Health Related Quality of Life of Patients with Bladder Cancer in the RAZOR Trial: A Multi-Institutional Randomized Trial Comparing Robot versus Open Radical Cystectomy

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Abbreviations and Acronyms

BL-Cys = bladder-cystectomy
BMI = body mass index
CUD = continent UD
ECOG = Eastern Cooperative Oncology Group
EWB = emotional well-being
FACT = Functional Assessment of Cancer Therapy
FWB = functional well-being
G = General
HRQoL = health related quality of life
MCS = mental component score
NCUD = noncontinent UD
OC = open cystectomy
PCS = physical component summary
PWB = physical well-being
RARC = robot-assisted radical cystectomy
RAZOR = Randomized Open versus Robotic Cystectomy
SF-8 = Short Form 8 Health Survey
SWB = social well-being
TOI = trial outcome index
UD = urinary diversion
VCI = Vanderbilt Cystectomy Index

Purpose: We evaluated health related quality of life following robotic and open radical cystectomy as a treatment for bladder cancer.

Materials and Methods: Using the Randomized Open versus Robotic Cystectomy (RAZOR) trial population we assessed health related quality of life by using the Functional Assessment of Cancer Therapy (FACT)-Vanderbilt Cystectomy Index and the Short Form 8 Health Survey (SF-8) at baseline, 3 and 6 months postoperatively. The primary objective was to assess the impact of surgical approach on health related quality of life. As an exploratory analysis we assessed the impact of urinary diversion type on health related quality of life.

Results: Analyses were performed in subsets of the per-protocol population of 302 patients. There was no statistically significant difference between the mean scores by surgical approach at any time point for any FACT-Vanderbilt Cystectomy Index subscale or composite score ($p > 0.05$). The emotional well-being score increased over time in both surgical arms. Patients in the open arm showed significantly better SF-8 sores in the physical and mental summary scores at 6 months compared to baseline ($p < 0.05$). Continent diversion (versus noncontinent) was associated with worse FACT-bladder-cystectomy score at 3 ($p < 0.01$) but not at 6 months, and the SF-8 physical component was better in continent-diversion patients at 6 months ($p = 0.019$).

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Conclusions: Our data suggests lack of significant differences in the health related quality of life in robotic and open cystectomies. As robotic procedures become more widespread it is important to discuss this finding during counseling.

Key Words: quality of life, cystectomy, urinary diversion

ACCORDING to the WHO, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.[1] HRQoL is a construct that contemplates the impact of a disease and treatment on physical, mental, and social spheres as related to overall well-being.[2] Hence, HRQoL has been recognized as an important parameter following the treatment of malignancies.[3]

Given that patients and providers often differ in their beliefs about the benefits of certain procedures, surgeons should fully discuss with patients their expectations for recovery and HRQoL after surgery. This is the case with radical cystectomy and UD. Although these procedures are necessary to achieve cancer control, they affect HRQoL with regard to body image, continence, sexual function, fertility, bowel function and derangements in metabolic parameters.[4] HRQoL impairments are potentially affected by the surgical approach (robotic vs open) and the type of urinary diversion (continent vs noncontinent) but there is limited data in this regard. Furthermore, while it is generally thought that continent diversions provide a better HRQoL, the current literature has conflicting results.[5,6]

Using a subset of the population of the RAZOR trial,[7] we investigate the impact of surgical approach on HRQoL. As a secondary objective we assessed the impact of UD on HRQoL.

MATERIALS AND METHODS

The RAZOR trial was a multicenter, open label, noninferiority phase 3 randomized trial comparing RARC to OC for treatment of bladder cancer. Fifteen participating institutions enrolled patients following Institutional Review Board approval at each site. Complete methodology including inclusion criteria as well as oncological, perioperative and pathological outcomes were reported elsewhere.[7]

Patients were centrally randomized via a web based system. All UDs were done extracorporeally according to patient/surgeon preference. Patients undergoing continent cutaneous reservoirs or neobladders were part of the CUD group whereas those undergoing an ileal conduit were part of the NCUD group. Perioperative management was according to institutional protocol.

HRQoL outcomes were measured using the FACT-VCI[8] and the SF-8 questionnaires administered at baseline, 3 and 6 months postoperatively.

