National Research Council (Pros-IT CNR) study.

METHODS: Pros-IT CNR is an ongoing, longitudinal and observational study, considering a convenience sample of patients enrolled at PCa diagnosis and followed at 6, 12, 24, 36, 48 and 60 months from the diagnosis. Patients were grouped according to the treatment received: nerve sparing radical prostatectomy (NSRP), non-nerve sparing radical prostatectomy (NNSRP), radiotherapy (RT), RT plus androgen deprivation (RT plus ADT) and active surveillance (AS). QoL was measured through the Italian versions of SF-12 and UCLA-PCI questionnaires at diagnosis and at 6-12 and 24-month. The minimal clinically important difference (MCID) was defined as half a standard deviation of the baseline domain.

RESULTS: Overall, 1537 patients were included in the study. The decline in urinary function exceeded the MCID at each timepoint only in the NSRP and NNSRP groups (at 24 months -14.7, P<0.001 and -19.7, P<0.001, respectively). The decline in bowel function exceeded the MCID only in the RT (-9.1, P=0.02) and RT plus ADT groups at 12 months (-10.3, P=0.001); after 24 months, most patients seem to recover their bowel complaints. The decline in sexual function exceeded the MCID at each timepoint in the NNSRP, NSRP and RT plus ADT groups (at 6 months -28.7, P<0.001, -37.8, P<0.001, -20.4, P<0.001, respectively).
CONCLUSIONS: Although all the treatments were relatively well-tolerated over the 24 month period following PCa diagnosis, each had a different impact on QoL.

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KEY WORDS: Prostatic neoplasms; Quality of life; Patient reported outcomes measure; Prostatectomy; Radiotherapy; Watchful waiting.

Disease-specific health-related quality of life (QoL) outcomes are essential components of decision-making process in prostate cancer (PCa) patients.[1, 2] Radiotherapy, prostatectomy or active surveillance represent the therapeutic options for localized PCa. Treatments with curative intent such as external beam radiotherapy, brachytherapy, and radical prostatectomy are able to achieve similar results in terms of overall survival and local control.[3] Nonetheless, comparing effectiveness and harms of such treatment modalities is critical for shared decision making (SDM).[4]

Recently, several studies reported very interesting results about QoL of patients with PCa submitted to one or more of the radical treatments previously mentioned.[5-7] However, generalizability of these results may be limited across different populations, due to differences in measurement tools, reporting methods and treatment modalities (*i.e.* older treatment *vs*. more contemporary such as minimally-invasive radical prostatectomy and intensity-modulated radiation therapy). Nonetheless, understanding the effectiveness and harms of each treatment is critical in patients' counseling and shared decision making. Therefore, the present study aimed at investigating the potential impact that radiation therapy, radical prostatectomy and active surveillance may have on QoL outcomes measured up to 24-month from PCa diagnosis in a contemporary Italian cohort of patients enrolled within the "PROState cancer monitoring in Italy" project from the National Research Council (Pros-IT CNR).

## Materials and methods

### Study design

The Pros-IT CNR project is an ongoing, longitudinal and observational study, whose aim is to monitor QoL in PCa patients.[8] Briefly, 97 Urology, Radiation Oncology and Medical Oncology facilities located throughout Italy enrolled a non-probability convenience sample of 1705 treatment-naïve patients with histologically confirmed PCa from September 2014 to September 2015. Patients were enrolled at PCa diagnosis (baseline) and are being followed at 6 timepoints after diagnosis (follow-ups at 6, 12, 24, 36, 48 and 60 months from the diagnosis).[9, 10] At enrollment, demographics and cancer characteristics and QoL were evaluated. Treatments and QoL were evaluated at each follow-up.

The Ethics Committee of the coordinating center (Sant'Anna Hospital, Como, Italy; register number 45/2014), as well as that of each center, approved the study protocol. The study was carried out in accordance with the principles of the Declaration of Helsinki. All participants signed an informed consent.

### Assessment of QoL outcomes

The Short-Form Health Survey (SF-12 Standard v1 scale)[11] was used to measure the Physical Component Score (PCS) and the Mental Component Score (MCS). The University of California Los Angeles-Prostate Cancer Index (Italian UCLA-PCI)[12, 13] was used to evaluate urinary (UF, UB), bowel (BF, BB) and sexual (SF, SB) function and bother. For both questionnaires,

scores range from 0 to 100, and higher scores represent better condition. All questionnaires were delivered by the referring physician and completed privately by each patient.

