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ORIGINAL REPORT

Effect of Neoadjuvant Chemoradiotherapy on Health-Related Quality of Life in Esophageal or Junctional Cancer: Results From the Randomized CROSS Trial

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ABSTRACT

Purpose

To compare pre-agreed health-related quality of life (HRQOL) domains in patients with esophageal or junctional cancer who received neoadjuvant chemoradiotherapy (nCRT) followed by surgery or surgery alone. Secondary aims were to examine the effect of nCRT on HRQOL before surgery and the effect of surgery on HRQOL.

Patients and Methods

Patients were randomly assigned to nCRT (carboplatin plus paclitaxel with concurrent 41.4-Gy radiotherapy) followed by surgery or surgery alone. HRQOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQ-C30) and –Oesophageal Cancer Module (QLQ-OES24) questionnaires pretreatment and at 3, 6, 9, and 12 months postoperatively. The nCRT group also received preoperative questionnaires. Physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24) were chosen as predefined primary end points. Predefined secondary end points were global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems (EM; QLQ-OES24).

Results

A total of 363 patients were analyzed. No statistically significant differences in postoperative HRQOL were found between treatment groups. In the nCRT group, PF, EA, GQOL, FA, and EM scores deteriorated 1 week after nCRT (Cohen's d: −0.93, $P < .001$; 0.47, $P < .001$; −0.84, $P < .001$; 1.45, $P < .001$; and 0.32, $P = .001$, respectively). In both treatment groups, all end points declined 3 months postoperatively compared with baseline (Cohen's d: −1.00, 0.33, −0.47, −0.34, and 0.33, respectively; all $P < .001$), followed by a continuous gradual improvement. EA, GQOL, and EM were restored to baseline levels during follow-up, whereas PF and FA remained impaired 1 year postoperatively (Cohen's d: 0.52 and −0.53, respectively; both $P < .001$).

Conclusion

Although HRQOL declined during nCRT, no effect of nCRT was apparent on postoperative HRQOL compared with surgery alone. In addition to the improvement in survival, these findings support the view that nCRT according to the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study–regimen can be regarded as a standard of care.

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ASSOCIATED CONTENT

Appendix
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INTRODUCTION

Esophageal cancer is characterized by high recurrence rates and poor 5-year survival after primary surgical resection.[1] To improve the radicality of surgery and long-term survival, many trials on the added value of neoadjuvant therapy have been undertaken.[2-8]

One of the largest and most recent trials is the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS). The randomized CROSS trial compared carboplatin plus paclitaxel–based neoadjuvant concurrent chemoradiotherapy

(nCRT) regimen plus surgery with surgery alone in patients with esophageal or esophagogastric junctional cancer from eight centers in the Netherlands. Long-term results showed a statistically significant and clinically relevant increase in survival for both squamous cell and adenocarcinoma subtypes, with acceptable toxicity.[9,10] On the basis of these results, the CROSS regimen is now standard treatment in many countries.

The enhanced emphasis on health-related quality of life (HRQOL) and other patient-reported outcome measures assumes a more prominent role for these factors as end points in clinical cancer trials.[11] An esophagectomy is a major operation with substantial morbidity and mortality and may have a profound effect on patients' QOL.[12-14] However, in the field of esophageal cancer, only limited high-quality data on HRQOL are available. So far, HRQOL data have been reported in two randomized esophageal cancer trials, which compared transthoracic versus transhiatal esophagectomy in patients who underwent primary surgery without neoadjuvant therapy and primary surgery versus definitive CRT.[15,16] Results from randomized trials in patients with esophageal cancer investigating the effect of combined neoadjuvant therapy and surgery on HRQOL have not yet been published. The available evidence comes from two small observational studies. Both studies suggested that the addition of nCRT to surgery had no influence on postoperative HRQOL, but they were likely influenced by selection bias and lacked statistical power.[17,18]

The primary aim of this substudy of the CROSS trial, with HRQOL as a secondary end point, was to compare HRQOL in patients with esophageal or junctional cancer who received nCRT plus surgery or surgery alone. Furthermore, the effect of nCRT on HRQOL before surgery and the effect of surgery on HRQOL were examined over time. It was hypothesized that nCRT impairs HRQOL before surgery but does not affect postoperative recovery in terms of HRQOL.

