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Quality of Life After Total Mesorectal Excision and Rectal Replacement: Comparing Side-to-End, Colon J-Pouch and Straight Colorectal Reconstruction in a Randomized, Phase III Trial (SAKK 40/04)

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ABSTRACT

Background. Functional outcomes of different reconstruction techniques have an impact on patients' quality of life (QoL), but information on long-term QoL is lacking. We compared QoL among three reconstruction techniques after total mesorectal excision (TME).

Methods. Quality of life was assessed within a randomized, multicenter trial comparing rectal surgery using side-to-end anastomosis (SEA), colon J-pouch (CJP), and straight colorectal anastomosis (SCA) by the Functional Assessment of Cancer Therapy-Colorectal scale (FACT-C) before randomization and every 6 months up to 2 years post-TME. The primary QoL endpoint was the change in the Trial Outcome Index (TOI), including the FACT-C subscales of physical and functional well-being and colorectal cancer symptoms (CSS), from baseline to month 12. Pair-wise comparisons of changes from baseline (pre-surgery) to each timepoint between the three arms were analyzed by Mann–Whitney tests.

Results. For the QoL analysis, 257 of 336 randomized patients were in the per protocol evaluation (SEA = 95; CJP = 63; SCA = 99). Significant differences between the reconstruction techniques were found for selected QoL scales up to 12 months, all in favor of CJP. Patients with SEA or SCA reported a clinically relevant deterioration for TOI and CSS at 6 months, those with SCA for CSS also at 12 months after TME. Patients with CJP remained stable.

Conclusions. Although the three reconstruction techniques differ in their effects on QoL at months 6 and 12, these differences did not persist over the whole observation period of 24 months. Patients with a colon J-pouch may benefit with respect to QoL in the short-term.

Total mesorectal resection (TME) has improved survival and reduced local recurrence in patients with rectal cancer.[1] Reconstruction techniques after TME include straight colorectal anastomosis (SCA), colon J-pouch (CJP), side-to-end anastomosis (SEA), and transverse coloplasty.[2] SCA leads to the loss of the rectal reservoir, which can cause high defecation frequency, fecal urgency, and

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incontinence. The other three techniques were developed as alternative strategies to improve postoperative function.[2,3] The evidence on functional outcomes from randomized, controlled trials (RCTs) that compared at least two of the reconstruction techniques includes a Cochrane review on 16 RCTs and a meta-analysis of 21 trials.[2,3] Conclusions were similar: superior functional outcomes for CJP compared with SCA, and no differences when comparing CJP with SEA or transverse coloplasty.[2,3] Although functional outcomes are closely related to patient's quality of life (QoL), RCTs that have included QoL as an endpoint are rather rare. Four trials compared SCA with CJP, two of which reported no differences in global QoL between the two reconstruction techniques,[4,5] and two reported better global or symptom-specific QoL outcomes for CJP.[6,7] For the comparison of SCA or CJP with transverse coloplasty, QoL was similar.[8,9] No QoL differences were found for CJP compared with SEA.[10]

A prospective, randomized trial (Swiss Group for Clinical Cancer Research, SAKK 40/04) investigated clinical function after TME and rectal replacement by comparing SEA, 5-cm CJP, and SCA, with respect to defecation quality, stool frequency, and surgery-related mortality and morbidity.[11] Evacuation and incontinence did not significantly differ among the three techniques up to 24 months after TME.[11] In this report, we address the QoL impact of SEA, 5-cm CJP, and SCA over this period.

METHODS

Study Design and Participants

The SAKK 40/04 phase 3, randomized, multicenter trial was designed to compare SEA, 5-cm CJP, and SCA in patients with histologically proven rectal adenocarcinoma or rectal adenoma with or without neoadjuvant radiotherapy or radiochemotherapy and TME requirement (ClinicalTrials.gov: NCT00238381). Further eligibility criteria were: age $\geq$ 18 years, clinically normal function of the sphincter muscles, an expected R0-resection, and a completed baseline QoL questionnaire. Detailed reconstruction techniques and eligibility criteria are described elsewhere.[11]

Exclusion criteria for QoL assessment were psychiatric or any disorder that could interfere with the assessment or inability to read any of the three languages available on the questionnaire. Patients were allowed to receive neoadjuvant and adjuvant therapy according to international guidelines. Adjuvant pelvic radiotherapy was not allowed. Depending on the staging of the tumor, patients were either operated as soon as possible after diagnosis or within 4–6 weeks after completion of a neoadjuvant radiochemotherapy. The trial was conducted in accordance with the Declaration of Helsinki, Guidelines for Good Clinical Practice. The ethics committees of each participating center approved the study protocol; all patients gave written informed consent before enrollment.