### Exposures

Treatments performed until the 24-month follow-up were considered as the "exposure". For the aim of this study, nerve sparing radical prostatectomy (NSRP), non-nerve sparing radical prostatectomy (NNSRP), both regardless of the surgical approach (considering the apparent equivalence in terms of functional outcomes[14, 15]), radiotherapy (RT), RT plus androgen deprivation therapy (RT plus ADT) and active surveillance (AS) were considered. Patients treated with either adjuvant RT or adjuvant ADT after prostatectomy, or with brachytherapy were excluded. High-risk patients according to the European Association of Urology definition submitted to AS and those who did not remain within this group up to the 24-month follow-up were excluded.

### Statistical analysis

Differences in baseline characteristics according to treatment type were assessed using Fisher's exact or Chi-squared tests and Wilcoxon rank-sum test or generalized linear models for categorical and continuous variables, respectively.

Multiple imputation (Markov chain Monte Carlo multiple imputation) of missing variables was performed; 10 imputed datasets were combined using Proc MI Analyze. Mixed-effects models evaluated changes in QoL scores according to treatment, time, and treatment*time interaction. Adjustment variables consisted of baseline QoL scores, age at diagnosis, education, Body Mass Index (BMI), smoking status, comorbidities according to Cumulative Illness Rating Scale (CIRS), family history of PCa, T-stage, ISUP grade group and PSA. Compound symmetry covariance structure and Tukey adjustment for multiple comparisons were considered. Subgroup analyses according to baseline UF, BF and SF scores (highest quartile vs. lower quartile) were also performed. Differences in QoL scores were interpreted as clinically significant if they were greater than the Minimal Clinically Important Differences (MCID). The MCID was defined as half a standard deviation of each baseline domain from the Pros-IT CNR data.[16, 17]

Two-tail P values <0.05 were considered statistically significant. The macro "type3_MI_mixed" was used to obtain a single weighted type III statistic.[18] The analyses were performed using SAS statistical package, release 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Characteristics of patients at diagnosis

From the Pros-IT CNR cohort, 1 537 patients were included in the current study, of whom 311 treated with NSRP, 187 with NNSRP, 334 with RT, 252 with RT plus ADT and 74 with AS (Supplementary Digital Material 1: Supplementary Figure 1). Overall, 1033 patients (89%) and 804 (69%) completed 12-month and 24-month follow-up, respectively. Response rates to the UCLA-PCI domains ranged from 96 and 98% at the baseline, while between 91 and 96% at the 24-month follow-up. Response rates to SF-12 were lower, but always higher than 85% (Supplementary Digital Material 2: Supplementary Table I).

Patients characteristics at diagnosis were summarized in Table I. Generally, patients treated with RT and RT plus ADT were older, more frequently obese, with higher comorbidities and had higher-risk disease features relative to those treated with NSRP, NNSRP or AS. Similar patterns were recorded within imputed data (Supplementary Digital Material 3: Supplementary Table II).

Minimally clinical important differences calculated within Pros-IT data were 10 and 13 points for UF and UB, 7 and 9 points for BF and BB, 14 and 17 points for SF and SB, respectively. For SF-12 domains, MCID was calculated as 4 points for both PCS and MCS.

### Urinary function and bother

Baseline UF and UB scores were high across all treatment groups (Table I). As shown in Table II and Figure 1, NNSRP and NSRP patients experienced the two highest (absolute and relative) declines during follow-ups. Moreover, they were significantly greater than the MCID. Indeed, rela-

TABLE I.—*Baseline characteristics of 1158 patients within in the Pros-IT CNR Study cohort at prostate cancer diagnosis, according to treatment modality.*