PATIENTS AND METHODS

Details of this randomized trial have been reported previously and are summarized in the Appendix Trial Design (online only).[9,10,19]

HRQOL Measurement

The self-report questionnaires were mailed after random assignment and 3, 6, 9, and 12 months postoperatively. Postoperative HRQOL was compared between both groups using date of surgery as reference point. Patients who were randomly assigned to the nCRT group also received questionnaires 1 week after nCRT (ie, 3 to 5 weeks before surgery).

Cancer-specific HRQOL was measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), a validated self-report questionnaire for patients with cancer.[20] Tumor-specific HRQOL was measured by the EORTC QLQ–Oesophageal Cancer Module (QLQ-OES24), because the currently used derivative QLQ-OES18 was not yet available.[21]

End points were predefined by consensus discussion with experienced upper-GI surgical oncologists, medical oncologists, and nurse practitioners before analysis of the data. End points were selected based on clinical relevance and hypothesized association with nCRT. This led to the primary end points of physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24). Secondary end points were defined as global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems (EM; QLQ-OES24).

Statistical Analysis

Data were analyzed on an intention-to-treat basis, with comparison of HRQOL as primary objective. Pretreatment characteristics were compared using the Mann-Whitney or Student's t test for continuous variables and the χ^2 or Fisher's exact test for categorical data.

Questionnaire scores were computed according to EORTC guidelines.[22] Baseline HRQOL scores were compared using the Student's t test. Differential effects over time between treatment groups and longitudinal comparison of the baseline scores and scores from follow-up measurements (3, 6, 9, and 12 months postoperatively) were performed using mixed modeling. If there were no statistically significant differences over time between both groups, baseline scores and scores from the postoperative measurements of both groups were combined to analyze longitudinal HRQOL. Use of mixed modeling enabled the analysis of all data, because it allowed for inclusion of questionnaire scores from patients with different numbers of completed measurements.[23] Therefore, the statistical analyses included data from patients who were unable to complete the questionnaires on one or more occasions and from those who dropped out during the trial. Mean differences over time and differential effects over time between treatment groups were described for statistically significant outcomes. Cohen's d (CD) effect sizes were calculated to give an indication of the clinical relevance of effects and to enable standardized comparison between results from different outcome variables. CD effect sizes were derived from the beta estimates in the mixed modeling procedure through standardization of both outcome and predictor variables. CD values of 0.2, 0.5, and 0.8 indicate small, medium, and large effects, respectively.[24] Values ≥ 0.5 were considered clinically relevant.[25] In a separate analysis, recurrence of disease and death in the subsequent time period were included as control variables, which enabled the evaluation of possible effect of recurrence of disease and death on the trajectory of HRQOL scores. Recurrence of disease was defined as the earliest occurrence of disease progression resulting in irresectability, locoregional recurrence (after completion of therapy), or distant dissemination (before, during, or after treatment). To correct for multiple testing, statistical significance was set at $P < .01$ (the main analyses included five comparisons, and thus, a Bonferroni correction of .05/5 was applied), except for baseline comparisons. For those latter analyses, $P < .05$ was considered significant. All reported P values are two sided. Statistical analysis was performed using Statistical Package for the Social Sciences software, version 21.0 (SPSS, Chicago, IL).

RESULTS

Of the 368 randomly assigned patients, 363 were included in the HRQOL analysis. Two withdrew consent, two were enrolled in the trial before the HRQOL study started, and one center (which included one patient) did not participate in the HRQOL study (Fig 1). There were no clinically relevant differences in pretreatment characteristics between groups (Table 1). Because of an administrative error, 89 patients did not receive baseline questionnaires (nCRT group, n = 58; surgery-alone group, n = 31). These patients were not excluded, because their baseline characteristics did not differ significantly from the study population (data not shown), and follow-up questionnaires were correctly completed.

Overall response rates at the different measurement points were 54% to 76% and were lower in the surgery-alone group than in the nCRT group (Table 2). At each measurement point, pretreatment characteristics (age, sex, tumor location, cT stage, cN stage, and WHO performance status) of patients who completed the questionnaires were not statistically different between the two groups (data not shown). In the nCRT group, the median time to