Random allocation was done by using the minimization method. Patients were stratified by surgical clinic, patient's gender, age at registration (< 70; ≥ 70 years), distance of the distal tumor margin from the dentate line (> 5 cm vs. ≤ 5 cm), neoadjuvant treatment (no/yes), and distant metastatic disease (M0 vs. M1). Treatment allocation was not masked.

Quality of Life

Patients completed a QoL questionnaire at baseline (i.e., before randomization) at the clinic before surgery. For the subsequent assessments at months 6, 12, 18, and 24 after TME, a designated staff member of the SAKK coordinating center mailed the questionnaires to the patients. Patients were asked to send back the completed questionnaire by a post-paid envelope within 2 weeks of receipt. They received written reminders if they did not return the questionnaire.

The assessment consisted of the 36-item Functional Assessment of Cancer Therapy-Colorectal (FACT-C), a widely used QoL questionnaire for patients with colorectal cancer, including rectal cancer.[12–15] It is short, with flexible scoring and available in many validated translations.[13] The FACT-C consists of the FACT-General (FACT-G), including four subscales: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB), and an additional subscale covering colorectal cancer symptoms (CCS). The FACT-C also provides the Trial Outcome Index (TOI), a summary score of the subscales PWB, FWB, CSS.

The primary endpoint was defined as difference among the three reconstruction techniques in the change of the TOI score (range 0–84) from baseline to month 12. Secondary outcomes included the difference in changes in the FACT-C (range 0–136) and FACT-G (range 0–108) total scores, and in all subscales (PWB, SWB, and FWB scored 0–28, EWB scored 0–24) from baseline to each assessment time-point. A change in score of at least 5 points for the FACT-C, 4 points for the TOI, 3 points for the FACT-G, and 2 points for PWB, SWB, EWB, FWB, and CCS was considered as clinically relevant.[16,17] Higher scores indicate a better condition. For each scale, the change from baseline to each time-point was calculated as timepoint score minus baseline score and summarized as the median at each time-point.

We explored the association between QoL and the composite evacuation score measured 12 months after TME (primary clinical endpoint). This score consists of seven questions addressing: medication to evacuate, difficulties to empty, digitation to evacuate, return to evacuate, feeling of incomplete evacuation, straining to evacuate, time needed to evacuate.[18] During a telephone interview, patient were asked to rate the frequency of these functional aspects by scoring 0, 1, 2, or 3. The composite score is the sum of these questions (range: 0–21), with a lower score indicating better functioning. Reliability was confirmed (Cronbach's alpha = 0.70), indicating that the individual set of items represents the same underlying construct.

Statistical Analysis

The sample size calculation was based on the primary objective of the study, i.e., to compare CJP, SEA, and SCA reconstruction techniques following TME regarding functional outcomes (defecation quality, evacuation problems). For the QoL analysis, no formal sample size calculation was performed.

The main analysis was based on the per protocol population (PPP): a subset of patients of the intention-to treat (ITT) population who fully complied with the protocol requirements. Patients with a reconstruction other than the randomized one or patients with adjuvant pelvic radiotherapy were excluded from the PPP. Patients with a permanent stoma were excluded from the PPP analysis for the primary endpoint, i.e., the composite evacuation score 12 months after TME as reported by Marti et al.[11] In fact, these patients were not asked to answer questions related to the functional outcomes. QoL questionnaires, however, were completed by these patients, because they covered questions related to different QoL domains not specific to evacuation or defecation.

Pairwise comparisons between the three treatment arms were analyzed by exact Mann–Whitney tests without correcting for multiple testing. Corresponding nonparametric confidence intervals for group differences were calculated to judge the relevance of the potential differences. In a complementary analysis taking into account all time points (0–24 months), differences in QoL score changes between the three arms were investigated by nonparametric ANOVA models for longitudinal data.[19]

To evaluate the association between QoL and the composite evacuation score, a covariate, lower versus higher composite evacuation score at 12 months, was added to the model by grouping the scores into the categories *less than* or *equal* versus *greater than* median value. Two-tailed tests with significance level of 0.05 were used for all analyses. Because no adjustment for multiple testing was applied, all analyses were exploratory. All analyses were performed using SAS 9.4 (SAS Institute) and R 3.2.4 (http://www.r-project.org).