The FACT-VCI is composed of the FACT-G, along with 17 additional questions (the VCI) assessing bladder cancer specific HRQoL compiled from 3 previously described instruments, namely the FACT-Bladder Cancer, FACT-Colorectal, and Functional Assessment of Incontinence Therapy-Urinary. The FACT-VCI consists of 8 domains including PWB, SWB, EWB, FWB, the FACT BL-Cys and the 3 derived scores TOI, FACT-G and FACT-BL-Cys Total. The FACT BL-Cys component is specific for bladder cancer while PWB, SWB, EWB and FWB are more general components. Questions are scored on a 5-point Likert-type scale, with a higher score indicating better quality of life. The ranges of scores for each domain are 0−28 for physical, social, and functional well-being; 0−24 for emotional well-being; 0−60 for BL-Cys; 0−116 for TOI (sum of physical well-being, functional well-being, and FACT BL-Cys scores); 0−108 for FACT-G (sum of physical, social, emotional, and functional well-being scores) and 0−168 for FACT-BL-Cys Total (sum of physical, social, emotional, functional well-being and FACT BL-Cys scores), also called FACT-VCI total.

The SF-8 provides PCS and MCS scores. The answers obtained were inserted into the Optum web based tool to derive the domain specific norm based scoring and convert the responses to scores from 0 to 100 for analysis (www.amihealthy.com). A higher score denotes a better HRQoL.

In this analysis we used a subset of the per protocol population from the RAZOR trial, consisting of patients with baseline and at least 1 post-surgery assessment of HRQoL.

Longitudinal HRQoL data were analyzed using the mixed models approach, using maximum likelihood estimation and assuming any missing data were missing at random. This analytical approach for repeated measures accommodates missing data and allows for flexible specification of covariance structure.

The surgical approach (OC vs RARC) and UD type (CUD vs NCUD) were the main predictors in the model. The mixed model for a particular HRQoL outcome included time, arm, UD, time×arm and time×UD type interactions with adjustment for age (continuous), sex, BMI (less than 25, 25 to 29.9, 30 or greater), ECOG performance status (0, 1+), T-stage (Ta, Tis, T1-T2 vs T3-T4), perioperative chemotherapy (no, yes) and accounted for site in the random effect component of the model. The interaction terms were included in models regardless of significance to allow evaluation of prespecified estimated mean comparisons of interest by time, arm and diversion type. We also included random intercept with subjects nested within site and assumed a heterogeneous autoregressive covariance matrix to account for the correlated data structure. For each HRQoL outcome we report estimated means with corresponding 95% confidence intervals, and p value adjusted for multiple comparisons using the Bonferroni method. In addition, multivariable linear regression analyses were conducted to assess predictors of

Table 1. *Patient characteristics by arm and type of urinary diversion*

	Robotic	Open	p Value	CUD	NCUD	p Value
No. total (%)	150 (100.0)	152 (100.0)		67 (100.0)	235 (100.0)	
No. arm (%):						
Robotic	150 (100.0)	-	Not applicable	37 (55.2)	113 (48.1)	0.303
Open	-	152 (100.0)		30 (44.8)	122 (51.9)	
No. type of diversion (%):						
CUD	37 (24.7)	30 (19.7)	0.303	67 (100.0)	-	Not applicable
NCUD	113 (75.3)	122 (80.3)		-	235 (100.0)	
Yrs age at consent:						
Mean (SD)	68.6 (10.3)	67.5 (9.0)	0.320	58.2 (7.8)	70.8 (8.3)	<0.0001
Median (p25, p75)	70 (60, 76)	67 (62, 74.5)		58 (52, 64)	71 (66, 76)	
Range	43, 90	37, 85		37, 79	43, 90	
No. male (%)	126 (84.0)	128 (84.2)	0.960	55 (82.1)	199 (84.7)	0.609
No. BMI (kg/m^2) (%):						
Less than 25	38 (25.3)	39 (25.7)	0.897	19 (28.4)	58 (24.7)	0.432
25—29.9	60 (40.0)	64 (42.1)		30 (44.8)	94 (40.0)	
30 or Greater	52 (34.7)	49 (32.2)		18 (26.9)	83 (35.3)	
No. ECOG performance status (%):*						
0	117 (78.0)	109 (71.7)	0.208	56 (83.6)	170 (72.3)	0.061
1+	33 (22.0)	43 (28.3)		11 (16.4)	65 (27.7)	
No. T stage (%):						
Ta,Tis, T1-T2	130 (86.7)	132 (86.8)	0.964	58 (86.6)	204 (86.8)	0.959
T3-T4	20 (13.3)	20 (13.2)		9 (13.4)	31 (13.2)	
No. periop chemotherapy (%)	61 (40.7)	71 (46.7)	0.290	32 (47.8)	100 (42.6)	0.448
No. neoadjuvant chemotherapy (%)	41 (27.3)	56 (36.8)	0.077	26 (38.8)	71 (30.2)	0.184
No. adjuvant chemotherapy (%)	25 (16.7)	17 (11.2)	0.169	7 (10.4)	35 (14.9)	0.354
No. grades III—V complications within 90 days (%)	33 (22.0)	34 (22.4)	0.939	12 (17.9)	55 (23.4)	0.340

* The category 1+ includes 6 patients with baseline performance status 2, and 2 patients with 3.