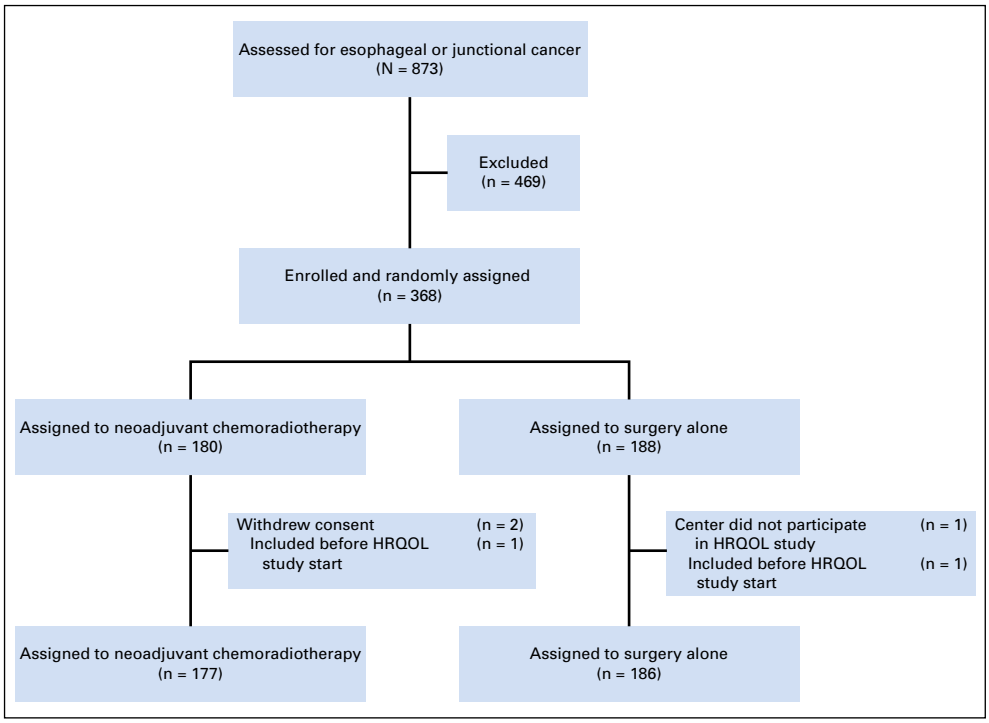

Fig 1. CONSORT diagram. HRQOL, health-related quality of life.

surgery calculated from the day of last radiation treatment was 46 days (interquartile range, 40 to 55 days). Mean scores of HRQOL domains that were not predefined end points are listed in Table 3.

Predefined Primary End Points

PF. As shown in Figure 2A, baseline PF levels and all changes over time were comparable between groups ($P = .60$ and $P = .18$, respectively). PF declined at 3 months postoperatively (−18; $P < .001$; CD, −1.00; 95% CI, −1.14 to −0.86) and improved from 3 to 6 months postoperatively (+5; $P < .001$; CD, 0.30; 95% CI, 0.18 to 0.41). From then, the improvement was no longer statistically significant (9 *v* 6 months, $P = .07$; 12 *v* 9 months, $P = .27$), and baseline levels were not reached during follow-up (−8; $P < .001$; CD, −0.53; 95% CI, −0.67 to −0.39). In the nCRT group, PF declined 1 week after nCRT (−17; $P < .001$; CD, −0.93; 95% CI, −1.12 to −0.74).

EA. As shown in Figure 2B, no statistically significant differences in EA were found at baseline ($P = .20$), and changes over time were comparable between groups ($P = .45$). Three months postoperatively, EA had worsened in both groups (+8; $P < .001$; CD, 0.32; 95% CI, 0.15 to 0.50) and thereafter improved from 3 to 6 months (−9; $P < .001$; CD, −0.32; 95% CI, −0.44 to −0.20) and from 6 to 9 months (+5; $P = .001$; CD, −0.22; 95% CI, −0.34 to −0.09). In both groups, 6 months postoperatively, EA levels returned to baseline ($P = .98$), and no further improvement was found after 12 months of follow-up compared with baseline levels ($P = .01$). The nCRT group reported a deterioration in EA 1 week after completion of nCRT (+12; $P = .001$; CD, 0.47; 95% CI, 0.21 to 0.72).

Predefined Secondary End Points

GQOL. As shown in Figure 2C, baseline GQOL scores and all changes in GQOL over time were comparable between groups ($P = .53$ and $P = .76$, respectively). GQOL scores significantly declined 3 months postoperatively (−10; $P = .002$; CD, −0.47; 95% CI, −0.62 to −0.31), improved between 3 and 6 months postoperatively (+4; $P = .001$; CD, 0.24; 95% CI, 0.10 to 0.37), reached baseline levels 9 months postoperatively ($P = .31$), and stabilized subsequently ($P = .34$). Compared with baseline, patients in the nCRT group reported significantly worse GQOL 1 week after nCRT (−17; $P < .001$; CD, −0.84; 95% CI, −1.08 to −0.60).