| | NSRP (N.=311) | NNSRP (N.=187) | RT (N.=334) | AS (N.=74) | P value |
|---|---|---|---|---|---|
| Age at diagnosis, years, mean±SD | 63.2±6.8 | 66.9±6.1 | 72.8±5.2 | 66.9±7.4 | <0.0001 |
| Education >lower secondary school, N. (%) | 178 (57.6) | 100 (53.8) | 144 (43.6) | 43 (58.1) | <0.0001 |
| BMI≥30 kg/m², N. (%) | 34 (11.1) | 29 (15.5) | 56 (17.1) | 8 (10.8) | 0.02 |
| Current smoker, N. (%) | 48 (15.8) | 35 (18.9) | 43 (13.2) | 11 (15.3) | 0.2 |
| Diabetes mellitus, N. (%) | 23 (7.4) | 28 (15.0) | 57 (17.2) | 5 (6.8) | <0.0001 |
| 3+ moderate/severe comorbidities*, N. (%) | 32 (10.3) | 22 (11.8) | 59 (17.7) | 11 (14.9) | 0.009 |
| Family history of prostate cancer, N. (%) | 71 (23.1) | 32 (17.5) | 39 (11.7) | 8 (10.8) | 0.001 |
| T staging at diagnosis, N. (%) | | | | | <0.0001 |
| T1 | 200 (65.6) | 97 (55.4) | 131 (41.6) | 66 (93.0) | |
| T2 | 102 (33.4) | 72 (41.1) | 150 (47.6) | 5 (7.0) | |
| T3 or T4 | 3 (1.0) | 6 (3.4) | 34 (10.8) | 0 (0.0) | |
| ISUP grade group at diagnosis, N. (%) | | | | | <0.0001 |
| 1 | 186 (60.0) | 76 (40.9) | 155 (47.1) | 70 (97.3) | |
| 2 | 78 (25.2) | 49 (26.3) | 86 (26.1) | 1 (1.3) | |
| 3 | 27 (8.7) | 36 (19.4) | 47 (14.3) | 1 (1.3) | |
| 4-5 | 19 (6.1) | 25 (13.4) | 41 (12.5) | 0 (0.0) | |
| PSA at diagnosis, ng/mL, median (Q1, Q3) | 6.3 (5, 8.7) | 6.9 (5.1, 10) | 7 (5.1, 9.9) | 6.2 (4.9, 7.7) | <0.0001 |
| D'Amico Risk Class, N. (%) | 120 (39.1) | 43 (23.6) | 70 (21.4) | 60 (85.7) | <0.0001 |
| Low | 152 (49.5) | 97 (53.3) | 146 (44.7) | 10 (14.3) | |
| Intermediate | 35 (11.4) | 42 (23.1) | 111 (33.9) | 0 (0.0) | |
| High | | | | | |
| Non-clinically significant PCa**, N. (%) | 52 (33.0) | 16 (9.9) | 36 (22.4) | 54 (33.5) | <0.0001 |
| UCLA PCI UF, mean±SD | 96.5±10.7 | 94.2±15 | 91.9±17.1 | 93.8±15 | 0.0006 |
| UCLA PCI UB, mean±SD | 92.8±20 | 92.3±19.5 | 86.2±24.5 | 92.5±17 | <0.0001 |
| UCLA PCI BF, mean±SD | 96.1±9.3 | 94.3±12.9 | 91.7±15.4 | 94.5±12.6 | 0.0004 |
| UCLA PCI BB, mean±SD | 92.3±12.9 | 94.6±16 | 92.9±18.4 | 95.9±14.4 | 0.01 |
| UCLA PCI SF, mean±SD | 66.6±27 | 56.4±29.2 | 37.9±30.3 | 61.1±30.2 | <0.0001 |
| UCLA PCI SB, mean±SD | 71.8±32.2 | 61.7±35.1 | 58.7±36.5 | 75.7±27.2 | <0.0001 |
| SF-12 PCS, mean±SD | 53.7±5.7 | 52.6±6.7 | 50.8±7.8 | 52.7±6.1 | <0.0001 |
| SF-12 MCS, mean±SD | 49.3±9.4 | 47.9±10 | 50.2±9.7 | 50.9±9.2 | 0.03 |

*Based on Cumulative Illness Rating Scale (CIRS); **ISUP grade group 1, and clinical T staging at diagnosis T1-T2a, and PSA at diagnosis <10 ng/mL, 1 or 2 positive cores involved.
Scores ranges from 0 to 100, with higher scores representing better quality of life in relation to functions or symptoms
NSRP: nerve-sparing exclusive radical prostatectomy; NNSRP: non nerve-sparing exclusive radical prostatectomy; ER: exclusive radiotherapy; RAD: radiotherapy and androgen deprivation; as: active surveillance. SD: standard deviation; BMI: Body Mass Index; Q1: quartile 1; Q3: quartile 3. SF-12: Short-Form Health Survey; PCS: Physical Component Subscale; MCS: Mental Component Subscale; UCLA: 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.

tive to baseline, UF scores declined -29.9 (95% confidence interval [CI] -32.9, -26.8) *vs.* -20.8 (-23.2, -18.4) at 6-month, -22.1 (-25.2, -19.1) *vs.* -12.3 (-14.6, -9.9) at 12-month and -19.7 (-22.9, -16.5) *vs.* -14.7 (-17.2, -12.2) at 24 months for NNSRP and NSRP, respectively. Conversely, a decrease in UF and UB scores in patients treated with RT, RT plus ADT and AS were not clinically meaningful (Table II, Figure 1). The decline in UF and UB scores was particularly evident among patients with the highest quartile baseline scores (Supplementary Digital Material 4: Supplementary Table III). Specifically investigating number of pads used per day, 32%, 46%, 2%, 3% *vs.* 0% declared to use pads at 6-month (P<0.001), 17%, 33%, 3%, 4% *vs.* 0% at 12-months (P<0.001) and 15%, 27%, 4%, 4% *vs.* 0% at 24-months (P<0.001) in NSRP, NNSRP, RT, RT plus ADT and AS groups, respectively.