RESULTS

Patient and Disease Characteristics

Between September 2005 and May 2014, 336 patients were enrolled. Of these patients, 112 were randomized to CJP, 112 to SEA, and 112 to SCA. The ITT population included 335 patients (1 patient randomized to CJP withdrew consent immediately after randomization). Patients excluded from the PPP received another reconstruction technique, than the one they were randomized to ($N = 68$) or had adjuvant pelvic radiotherapy ($N = 10$), leaving 257 patients in the PPP (Fig. 1).

Patient and disease characteristics were generally balanced between the three arms (Table 1). Approximately two third of the patients were male. Median age was 68.6 years for the CJP, 76.2 years for the SEA, and 66.3 years for the SCA group, respectively. Overall, 60% of patients received combined neoadjuvant radiochemotherapy. Twenty-two (9%) of 257 patients in the PPP did not receive a temporary stoma. Ileostomy was the most common type of stoma (for details see Table S1) in each group. Stoma closure was performed in 90% of patients with SEA, in 84% with CJP, and in 88% with SCA, respectively, at a median time of around 5 months after TME. More than 50% of patients in each arm received adjuvant chemotherapy.

Quality of life questionnaire submission rates (Fig. 1) of the PPP diminished over time. The CJP group had the highest submission rates throughout all assessment time points. Submission rates for the CJP and SEA arms were above 80% up to the 12-month follow-up and decreased to 76% and 73%, respectively, at 24 months. Submission rates for the SCA arm decreased from 77% at month 6 to 66% at month 24. Baseline QoL scores were similar for all three arms (Table 2).

Comparisons of the Three Reconstruction Techniques

Pairwise comparisons of the three arms revealed no significant differences in changes in the TOI at 12 months (primary QoL endpoint). However, a clinically relevant short-term worsening (Fig. 2; Table S1) was observed for the TOI up to 6 months after TME in patients with a SEA (median change − 4.0; min, max: − 41.0, + 29.0) or SCA (median change − 4.3; min, max − 63.2, + 19.0), with subsequent improvements to baseline levels at 24 months. TOI scores remained rather stable for the CJP group during the whole observation period.