FACT-BL-Cys Total at 3 and 6 months in the same subset of patients with non-missing data at these time points. Data analysis was conducted in SAS version 9.4 (SAS Institute, Inc.).

RESULTS

A total of 302 patients were included, of which 150 were randomly assigned to the RARC arm and 152 to the OC arm. Demographic and perioperative characteristics are shown in table 1. Younger individuals and those with a better performance status were more likely to receive a CUD ($p < 0.0001$ and $p = 0.061$, respectively).

Baseline and at least 1 postoperative assessment of HRQoL questionnaires were available for 231 (76.5%) and 216 (71.5%) patients for the FACT-VCI and SF-8, respectively, and these patients were eligible for inclusion in the analysis. At 3 months following surgery, 206 (68%) patients had data for FACT-VCI and 179 (59.3%) had data for the SF-8. At 6 months the numbers were 198 (65.6%) and 178 (58.9%), respectively. There were no significant differences between included and excluded patients with respect to the baseline patient characteristics (supplementary table 1, https://www.jurology.com).

Figures 1 and 2 depict the FACT-VCI mean scores for subscales and composite scores by surgical arm and UD type, respectively. They were adjusted for age, sex, BMI, ECOG, T-stage, perioperative chemotherapy and site as a random effect.

There was no statistically significant difference between arms at any time point for all FACT-VCI outcomes ($p > 0.05$). When comparing the component scores to baseline, the EWB scores significantly improved (more than 2 points) at 3 and 6 months postoperatively in both arms. In the robotic arm the EWB mean scores were 19.5 at 3 months ($p < 0.01$) and 19.3 at 6 months ($p < 0.01$) compared to baseline (17.4). Similarly, in the OC arm the estimated EWB mean scores were 20 at 3 and 6 months ($p < 0.05$) versus 17.7 at baseline (supplementary table 2, *A*, https://www.jurology.com).

We performed an analysis of the predictors of FACT-BL-Cys Total (FACT-VCI total) score at 3 and 6 months postoperatively (table 2).

Significant predictors at the 5% level were baseline FACT-BL-Cys total, BMI 30 or greater and grade III-IV complications within 90 days from surgery for the 3-month outcome, and only baseline FACT-BL-Cys total for the 6-month outcome. A 10-point increase in the baseline FACT-BL-Cys total score was associated with a significant increase of 5.47 in the score at 3 months (95% CI 4.24 to 6.70; $p < 0.0001$) and an increase of 4.90 in the score at 6 months (95% CI 3.57 to 6.23; $p < 0.0001$). BMI 30 or greater was associated with a decrease of 6.66 points (95% CI -12.05 to -1.28; $p = 0.016$) and grade III-IV complications within 90 days from surgery was associated with a decrease of 7.31 points (95%CI -14.07 to -0.54; $p = 0.035$) in FACT-BL-Cys total at 3 months, but were not