In the analyses comparing scores between different treatment groups, adjusted UF mean values in NNSRP group were significantly worse and differences exceeded the MCID relative to those observed in the RT, RT plus ADT and AS groups. Conversely, adjusted UF mean values in NSRP group were significantly lower only at 6-month relative to patients treated with either AS or RT plus ADT. Finally, no clinically meaningful differences were observed between RT and RT plus ADT groups, between RT and AS, as well as be-

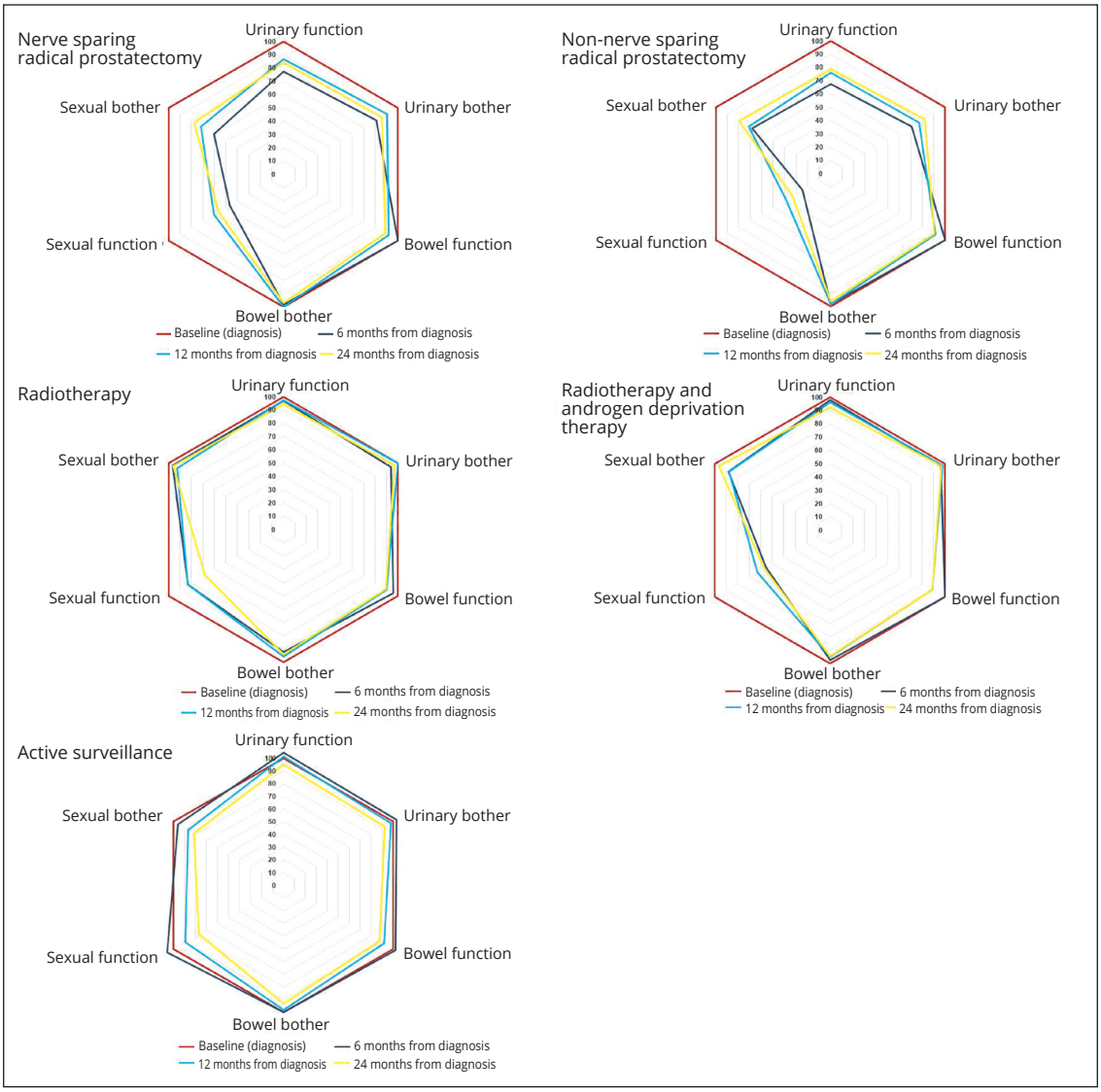


Figure 1.—Radar plots of scores for UCLA-PCI UF, UB, BF, BB, SF and SB over time, by prostate cancer treatments. Scores are presented as percentage of the baseline value.