FA. As shown in Figure 2D, baseline FA levels were comparable between groups ($P = .42$), and there were no statistically significant differences in changes over time ($P = .30$). Postoperatively, FA levels worsened (+24; $P < .001$; CD, 1.01; 95% CI, 0.86 to 1.16) but subsequently improved in the periods from 3 to 6 months (−8; $P < .001$; CD, −0.34; 95% CI, −0.46 to −0.22). Thereafter, FA levels remained stable from 6 to 9 months ($P = .04$) and from 9 to 12 months ($P = .58$) but did not return to baseline levels (+10; $P < .001$; CD, 0.52; 95% CI, 0.38 to 0.65). In the nCRT group, a significant deterioration was reported 1 week after nCRT (+34; $P < .001$; CD, 1.45; 95% CI, 1.23 to 1.66).

EM. As shown in Figure 2E, baseline EM scores were comparable between groups ($P = .26$), and both groups reported comparable changes over time ($P = .75$). Three months postoperatively, EM worsened (+8; $P < .001$; CD, 0.33; 95% CI, 0.18 to 0.49) but improved from 3 to 6 months (−6; $P < .001$; CD, −0.26; 95% CI, −0.40 to −0.13) and from 6 to 9 months (−5; $P = .003$; CD, −0.22; 95% CI, −0.36 to −0.08) postoperatively and stabilized thereafter (9 to 12 months, $P = .74$). Baseline levels were reached at 6 months ($P = .39$) and stabilized thereafter ($P = .05$). Patients in the nCRT group reported a deterioration in EM 1 week after nCRT (+9; $P = .001$; CD, 0.32; 95% CI, 0.14 to 0.50).

Results of the model including randomized grouping for longitudinal effects are shown in Appendix Tables A1 to A5 (online only).

Table 1. Baseline Characteristics of Patients With Potentially Curable Esophageal or Esophagogastric Junction Cancer According to Treatment Group

Characteristic	No. (%)	
	nCRT Plus Surgery (n = 177)	Surgery Alone (n = 186)
Age, years		
Median	60	60
IQR	55-67	54-66
Male sex	134 (76)	151 (81)
Tumor type		
Adenocarcinoma	134 (76)	140 (75)
Squamous cell carcinoma	40 (23)	42 (23)
Large-cell undifferentiated	3 (2)	4 (2)
Tumor location*		
Esophagus		
Proximal third	4 (2)	4 (2)
Middle third	24 (14)	23 (12)
Distal third	104 (59)	107 (58)
Esophagogastric junction	39 (22)	48 (26)
Missing data	6 (3)	4 (2)
Clinical T stage†		
cT1	1 (1)	1 (1)
cT2	26 (15)	35 (19)
cT3	149 (84)	145 (78)
cT4‡	0	1 (1)
Could not be determined§	1 (1)	4 (2)
Clinical N stage‖		
N0	59 (33)	58 (31)
N1	115 (65)	118 (63)
Could not be determined§	3 (2)	10 (5)
WHO performance status¶		
0	144 (81)	161 (87)
1	33 (19)	25 (13)

NOTE. Percentages may not add up to 100 because of rounding.
Abbreviations: IQR, interquartile range; nCRT, neoadjuvant chemoradiotherapy.
*Tumor length and location were determined by means of endoscopy.
†Clinical T stage was assessed by means of endoscopic ultrasonography or computed tomography and was classified according to the International Union Against Cancer TNM classification (sixth edition).[26]
‡One patient was originally staged as cT3, but this was revised to cT4 based on central revision of all endoscopy reports.[9]
§This category included patients in whom the tumor could not be fully investigated by means of a transducer for endoscopic ultrasonography because of stenosis caused by the tumor.
‖Clinical N stage was assessed by means of endoscopic ultrasonography, computed tomography, or [^{18}F]fluorodeoxyglucose positron emission tomography and was classified according to the International Union Against Cancer TNM classification (sixth edition).[26]
¶WHO performance status on a scale of 0 to 5, with lower numbers indicating better performance status; 0 indicates fully active, and 1 unable to carry out heavy physical work.