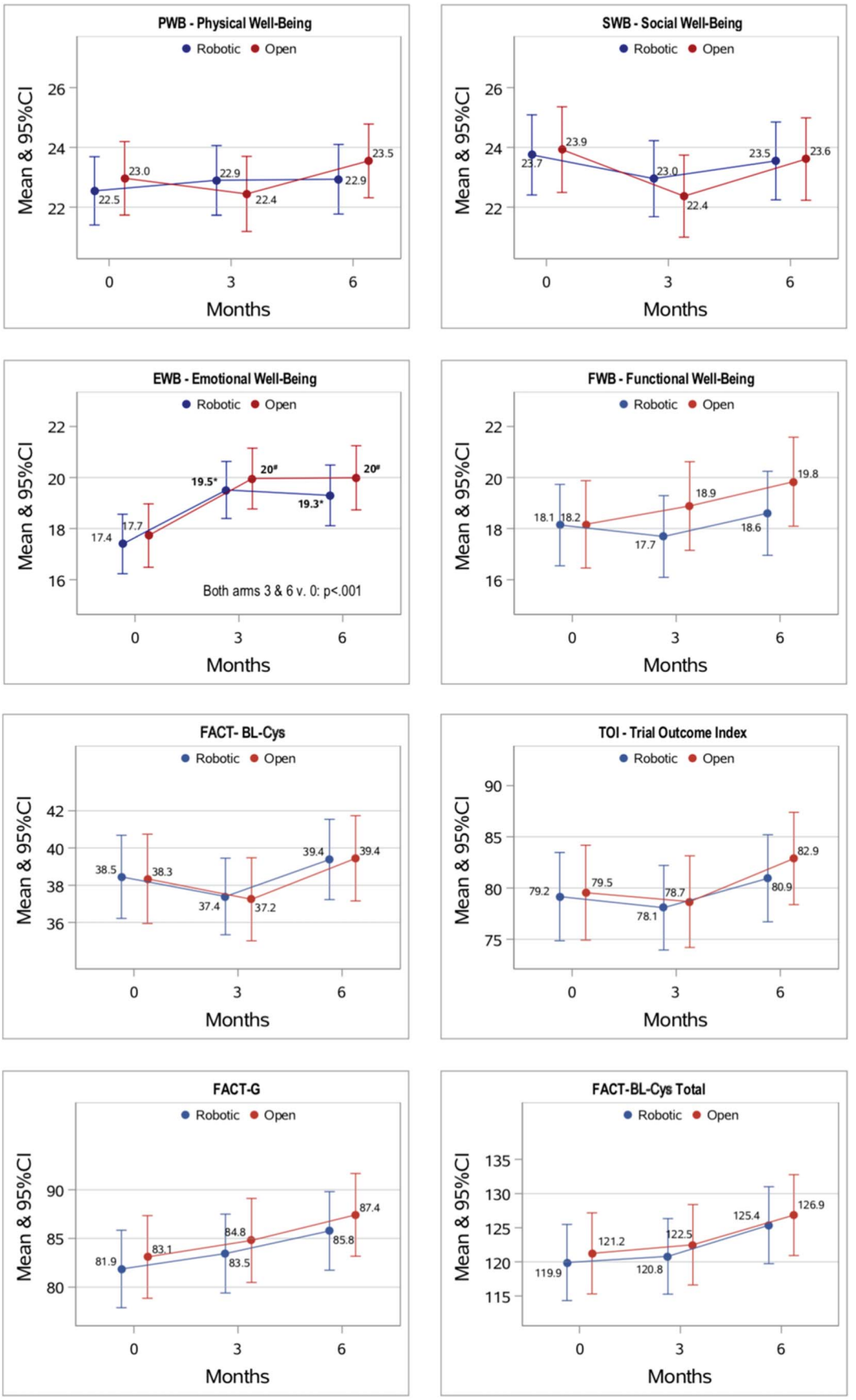

Figure 1. FACT-VCI subscales and composite scores by arm. All measurements were taken at 0, 3 and 6 months. Statistically significantly difference ($p < 0.05$) from baseline marked by asterisk in robotic and number symbol in open approach.