tween the RT plus ADT and AS patients (Supplementary Digital Material 5: Supplementary Table IV, Supplementary Digital Material 6: Supplementary Table V).

### Bowel function and bother

Baseline BF and BB scores were similar across treatment groups (Table I). Both BB and BF scores decline to a similar extent at 6-, 12- and 24-month follow-up in each treatment group (Table II, Figure 1). Nonetheless, only BF scores decline exceeded the MCID at 12-month in patients treated with RT (-9.1, 95% CI [-11, -7.2], P=0.02) and RT plus ADT (-10.3, 95% CI [-12.5, -8.1], P=0.001), while at 24-month in all treatment groups. Conversely, the decrease in BB scores did not exceed the MCID at any time point and for each treatment group (Table II, Figure 1). The decline in BF within each treatment group was even more evident among men with the highest quartile baseline scores at diagnosis (Supplementary Table III).

TABLE II.—*Comparison of variation of UCLA-PCI and SF-12 scores over time (numbers indicate adjusted mean difference and 95% confidence intervals).*

| | 6-month *vs.* baseline | P* | P† | 12-month *vs.* baseline | P* | P† | 24-month *vs.* baseline | P* | P† |
|---|---|---|---|---|---|---|---|---|---|
| UCLA-PCI UF | | | | | | | | | |
| NSRP | -20.8 (-23.2, -18.4) | <0.0001 | <0.0001 | -12.3 (-14.6, -9.9) | <0.0001 | 0.0294 | -14.7 (-17.2, -12.2) | <0.0001 | 0.0001 |
| NNSRP | -29.9 (-32.9, -26.8) | <0.0001 | <0.0001 | -22.1 (-25.2, -19.1) | <0.0001 | <0.0001 | -19.7 (-22.9, -16.5) | <0.0001 | <0.0001 |
| RT | -3.0 (-5.3, -0.7) | 0.0092 | 1.0000 | -2.5 (-4.8, -0.2) | 0.0359 | 1.0000 | -5.3 (-7.6, -3.0) | <0.0001 | 1.0000 |
| RT+ADT | -2.2 (-4.8, 0.4) | 0.1043 | 1.0000 | -3.7 (-6.3, -1.1) | 0.0048 | 1.0000 | -7.1 (-9.9, -4.4) | <0.0001 | 0.9804 |
| AS | 3.9 (-0.9, 8.7) | 0.1129 | 0.9932 | 1.3 (-3.6, 6.1) | 0.6078 | 0.9998 | -4.6 (-9.5, 0.3) | 0.0657 | 0.9841 |
| UCLA-PCI UB | | | | | | | | | |
| NSRP | -16.6 (-20.0, -13.2) | <0.0001 | 0.0196 | -8.4 (-11.9, -4.9) | <0.0001 | 0.9953 | -12.5 (-15.9, -9.0) | <0.0001 | 0.6163 |
| NNSRP | -26.6 (-30.9, -22.2) | <0.0001 | <0.0001 | -20.8 (-25.1, -16.5) | <0.0001 | 0.0002 | -16.6 (-21.5, -11.8) | <0.0001 | 0.0701 |
| RT | -5.3 (-8.5, -2.0) | 0.0014 | 1.0000 | -0.3 (-3.6, 3.0) | 0.8454 | 1.0000 | -3.0 (-6.2, 0.3) | 0.0776 | 1.0000 |
| RT+ADT | -3.2 (-7, 0.6) | 0.0962 | 1.0000 | -2.1 (-5.9, 1.6) | 0.2704 | 1.0000 | -2.9 (-6.6, 0.8) | 0.1283 | 1.0000 |
| AS | 2.7 (-4.1, 9.6) | 0.4372 | 0.9984 | -1.9 (-9.1, 5.4) | 0.615 | 0.9988 | -6.8 (-13.8, 0.3) | 0.0601 | 0.9589 |
| UCLA-PCI BF | | | | | | | | | |
| NSRP | -0.4 (-2.2, 1.3) | 0.6380 | 1.0000 | -7.8 (-9.8, -5.8) | <0.0001 | 0.2238 | -10.3 (-12.3, -8.2) | <0.0001 | 0.0009 |
| NNSRP | 0.9 (-1.4, 3.2) | 0.4610 | 1.0000 | -7.4 (-10.0, -4.8) | <0.0001 | 0.3833 | -8.2 (-11.5, -4.9) | <0.0001 | 0.2262 |