Influence of Recurrence of Disease and Death

Inclusion of recurrence of disease and death as control variables did not influence the overall trends in HRQOL trajectories (data not shown). However, the deterioration and restoration of primary and secondary end points during follow-up were worse for patients who developed recurrent disease and for patients who died in the subsequent time period (data not shown). Patients in the surgery-alone group who died during follow-up showed the most severe deteriorations, especially in the 6- and 9-month follow-up measures.

Influence of Missing Baseline Questionnaires

Availability of a completed baseline questionnaire was included as control variable. Inclusion of this variable did not influence the described overall trends in HRQOL trajectories (data not shown).

DISCUSSION

This randomized trial did not show statistically significant differences in postoperative HRQOL in patients with esophageal or junctional cancer treated with a multimodality regimen based on carboplatin plus paclitaxel with 41.4 Gy of concurrent radiotherapy plus surgery, compared with patients who underwent surgery alone. Patients in the nCRT group experienced deterioration in all HRQOL end points immediately after completion of nCRT, but this did not affect recovery during the first postoperative year in terms of HRQOL.

In both treatment groups, all primary and secondary HRQOL end points declined postoperatively, but most were restored to pretreatment levels within 1 year postoperatively. GQOL, EA, and EM reached baseline levels 6 months (GQOL and EA) and 9 months postoperatively (EM) and stabilized from then. However, PF and FA levels were not restored to pretreatment levels during the first year of follow-up, and corresponding effect sizes were clinically relevant (CD, −0.53 and 0.52, respectively). The scores of these domains stabilized 6 and 9 months postoperatively, which suggests that further spontaneous improvement to be unlikely.

This study is the first clinical trial and the largest available analysis to our knowledge comparing HRQOL in patients with esophageal cancer who underwent neoadjuvant therapy plus surgery or surgery alone. Two small observational studies have suggested that postoperative HRQOL is not affected by addition of nCRT to surgery, but these studies used different nCRT regimens and were criticized because of the potential influence of selection bias and lack of statistical power.[17,18] The randomized design of our study largely excludes selection bias, and the relatively large sample size increases the power to detect small but clinically relevant differences. Hence, these results demonstrate more reliably that postoperative HRQOL is not affected by nCRT, thereby confirming the results from these previous studies. These findings can help clinicians and patients to make more properly informed treatment decisions, especially patients who fear the negative effect of neoadjuvant treatment. Besides the relatively low toxicity and the strong effect on survival after nCRT plus surgery according to CROSS,[9,10] the comparable effect on postoperative HRQOL with surgery alone confirms that the benefits of this effective regimen outweigh its harms. Nevertheless, it should be noted that the application of nCRT delays surgery and subsequent postoperative recovery by 2 to 3 months. This delay is substantial, especially for patients who turn out to be nonsurvivors. Furthermore, the long-term effects of adding nCRT to surgery on HRQOL are largely unknown and need to be further explored. Although it has been shown that nCRT containing cisplatin and fluorouracil with 66 Gy of concurrent radiotherapy significantly hampers long-term HRQOL, the CROSS regimen theoretically may have fewer negative effects because of the mild toxicity of the applied chemotherapeutic agents and the relatively low radiation dose.[27]

In line with our study, a profound deterioration in HRQOL scores immediately after completion of nCRT has been described in the phase II CROSS-I trial and other observational studies.[17,18,28]

Table 2. Patient QOL Questionnaire Completion

Status	Measurement Point					
			Postsurgery (months)			
	Baseline	Post-nCRT	3	6	9	12
Eligible	363	177	342	308	285	260
nCRT + surgery	177	177	163	151	145	136
Surgery alone	186		179	157	140	124
Returned total (% of eligible)	235 (65)	104 (59)	228 (67)	210 (68)	185 (65)	166 (64)
nCRT + surgery	134 (76)	104 (59)	119 (73)	113 (75)	103 (71)	94 (69)
Surgery alone	101 (54)	NA	109 (61)	97 (62)	82 (59)	72 (58)
Died	0	0	21	55	78	103
Too ill	0	24	38	27	36	32
Randomly missing/other	128*	49	76	71	64	62

Abbreviations: NA, not applicable; nCRT, neoadjuvant chemoradiotherapy; QOL, quality of life.
*Eighty nine missing because of administrative error.