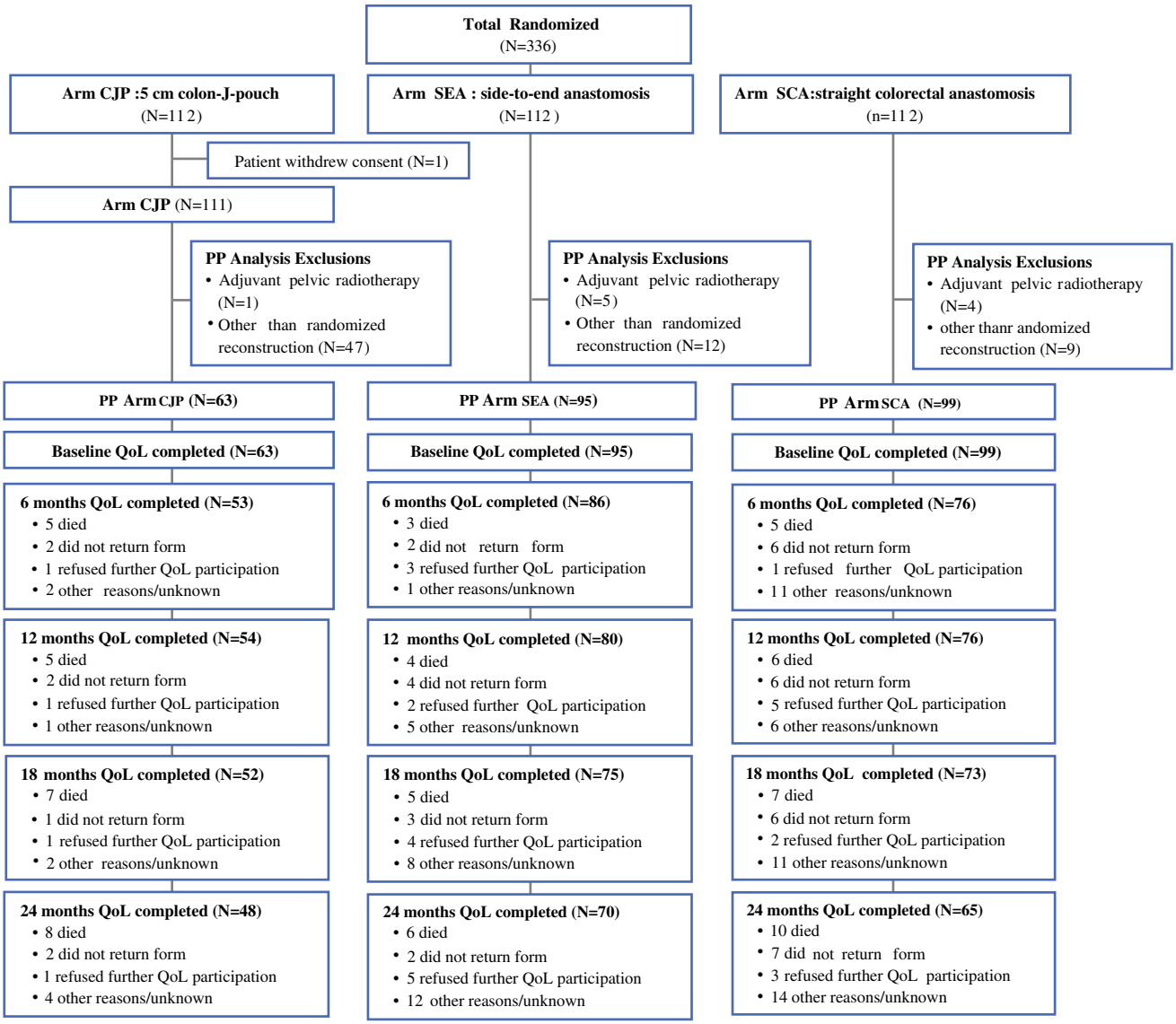


FIG. 1 CONSORT Flow diagram to identify the per protocol population with quality of life (QoL) data

In addition, changes in CCS (secondary QoL endpoint) differed significantly at 12 months between SCA and CJP ($p = 0.007$). A clinically relevant worsening was observed up to 6 months after TME in patients with SEA (median change − 2.0; min, max − 12.0, + 12.0) and up to 12 months in patients with SCA (at 6 months: median change − 2.0; min, max − 15.2, + 11.0; at 12 months: median change: − 2.0; min–max: − 16.3, + 10.0). Scores in these arms remained below baseline levels up to 24 months after TME (Fig. 2; Table S1).

At 6 months, statistically significant differences in changes were found for PWB between CJP and SEA ($p = 0.009$), for EWB between CJP and SCA ($p = 0.03$), and for the FACT-G between CJP and either SEA ($p = 0.04$) or SCA ($p = 0.04$), all in favor of the CJP. During this period, patients with SCA reported a clinically relevant worsening in FACT-C scores (median change − 5.0; min, max − 86.0, + 42.8).

No significant differences in changes from baseline to month 18 were found for any of the subscales and pairwise comparisons. At month 24, changes in EWB from baseline were significantly better for CJP compared with SCA ($p = 0.01$). Clinically relevant improvements were observed for EWB in patients with CJP at 6, 18, and 24 months and for SEA at 24 months (Fig. 2; Table S1). Results of the complementary longitudinal analyses are presented in the supplementary file. The intention-to-treat (ITT) analysis, including all 336 patients revealed similar results (data not shown).