| RT | -4.1 (-5.8, -2.4) | <0.0001 | 0.9997 | -9.1 (-11, -7.2) | <0.0001 | 0.0165 | -9.7 (-11.9, -7.5) | <0.0001 | 0.0069 |
| RT+ADT | -0.2 (-2.2, 1.7) | 0.829 | 1.0000 | -10.3 (-12.5, -8.1) | <0.0001 | 0.0014 | -10.3 (-12.6, -8) | <0.0001 | 0.0023 |
| AS | 2.1 (-1.5, 5.7) | 0.2562 | 0.9965 | -7.7 (-11.9, -3.6) | 0.0002 | 0.3607 | -11.5 (-16.2, -6.9) | <0.0001 | 0.0267 |
| UCLA-PCI BB | | | | | | | | | |
| NSRP | -1.5 (-3.9, 0.8) | 0.202 | 1.0000 | -0.3 (-2.9, 2.4) | 0.8396 | 0.5000 | -3 (-5.7, -0.3) | 0.0295 | 1.0000 |
| NNSRP | -1 (-4, 2.1) | 0.5403 | 1.0000 | -0.9 (-4.3, 2.5) | 0.6011 | 1.0000 | -3 (-6.7, 0.8) | 0.1232 | 0.9992 |
| RT | -7.3 (-9.6, -5) | <0.0001 | 0.9294 | -4 (-6.5, -1.5) | 0.0018 | 0.9999 | -5.6 (-8.2, -2.9) | <0.0001 | 0.9941 |
| RT+ADT | -2.4 (-5, 0.2) | 0.0707 | 1.0000 | -4.9 (-8, -1.8) | 0.0021 | 0.9951 | -5.4 (-8.6, -2.2) | 0.0011 | 0.9873 |
| AS | -0.1 (-4.9, 4.7) | 0.9728 | 0.9999 | -1.8 (-7.1, 3.5) | 0.51 | 0.9960 | -6.3 (-11.9, -0.7) | 0.0268 | 0.8299 |
| NSRP | -28.7 (-31.7, -25.7) | <0.0001 | <0.0001 | -21.3 (-24.3, -18.4) | <0.0001 | <0.0001 | -23.5 (-26.5, -20.5) | <0.0001 | <0.0001 |
| NNSRP | -37.8 (-41.6, -34) | <0.0001 | <0.0001 | -30.1 (-34, -26.3) | <0.0001 | <0.0001 | -33.1 (-37.6, -28.7) | <0.0001 | <0.0001 |
| RT | -7.5 (-10.4, -4.7) | <0.0001 | 1.0000 | -7.5 (-10.5, -4.6) | <0.0001 | 1.0000 | -14.2 (-17.1, -11.3) | <0.0001 | 0.4531 |
| RT+ADT | -20.4 (-23.7, -17.1) | <0.0001 | 0.0001 | -17 (-20.4, -13.5) | <0.0001 | 0.0454 | -19.7 (-23.2, -16.2) | <0.0001 | 0.0007 |
| AS | 3 (-3.1, 9) | 0.3382 | 0.9998 | -5.5 (-12, 0.9) | 0.0911 | 0.9951 | -12.1 (-18.7, -5.5) | 0.0004 | 0.7128 |
| SF-12 PCS | | | | | | | | | |
| NSRP | -1.3 (-2.2, -0.4) | 0.0032 | 1.0000 | -0.8 (-1.7, 0.1) | 0.0653 | 1.0000 | -1.5 (-2.5, -0.4) | 0.0066 | 1.0000 |
| NNSRP | -2.1 (-3.2, -0.9) | 0.0004 | 0.9995 | -0.8 (-1.9, 0.4) | 0.1823 | 1.0000 | -1.8 (-3.1, -0.5) | 0.0064 | 0.9996 |
| RT | -1.3 (-2.2, -0.5) | 0.0025 | 1.0000 | -1.2 (-2.1, -0.4) | 0.0055 | 1.0000 | -1.6 (-2.5, -0.7) | 0.001 | 1.0000 |
| RT+ADT | -1 (-2, -0.1) | 0.0342 | 1.0000 | -2 (-3, -1.1) | <0.0001 | 0.9999 | -3.3 (-4.7, -1.9) | <0.0001 | 0.8536 |
| AS | -0.7 (-2.5, 1.2) | 0.4799 | 0.9998 | -0.7 (-2.6, 1.1) | 0.4292 | 0.9998 | -1.1 (-3, 0.8) | 0.2593 | 0.9986 |
| SF-12 MCS | | | | | | | | | |
| NSRP | 2.7 (1.7, 3.7) | <0.0001 | 0.9948 | 5.3 (4.3, 6.3) | <0.0001 | 0.0061 | 1.9 (0.9, 2.9) | 0.0003 | 1.0000 |
| NNSRP | 3.6 (2.3, 4.9) | <0.0001 | 0.7403 | 6.2 (4.9, 7.6) | <0.0001 | 0.0006 | 2.3 (1, 3.6) | 0.0007 | 0.9957 |
| RT | 0.2 (-0.8, 1.2) | 0.6729 | 1.0000 | 3.7 (2.8, 4.7) | <0.0001 | 0.7073 | -0.4 (-1.4, 0.5) | 0.3764 | 1.0000 |
| RT+ADT | 0 (-1.2, 1.1) | 0.9731 | 1.0000 | 4.2 (3.1, 5.3) | <0.0001 | 0.3469 | -0.8 (-2, 0.4) | 0.1749 | 1.0000 |
| AS | 1 (-1, 3.1) | 0.3185 | 0.9975 | 3.2 (1.1, 5.2) | 0.0025 | 0.7845 | -0.9 (-3, 1.2) | 0.4069 | 0.9983 |