This decline in all end points 1 week after completion of nCRT is explained by persisting adverse effects of chemotherapy and radiotherapy, such as anorexia, FA, esophagitis, and hematologic toxicity. This emphasizes the need for sufficient time between nCRT and surgery, which allows patients to recover and reach more optimal physical condition before surgery. Earlier studies have suggested that postponement of surgery to at least 12 weeks after nCRT does not jeopardize long-term oncologic outcome and even tends to increase the pathologic complete response rate, which might improve prognostication.[29,30] Unfortunately, no HRQOL

Table 3. Mean Scores for All Domains in Two EORTC Questionnaires That Were Not Predefined End Points According to Treatment Group

Measure	Measurement Point Mean (SD)											
					Postsurgery (months)							
	Baseline		Post-nCRT		3		6		9		12	
	Surgery Alone	nCRT	Surgery Alone	nCRT	Surgery Alone	nCRT	Surgery Alone	nCRT	Surgery Alone	nCRT	Surgery Alone	nCRT
QLQ-C30												
Functional scales												
Role	85 (22)	88 (24)	NA	57 (29)	55 (32)	60 (30)	68 (29)	68 (30)	73 (26)	76 (28)	78 (24)	77 (27)
Emotional	71 (20)	71 (21)	NA	74 (21)	75 (24)	78 (21)	76 (22)	80 (23)	80 (18)	82 (19)	77 (20)	83 (20)
Cognitive	89 (16)	93 (15)	NA	84 (21)	82 (21)	82 (22)	85 (18)	85 (17)	84 (18)	86 (17)	84 (19)	87 (19)
Social	85 (20)	87 (20)	NA	77 (24)	68 (27)	69 (28)	75 (25)	80 (21)	78 (25)	84 (22)	83 (23)	85 (23)
Symptom scores												
Nausea and vomiting	12 (20)	8 (14)	NA	22 (28)	21 (24)	19 (23)	13 (20)	21 (24)	12 (18)	13 (18)	11 (16)	12 (19)
Pain	14 (20)	14 (20)	NA	31 (29)	23 (28)	17 (23)	21 (25)	17 (24)	15 (24)	13 (22)	17 (20)	11 (19)
Dyspnea	10 (20)	5 (12)	NA	20 (26)	26 (27)	28 (29)	22 (27)	24 (26)	22 (26)	18 (23)	16 (22)	17 (24)
Insomnia	20 (28)	23 (26)	NA	29 (31)	26 (31)	22 (30)	22 (26)	20 (28)	26 (30)	15 (23)	19 (26)	17 (26)
Loss of appetite	14 (24)	13 (25)	NA	41 (36)	30 (33)	34 (33)	18 (27)	24 (33)	13 (25)	12 (20)	13 (22)	14 (24)
Constipation	6 (15)	8 (19)	NA	24 (33)	13 (26)	9 (23)	10 (19)	6 (17)	9 (20)	6 (16)	10 (22)	9 (20)
Diarrhea	5 (12)	2 (10)	NA	14 (26)	21 (27)	21 (28)	22 (26)	20 (25)	16 (22)	17 (23)	17 (21)	15 (23)
Financial worries	6 (17)	9 (20)	NA	8 (19)	10 (20)	12 (24)	14 (24)	13 (21)	9 (18)	13 (20)	13 (24)	12 (22)
QLQ-OES24												
Dysphagia	62 (34)	64 (35)	NA	53 (32)	70 (31)	74 (28)	79 (29)	75 (30)	75 (33)	76 (30)	74 (34)	77 (29)
Deglutition	16 (23)	15 (24)	NA	14 (20)	19 (23)	21 (23)	15 (24)	13 (21)	18 (26)	15 (21)	13 (20)	15 (23)
Swallowing of saliva	17 (30)	18 (31)	NA	18 (29)	18 (31)	18 (30)	15 (29)	11 (26)	17 (30)	16 (29)	12 (22)	15 (27)
Aspiration	13 (23)	13 (24)	NA	9 (19)	19 (25)	23 (26)	16 (25)	15 (23)	17 (25)	15 (21)	14 (23)	16 (23)
GI symptoms (24)	22 (19)	15 (15)	NA	21 (19)	23 (21)	18 (18)	22 (19)	20 (18)	21 (21)	21 (20)	24 (23)	20 (21)
GI symptoms (18)	9 (19)	7 (16)	NA	16 (23)	17 (26)	12 (20)	18 (23)	17 (22)	18 (24)	20 (24)	21 (25)	18 (24)
Pain	23 (24)	18 (21)	NA	32 (25)	12 (16)	12 (19)	12 (18)	11 (13)	11 (17)	11 (19)	12 (19)	8 (13)
Dry mouth	14 (24)	9 (20)	NA	25 (31)	19 (29)	21 (30)	13 (24)	21 (26)	16 (25)	20 (31)	18 (24)	16 (24)
Trouble with taste	10 (23)	7 (21)	NA	37 (37)	24 (33)	24 (33)	13 (26)	14 (25)	13 (24)	11 (24)	13 (23)	9 (21)
Trouble with coughing	16 (22)	13 (21)	NA	31 (31)	37 (34)	41 (35)	29 (29)	25 (30)	29 (29)	24 (27)	22 (24)	16 (20)
Trouble with speaking	6 (17)	4 (16)	NA	6 (17)	19 (28)	18 (29)	11 (25)	11 (25)	13 (28)	11 (25)	14 (28)	11 (25)
Hair loss	0 (0)	0 (0)	NA	24 (29)	8 (24)	23 (34)	24 (25)	18 (30)	29 (37)	26 (40)	19 (26)	15 (29)