TABLE 1 Patient and disease characteristics for per protocol population

Variable	Arm CJP (N = 63) n (%)	Arm SEA (N = 95) n (%)	Arm SCA (N = 99) n (%)
Sex			
Female	25 (39.7%)	33 (34.7%)	32 (32.3%)
Male	38 (60.3%)	62 (65.3%)	67 (67.7%)
Age at registration			
< 70	36 (57.1%)	54 (56.8%)	59 (59.6%)
≥ 70	27 (42.9%)	41 (43.2%)	40 (40.4%)
Median [min, max]	68.6 [30.9, 85.5]	67.2 [32.3, 88.9]	66.3 [32.3, 90.9]
ASA status			
I	9 (14.3%)	17 (17.9%)	8 (8.1%)
II	42 (66.7%)	53 (55.8%)	65 (65.7%)
III	12 (19.0%)	24 (25.3%)	24 (24.2%)
IV		1 (1.1%)	2 (2.0%)
UICC classification preoperative			
I	10 (15.9%)	13 (13.7%)	10 (10.1%)
II	6 (9.5%)	14 (14.7%)	13 (13.1%)
III	32 (50.8%)	39 (41.1%)	46 (46.5%)
IV	2 (3.2%)	4 (4.2%)	7 (7.1%)
Missing	13 (20.6%)	25 (26.3%)	23 (23.2%)
T classification preoperative			
T0			1 (1.0%)
T1	3 (4.8%)	4 (4.2%)	4 (4.0%)
T2	11 (17.5%)	17 (17.9%)	14 (14.1%)
T3	48 (76.2%)	69 (72.6%)	73 (73.7%)
T4	1 (1.6%)	4 (4.2%)	5 (5.1%)
Tx		1 (1.1%)	2 (2.0%)
Distant metastatic disease			
M0	61 (96.8%)	91 (95.8%)	93 (93.9%)
M1	2 (3.2%)	4 (4.2%)	6 (6.1%)
Distance of distal tumor margin from dentate line (cm)			
≤ 5	18 (28.6%)	29 (30.5%)	35 (35.4%)
> 5	45 (71.4%)	66 (69.5%)	64 (64.6%)
Median [min, max]	6.0 [1.0, 11.0]	7.0 [1.0, 15.0]	5.0 [1.0, 12.0]
Neoadjuvant treatment (more than one possible)			
Chemotherapy		3 (3.2%)	4 (4.0%)
Combined chemoradiotherapy	45 (71.4%)	66 (69.5%)	70 (70.7%)
Radiotherapy	4 (6.3%)	3 (3.2%)	6 (6.1%)
Adjuvant treatment (more than one possible)			
None	29 (46%)	42 (44%)	47 (47%)
Chemotherapy	34 (54%)	53 (56%)	52 (53%)
Stoma closure			
Yes	48 (84%)	80 (90%)	78 (88%)
No	9 (16%)	9 (10%)	11 (12%)
Median time to stoma closure (months; [95% CI]	5.3 [3.9–6.1]	4.6 [3.5–5.9]	4.8 [3.4–5.6]

Association Between Clinical Outcome and QoL

To investigate the association between clinical outcome and QoL, we added the dichotomized composite evacuation score as covariate at 12 months to the model. We found small, significant effects for the evacuation score on all QoL scales (except for SWB; Fig. S1) but without any explicit trend favoring patients with lower or higher composite evacuation scores at 12 months.

DISCUSSION

In this multicenter, randomized trial comparing, SEA, 5-cm CJP, and SCA after TME in patients with rectal cancer, there was no significant difference in changes in the TOI at 12 months from baseline. In general, differences in changes between reconstruction techniques were small and for the majority of comparisons not statistically significant. We mainly observed differences in QoL in the short-term (at 6 months after TME). Patients who had a CJP reported better physical, emotional, and overall QoL than patients who had SEA or SCA. This group also reported significantly better symptom-specific QoL compared with patients with SCA 12 months after TME. The FACT-C baseline values (presurgery) of our sample were similar to those reported for patients diagnosed with colorectal cancer without metastases and having a performance status rating (self-reported) of 0 (fully ambulatory).[12] Taking into account the changes over 24 months within each arm, patients with a CJP showed a rather stable QoL profile. Patients with SEA or SCA, however, reported a clinically relevant worsening for some of the QoL domains, with patients who had a SCA reporting elevated levels of colorectal-specific symptoms up to 12 months after TME, including stomach cramps, loss of bowel control, diarrhea, digesting problems, diminished appetite, weight loss, and negatively perceived body appearance.