*Testing whether changes are significantly different from 0; † testing whether changes are significantly greater than the MCID Estimated mean differences and 95% CI from mixed-model repeated measures analyses adjusted for score at diagnosis, age at diagnosis, education, BMI, smoking status, presence of diabetes mellitus or three+ moderate/severe comorbidities according to CIRS, family history of prostate cancer, T-staging, ISUP grade group and PSA at diagnosis.

In the analyses comparing scores between different treatment groups, patients treated with either RT or RT plus ADT showed lower BF scores at 6- and 12-month follow-ups relative to patients treated with NSRP, NNSRP or AS. Nonetheless, these differences did not exceed the MCID for each comparison. Finally, no statistically significant and clinically meaningful differences were recorded at 24-month between each treatment comparison (Supplementary Table IV, V).

## Sexual function and bother

Baseline SF and SB were higher in patients treated with NSRP, NNSRP and AS (Table I). During follow-ups, NNSRP (at 6-months -28.7, 95% CI [-31.7, -25.7], P<0.001), NSRP (at 6-months -37.8, 95% CI [-41.6, -34.0], P<0.001) and RT plus ADT [at 6-month -20.4, 95% CI (-23.7, -17.1), P<0.001] patients experienced the highest absolute and relative decline in SF (Table II,

Figure 1) that were significantly greater than the MICD at each time point. These differences were particularly evident among men with the highest quartile baseline SF (Supplementary Table III). Conversely, the decrease in SB scores did not exceed the MCID, except for NSRP group at 6-month. Specifically investigating potent patients at baseline, 36%, 11%, 51%, 19% vs 88% declared erections firm enough for sexual intercourse at 6-month (P<0.001), 45%, 22%, 44%, 21% *vs.* 89% at 12-month (P<0.001) and 53%, 23%, 38%, 23% *vs.* 79% at 24-months (P<0.001) in for NSRP, NNSRP, RT, RT plus ADT and AS groups, respectively.

In the analyses comparing scores between different treatment groups (Supplementary Table IV, V), differences in adjusted SF mean values exceeded the MCID in the comparisons NSRP vs RT or AS (P<0.001 at 6-months), NNSRP vs RT or RT plus ADT or AS (P<0.05 at each follow-up), RT plus ADT vs RT or AS (P<0.05 at each follow-up) and RT vs AS (P<0.05 at 6- and 12-months).

### Health-related QoL

Baseline PCS and MCS were similar across treatment groups (Table I). The decrease in PCS was generally small within each treatment with no variations larger than the MCID over time (Table II). Conversely, MCS significantly increases at 12-month within each treatment group. However, these increases exceed the MCID only in patients treated with either NSRP or NNSRP (Table II).

In the analyses comparing scores between different treatment groups, neither statistically significant nor clinically meaningful differences were recorded within each comparison for both PCS and MCS (Supplementary Table IV, V).