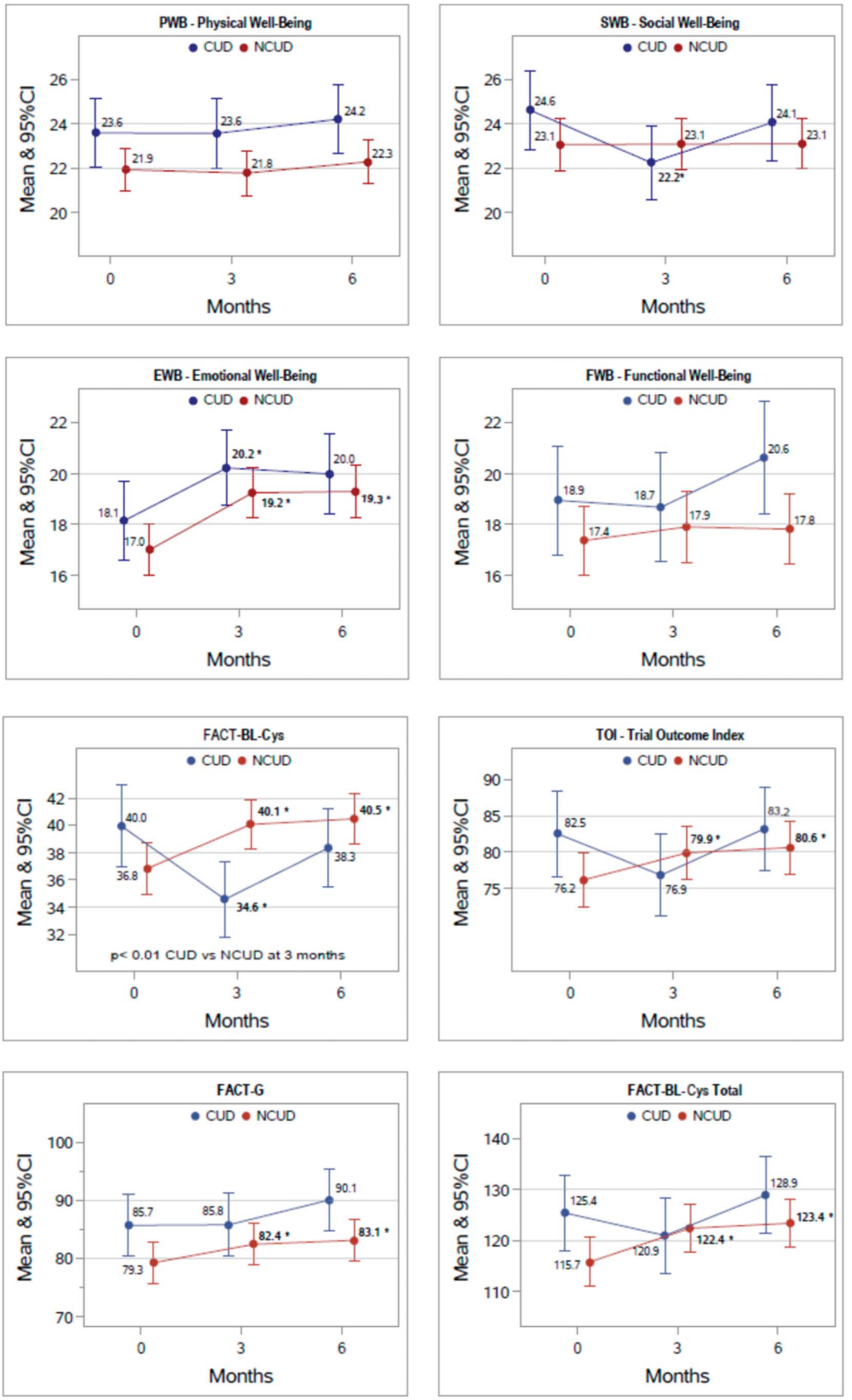

Figure 2. FACT-VCI subscales and composite scores by urinary diversion type. All measurements were taken at 0, 3 and 6 months. Asterisk indicates statistically significantly difference ($p < 0.05$) from baseline.

Table 2. *Multiple regression analysis evaluating predictors of FACT-BL-Cys (FACT-VCI) total score at 3 and 6 months after radical cystectomy*

		β Estimate Outcome FACT-BL-Cys (FACT-VCI) Total Score (95% CI)			
	Category	3 Mos	p Value	6 Mos	p Value
Intercept	–	61.34 (45.28, 77.39)	<0.0001	67.64 (50.20, 85.08)	<0.0001
Arm	Robotic vs open	0.28 (-4.87, 5.43)	0.915	1.27 (-4.33, 6.87)	0.654
Urinary diversion	CUD vs NCUD	-5.50 (-11.47, 0.48)	0.071	2.37 (-4.12, 8.86)	0.471
Periop chemotherapy	Yes vs No	4.47 (-0.72, 9.66)	0.091	4.13 (-1.51, 9.76)	0.150
Baseline FACT-BL-Cys Total	10-Point increase	5.47 (4.24, 6.70)	<0.0001	4.90 (3.57, 6.23)	<0.0001
BMI	30 or greater vs less than 30	-6.66 (-12.05, -1.28)	0.016	-4.27 (-10.12, 1.57)	0.151
T stage	T3-T4 vs Ta,Tis,T1-T2	-4.53 (-13.49, 4.44)	0.320	-5.69 (-15.42, 4.04)	0.250
Complications within 90 days	Grade III-IV vs 0-II	-7.31 (-14.07, -0.54)	0.035	-5.05 (-12.40, 2.30)	0.176
Adjusted R^2		0.388		0.285	

β estimate is estimated variable coefficient in predicting FACT-BL-Cys Total score at 3 months or at 6 months.
Adjusted R^2 is adjusted coefficient of determination; proportion of variation of the outcome variable explained by the model adjusted for the number of terms in the model and sample size.

significant predictors at 6 months. Neither arm, type of diversion, perioperative chemotherapy or T-stage were significant predictors of FACT-BL-Cys total at 3 and 6 months.