FIG. 2 Median changes from baseline for Trial Outcome Index (TOI), colorectal cancer symptoms (CCS), FACT-C, FACT-G, physical well-being (PWB), functional well-being (FWB), social well-being (SWB), and emotional well-being (EWB) scores (per protocol population). Red dashed line: clinically relevant change ▶

In contrast, evacuation and incontinence scores did not show statistically significant differences among the three groups at any of the time points.[11] Looking at the impact of the severity of evacuation problems at month 12 on the various QoL scales, we did not find an explicit trend that those patients who reported more severe evacuation problems had worse QoL compared with those who reported less severe problems. Patients' perception and weighting of these symptoms may be associated with the adaptation process and thus differ from these functional outcomes.[20]

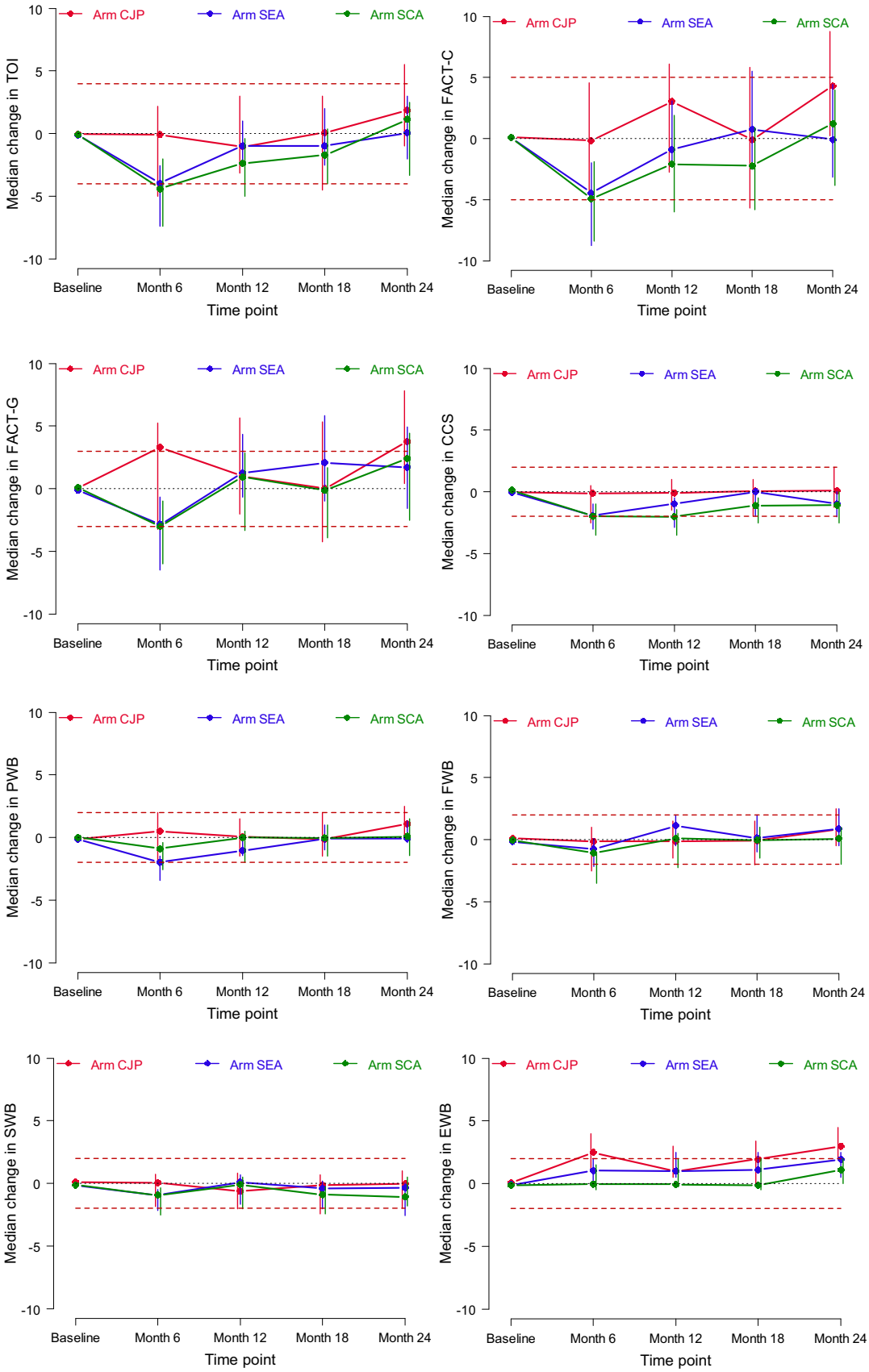
Our findings support those two studies that reported CJP to be favorable in terms of both global and symptom-specific QoL in the early phase after surgery.[6,7] Parc et al. specifically found that QoL domains related to lifestyle and embarrassment were significantly better in the CJP group.[7] The FACT-G SWB subscale focuses on social support rather than on social activities or interactions. This may explain why no changes were seen for this subscale in our study. Comparisons between CJP and SEA point to the same direction, with a favorable QoL profile for the former technique. The only study comparing CJP with SEA with regard to QoL outcomes reported that the differences found in functional outcome between groups did not influence symptom-specific and overall QoL.[10]