NOTE. Scores are presented as mean. Standard deviations are shown between parentheses.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NA, not applicable; nCRT, neoadjuvant chemoradiotherapy; QLQ-C30, Quality of Life Questionnaire–Core 30; QLQ-OES24, Quality of Life Questionnaire–Oesophageal Cancer Module; SD, standard deviation.

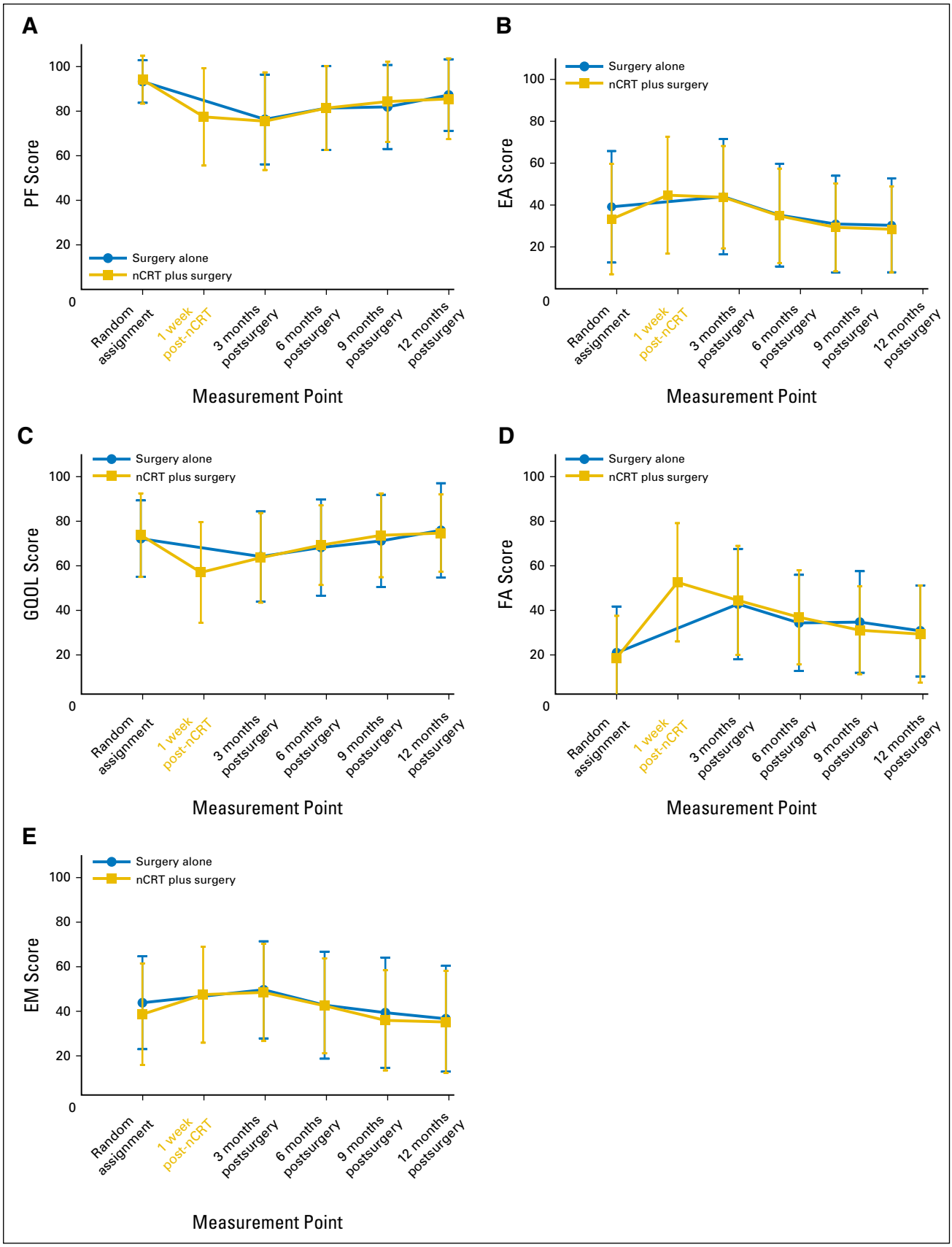

Fig 2. Mean scores with standard deviations for primary end points (A) physical functioning (PF) and (B) eating problems (EA) and secondary end points (C) global quality of life (GQOL), (D) fatigue (FA), and (E) emotional problems (EM) according to treatment group. nCRT, neoadjuvant chemoradiotherapy.

assessment was performed during nCRT or just before surgery. In clinical practice, we have witnessed general improvements in patients' condition in the period between nCRT and surgery. Therefore, we recommend timing of surgery to be guided by patients' condition, and we advocate that surgery should be postponed to up to 12 weeks after completion of nCRT in case of persisting adverse events or bad general condition. To further optimize the timing of surgery, the course of HRQOL in the period between nCRT and surgery should be monitored more carefully. On the basis of the available literature and our clinical experience, it seems that HRQOL substantially improves over a period of 6 to 12 weeks.[17]

Although some studies have suggested that the effect of esophagectomy on HRQOL is restored within 1 year postoperatively[15] or can be attributed to only a small group of patients,[31] most studies have shown lasting and substantial negative effects.[13,14,32] This is confirmed by the results of our study, in which two of the five end points (ie, PF and FA) did not return to baseline levels during the first year follow-up, and none of the end points improved compared with baseline levels (for patients suffering from esophageal cancer). These effects could only partly be explained by recurrence of disease or death in the subsequent study period, emphasizing the adverse effect of esophagectomy on HRQOL. Cognitive behavioral therapy, which was not routinely offered in our study, might be successful in treating patients with lasting FA.[33] Furthermore, new treatment strategies, such as minimally invasive esophagectomy and an active surveillance approach after nCRT (instead of standard surgery), might improve HRQOL in these patients.[34,35]