Figure 3 shows the estimated mean scores for SF-8 physical and mental component summaries by arm and UD type. There was no significant difference between arms ($p > 0.05$) for either PCS or MCS at any time point. Nevertheless, patients in the open arm showed significantly better PCS and MCS scores at 6 months compared to baseline ($p < 0.05$) with an increase of 5 points for PCS (50.4 vs 45.4) and 4.2 points for MCS (51 vs 46.8) (supplementary table 3, https://www.jurology.com).

The results of our exploratory analysis on CUD versus NCUD revealed that there was no statistically significant difference between diversion types at any time point ($p > 0.05$) except for the FACT-BL-Cys which was lower in CUD by 5.5 points at 3 months ($p < 0.01$). There were significant differences in some of the component scores when compared to the baseline in both groups as seen in supplementary table 2, *B* (https://www.jurology.com).

When evaluating SF-8 results by UD type, MCS scores did not show any significant difference between diversion types ($p > 0.05$) at any time point as well as over time compared to baseline. However, PCS scores were significantly better in the CUD compared to NCUD group at 6 months (51.8 vs 46.2, $p = 0.019$). When comparing PCS scores over time we only found an improvement in PCS scores in the CUD group at 6 months compared to baseline (in CUD by 4.6 points, 51.8 vs 47.2, adjusted $p = 0.043$).

DISCUSSION

Retrospective and prospective studies have shown RARC has lower perioperative blood loss, fewer transfusions, fewer narcotic analgesic requirements and shorter length of stay[5,9] while maintaining oncological outcomes compared to OC.[10,11] However, improvement in HRQoL outcomes has not been evident.

Three recent randomized controlled trials comparing RARC to OC evaluated HRQoL and found no significant differences between RARC and OC at 3 and 6 months.[9,12,13] However, they were single institution studies while this was a multicenter trial and included the largest patient population, providing the most conclusive evidence on the topic. In line with previous evidence, our study did not show a statistically significant difference between open and robotic approaches at any time point for all FACT-VCI endpoints. Nevertheless, EWB scores were significantly higher at 3 and 6 months for robotic and open surgeries versus their respective baselines. Even though we did not find other studies with similar results, our data suggest that the impact of surgery on patient EWB is largely positive, which may be due to a perceived relief about treatment completion or the absence of cancer. Previous studies in breast cancer have shown that HRQoL including EWB improves as time since diagnosis elapses.[14]

For SF-8 questionnaires, there was a trend to improvement in PCS and MCS in both groups after surgery but the only finding that reached statistical significance was the open arm that showed significantly better PCS and MCS scores at 6 months compared to baseline. The clinical relevance of this finding is unclear and could be just statistical. Nevertheless, this is particularly relevant to patient counseling, and patients who suffer or are at risk of depression should be properly evaluated and should have access to experts who are properly trained to manage this condition. The improvement could also be related