## Discussion

Current therapeutic options for localized prostate cancers within each risk class are similarly successful in providing local and distant cancer control, as well as survival.[19] Nonetheless, cancer treatments often intrude upon patients' physical, emotional and social life.[20-22] This updated analysis from Pros-IT CNR study provided a real-life report on QoL change at 12- and 24-month after diagnosis of PCa. Our analysis confirmed that each treatment was relatively well-tolerated, albeit showing a different impact on QoL.

In our analysis, men submitted to RP seemed to have an increased risk of developing symptomatic acute urinary side effects, particularly if they had an excellent score at diagnosis. Indeed, these patients reported a decrease in UCLA-PCI UF scores from baseline to follow-ups. Even if some improvements in UF were then observed at 12- and 24-month follow-up, their adjusted UF means were significantly worse with respect to those observed in men on RT or RT plus ADT or AS demonstrating that RP could significantly affect urinary functions. Similarly, RP and RT plus ADT were associated with worsening in SF at 6-, 12- and 24-month and the decline was particularly evident among men with excellent score at diagnosis. Adjusting for baseline score and other covariates, participants submitted to RP had a larger decline in SF than men on RT (at 6 months -18 points, 95% CI (-21.2, -14.9). Noteworthy, patients with excellent baseline scores showed more pronounced differences at follow-ups. Interestingly, such differences were of similar magnitude for all curative options, and, surprisingly, also for AS. This result partially justify the worse results of surgical treatments, since in this group there was a larger rate of patients with excellent performances at baseline.

Previous studies showed that RP, RT and AS differently affect QoL domains of men with localized PCa.[23] To date, only one randomized trial reported on HRQoL after treatment for localized PCa.[20] The ProtecT trial showed that RP had the greatest negative effect on the patients' SF and UF. Conversely, RT had the highest negative impact on BF, albeit of a lower magnitude. However, the trial suffered from its historical cohort and outmoded treatments. While series from center of excellence may not be generalizable, population-based studies may provide more representative information. Our findings are consistent with contemporary United States[4, 21, 22, 24] and Danish[25] population-based studies. A direct comparison cannot be made, since these studies applied different questionnaires and methodologies. Nonetheless, consistently with previous reports, we showed that the most pronounced im-

pact on QoL occurred within the first year from diagnosis. Additionally, similarly to Barocas *et al.*,[4] we also showed that the highest impact on QoL was recorded among patients with the highest scores at baseline.

These findings underline that patient-reported outcome measures should be used to inform the patients after PCa diagnosis, alongside with survival data. From this perspective, an appropriate discussion with a multidisciplinary team should be encouraged, in order to clearly explain advantages and disadvantages of each treatment option. A recent study[26] showed that almost 25% of men diagnosed with localized PCa reported clinically relevant treatment regret, irrespectively of the treatment modality. A patient-centered approach to treatment and SDM may promote a better compliance of treatment adherence and a reduction of negative feelings about QoL by patients.[27]

### Limitations of the study

This study is not devoid of limitations. First, the observational design of the study may have made analyses susceptible to possible confounders. Second, the involvement of each center was on a voluntary basis and this may have introduced selection biases. Third, different schedules of the combination of RT and AD, in terms of starting time and duration of ADT, as well as different surgical techniques and surgeon's experience were considered and this may have represented unmeasured confounding factors. Fourth, information on patients variables known to impact on QoL, such as income and social network, were not available in the Pros-IT CNR study. Fifth, our cohort was weighted towards ISUP 1 diseases and therefore it may be postulated that a non-negligible proportion of patients was overtreated. Nonetheless, among patients who fit criteria for non-clinically significant PCa, one third of the patients was treated with AS, in agreement with previous reported trend of AS use,[28] suggesting a moderate good selection of proper treatment. Finally, large variability in terms of waiting list from diagnosis to the effective start of treatment existed within each center and each treatment type. This means that each patient waited a different time between diagnosis (*i.e.* prostate biopsy) and start of scheduled treatment (*i.e.* surgery vs. radiation therapy vs. AS) that we were not able to account for.

## Conclusions

Each treatment modality was confirmed to differently impact on QoL, albeit being relatively well-tolerated within 24-months from PCa diagnosis. Our findings may be helpful in counseling the patients on possible QoL impairment after each treatment. Additionally, clinical interventions for improving symptoms should be focused particularly within the first year after PCa diagnosis as well as on patients with the highest baseline QoL. Finally, since sexual function showed the greatest negative impact on QoL, patients should promptly be addressed to rehabilitative care.

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