TABLE 2 Baseline QoL scores

Variable	Arm CJP (N = 63)			Arm SEA (N = 95)			Arm SCA (N = 99)		
	n	median	(min, max)	n	median	(min, max)	n	median	(min, max)
TOI	62	69.1	(40.0, 84.0)	93	69.0	(29.0, 82.0)	97	69.0	(32.0, 84.0)
PWB	62	25.0	(5.0, 28.0)	94	26.0	(6.0, 28.0)	98	26.0	(8.0, 28.0)
FWB	62	21.5	(8.0, 28.0)	94	21.0	(0.0, 28.0)	97	21.0	(0.0, 28.0)
SWB	61	23.3	(8.4, 28.0)	93	25.0	(0.0, 28.0)	97	24.0	(0.0, 28.0)
EWB	62	19.0	(9.0, 24.0)	94	19.0	(4.0, 24.0)	97	20.0	(1.0, 24.0)
CCS	62	23.0	(12.0, 28.0)	93	23.0	(9.0, 28.0)	98	24.0	(8.0, 28.0)
FACT-C	61	113.0	(70.4, 136.0)	92	113.0	(52.0, 131.0)	95	111.0	(49.0, 136.0)
FACT-G	61	89.0	(52.4, 108.0)	93	89.0	(41.0, 105.0)	95	89.0	(34.0, 108.0)

Higher scores for all scales indicate a better condition

TOI Trial Outcome Index, *PWB* physical well-being, *FWB* functional well-being, *SWB* social well-being, *EWB* emotional well-being, *CCS* colorectal cancer symptoms, *FACT-C* FACT Colorectal Total Score, *FACT-G* FACT General Total score


Arm CJP
Arm SEA
Arm SCA
Median change in TOI
Median change in FACT-C
Median change in FACT-G
Median change in CCS
Median change in PWB
Median change in FWB
Median change in SWB
Median change in EWB
10
5
0
-5
-10
Baseline
Month 6
Month 12
Month 18
Month 24
Time point

Previous studies compared mainly two different techniques in small samples over shorter time-periods after surgery.[4–7,10] A study comparing TME with or without short-term preoperative radiotherapy in rectal cancer showed that the largest changes were seen during the first 2 years after treatment and that QoL did not differ from the general population after a period of 5–14 years.[21]

A limitation is that we did not assess sexual functioning. There is some evidence that sexuality is affected after rectal cancer treatment, and different outcomes may be expected depending on reconstruction technique.[22,23] We did not adjust for the three pairwise comparisons to look for consistency of the signal among comparable QoL domains. Only those patients who survived and sent back the QoL questionnaires were included in the analysis. Patients in whom the stoma was not reversed were included. Given that their number was balanced between the three arms, we expect that excluding these patients would not change the results. Questionnaire submission rate was highest in the CJP group, suggesting a bias toward an underestimation of the differences in favor of CJP regarding the changes in other groups. However, a lower number of patients was analyzed for QoL in the CJP group compared with the other two groups. Due to safety reasons, in patients who were randomized to receive CJP, surgeons have occasionally reconstructed bowel continuity not according to randomization. This may result in an overestimation of the QoL benefit found for this group. We did not investigate the impact of complications of the different reconstruction techniques on QoL, because no differences in morbidity and mortality were observed among the patients included in the three different treatment arms.[11]

CONCLUSIONS

Our results provide complementary information to the functional outcome assessments of three surgical reconstruction techniques in patients with rectal cancer. No major differences in QoL scores were found between the three reconstruction techniques over the whole observation period of 2 years after TME. Patients who had a colon J-pouch may benefit with respect to QoL in the short-term.

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