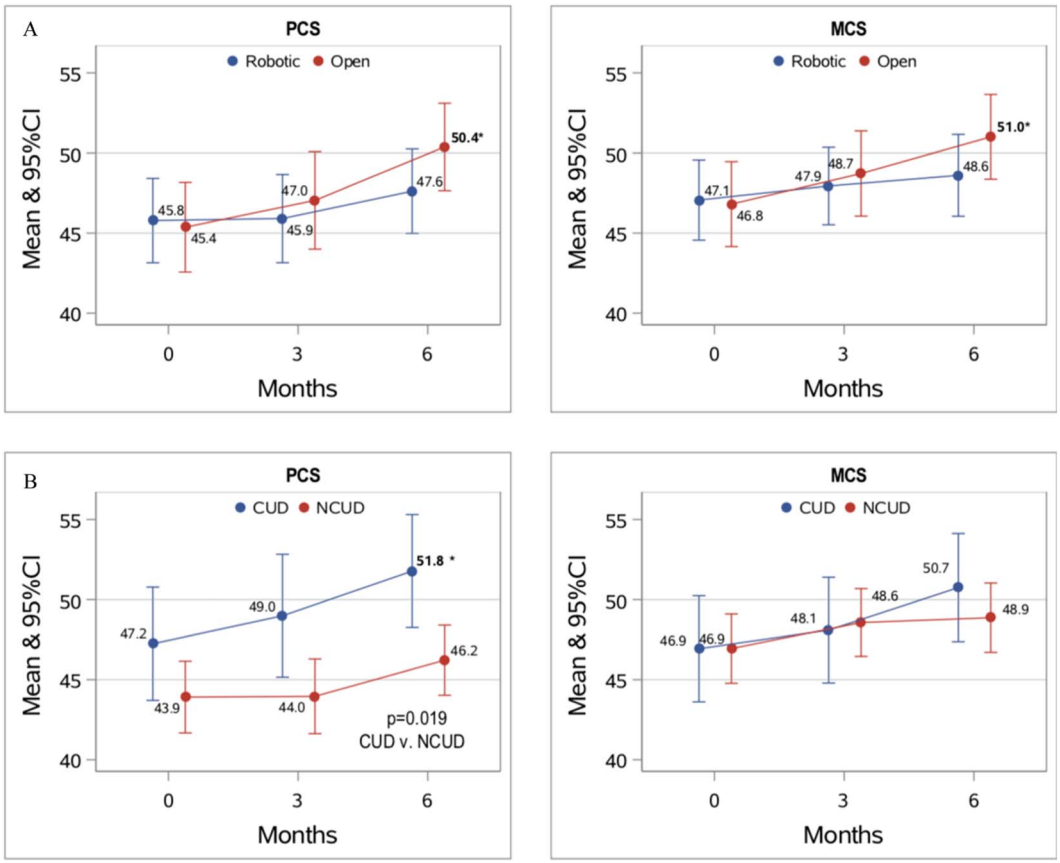

Figure 3. SF-8 physical and mental component summary scores by arm (*A*) and type of diversion (*B*). All measurements were taken at 0, 3 and 6 months. Asterisk indicates statistically significant increase ($p < 0.05$) from baseline.

to preoperative expectations suggesting that patients undergoing OC recuperate physically and mentally faster than patients in the robotic surgery arm. This finding has not been previously reported and could possibly be explained by higher expectations in patients receiving the robotic approach with regards to postoperative recovery. However, it should also be kept in mind that while these differences were statistically significant, their magnitude has questionable clinical relevance.

The literature is controversial regarding which UD type offers the best HRQoL. Overall, studies evaluating HRQoL across diversion types have demonstrated comparable patient-reported outcomes regardless of diversion type except in recent years, where a trend in favor of neobladders has been observed.[15] Ali et al performed a systematic review of 21 nonrandomized studies, 16 of which reported similar HRQoL between CUD and NCUD.[16] Despite this, many surgeons recommend orthotopic neobladders as they assume patient satisfaction is higher due to replication of physiological voiding.[17] NCUD showed a significant improvement in multiple component scores postoperatively versus baseline scores, while the only component score that improved in the CUD group was the EWB at 3 months, with a decrease in SWB and FACT-BL-Cys. The clinical relevance of our findings is unclear, and it is possible that the adjustment and training needed initially in CUD necessitates a longer duration for improvement in HRQoL to manifest. However, we do not have data beyond 6 months. Furthermore, this trial was not powered to determine significant differences between diversion types.

Commonly, younger and healthier patients tend to undergo CUD, but they may have had potentially unrealistic expectations of postoperative recovery, necessitating better counseling on the part of surgeons. Furthermore, given that robotic and open procedures display a similar behavior our data suggest that the HRQoL maybe more related to the type of UD than to the surgical approach. Nevertheless, to confirm this finding a randomized controlled trial powered to detect the differences specific to the type of UD is needed.

For both FACT-VCI and SF-8 there was an overall trend towards improvement in the postoperative scores in both arms and UD types versus baseline, suggesting that HRQoL improves after the treatment of the cancer. This may be partly due to the emotional component of quality of life but it is also likely that the benefits are physical and symptomatic as well. Analogous to our findings, other studies have also reported rise in general HRQoL increased throughout the postoperative time course.[18,19] Previous studies have reported up to 12 months for HRQoL to return to baseline depending on the surgical approach.[20] We noted HRQoL scores at baseline and 6 months postoperatively were equivalent suggesting recovery of the different composite scores postoperatively depend on adjustment of the patient to UD, social/family support systems and patient perceptions of their current status.[9] Nevertheless, support systems of the patients in the study were not collected as a study variable so we cannot comment further.

The present study has limitations. First, our study is limited by the response rate to the questionnaires. This response rate may have artificially elevated our HRQoL scores, as patients are more likely to return if they are feeling better.[9] Second, UDs were done according to patient/surgeon preference, therefore there is a bias in the interpretation of findings related to CUD versus NCUD. Third, there was a predominant use of NCUD that may have had an impact on the analysis as our study was not powered to specifically determine the effect of UD on HRQoL, making this analysis exploratory. Lastly, while the implemented instruments have been validated before in bladder cancer, to our knowledge there are no validated cutoff points to denote a relevant change in scores. Therefore, the clinical significance remains to be evaluated.

Despite the limitations, we provide important prospective data in a randomized contemporary population for adequate patient counseling to narrow the discrepancy between patient expectations and reality, thus empowering patients to make informed treatment decisions. Furthermore, this study reiterates the importance of evaluating HRQoL after major surgical procedures to reach a better understanding of how they can be affected and potentially improved.

CONCLUSIONS

Using data from a multicenter, randomized trial we found no HRQoL differences in the mean scores between RARC and OC at baseline or postoperatively. The lack of significant differences in the health related quality of life when comparing robotic and open cystectomy should be discussed with the patient during counseling, and is reassuring as more surgeons become comfortable with robotic surgery and patients are demanding more robotic procedures.

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EDITORIAL COMMENTS

Becerra et al present the health related quality of life outcomes that were assessed during the well-anticipated randomized RAZOR trial (reference 7 in article.[1] Even though the trial was not powered to assess HRQoL, as the primary endpoint was the 2-year progression-free survival, this study is the first to highlight HRQoL outcomes after radical cystectomy in a randomized clinical trial. While many studies (rightfully?) focused on oncological outcomes, this area of investigation has suffered from niche existence for many years and the authors should be applauded for their effort to improve current evidence substantially.

Using the validated FACT-VCI questionnaire, the authors did not find any significant differences in the respective subscales between the open and the laparoscopic robot-assisted surgical approach after a followup of up to 6 months after cystectomy. While these results might not be surprising to many readers, the authors do also provide important insights regarding respective HRQoL outcomes after continent and incontinent urinary diversion. Hereby, no conclusive differences were found, which further strengthens the assumption that continent diversion does not necessarily lead toward better HRQoL outcomes. However, given the results of recent prospective nonrandomized trials that found a separation of HRQoL outcomes between continent and incontinent urinary diversion after an observation period of up to 2 years (reference 19 in article), further analyses of the RAZOR cohort with a longer followup are warranted.

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REFERENCE

1. Venkatramani V, Reis IM, Castle EP et al: Predictors of recurrence, and progression-free and overall survival following open versus robotic radical cystectomy: analysis from the RAZOR trial with a 3-year followup. J Urol 2020; **203:** 522.

As the pendulum continues to shift away from open surgery, it is imperative the data justifies this migration. Accordingly, Becerra et al explore the differences in HRQoL in a multi-institutional randomized trial of patients undergoing robotic versus open radical cystectomy from baseline through 6 months of followup. Notably, the authors find that neither robotic versus open surgery nor diversion type has a noticeable difference on HRQoL. Although it would have been helpful to see if there were differences in HRQoL when stratified by surgeon level of experience with both robotic and open cystectomy, this article underscores the need for academic programs to continue allowing trainees to develop a broad experience with both. Clearly, the perceived advantages of robotic surgery are not translating into improved HRQoL outcomes (reference 7 in article).

Interestingly, both the PCS and MCS scores of the SF-8 improved from baseline to 6 months, with a slightly greater effect in the open group. Some of this may be attributable to differences in patient framing but, at baseline, the mean MCS was 47.1 versus 46.8 in the robotic versus open group, respectively. These scores are below average compared to the general U.S. population (<50),[1] highlighting that providers must be cognizant of mental health and not just assume patients are

coping well. Understanding how social support affects HRQoL is critical moving forward.

Altogether, the article adds to the growing body of literature showing a lack of long-term difference between robotic versus open radical cystectomy. Future HRQoL studies will hopefully include longer followup, a deeper analysis on gender differences and an assessment into whether intracorporeal diversion has any meaningful effect on HRQoL.

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1. Ware K, Kosinki M, Dewey J et al: How to score and interpret single-item health status measures: a manual for users of the SF-8 Health Survey. Boston: QualMetric 2001.