Limitations of this study include overall attrition and lower response rates in the surgery-alone group than in the nCRT group. Attrition is inevitable in HRQOL studies with severely ill patients. Nevertheless, at each measurement point, pretreatment prognostic parameters of patients who completed the questionnaires were comparable between the two treatment groups, suggesting the effect of attrition bias to be small. Lower response rates in the surgery-alone group might be explained by primary surgery being standard treatment during the performance of the trial. Consequently, patients in the surgery-alone group could have been less motivated to complete HRQOL questionnaires than patients in the experimental nCRT group. Another possible explanation is the increasing rate of recurrence being more common in the surgery-alone group.

Because of the relatively low number of older patients (patients age $\geq$ 76 years were excluded from the trial) and patients with poorer performance status (patients with WHO $>$ 2 were also excluded), results from this study cannot be generalized to these specific categories of vulnerable patients. The effect of this treatment regimen on HRQOL will need to be tested for these subgroups of patients in future studies.

Furthermore, it has been pointed out previously that patients who receive neoadjuvant treatment may report better recovery from surgery, as a result of adjustments to toxicity as experienced during neoadjuvant treatment leading to a re-evaluation of internal standards (ie, response shift). In our study, it was not possible to correct for this potential effect.[17]

Finally, although formally validated, sensitivity of HRQOL questionnaires remains uncertain, and these questionnaires might be too crude to detect small but clinically relevant differences. To optimize precision, both generic and disease-specific questionnaires were used, and together with the large sample size of the current trial, we expect sensitivity to be relatively high compared with that of earlier studies on this topic. Of note, the QLQ-OES24 questionnaire has been refined into the QLQ-OES18, with revision of the hypothesized scales and the removal of two single items. We do not believe this invalidates the results of our study, because the EA scale was retained in its original form. The EM scale showed modest to high correlations within all validation analyses but was deleted because of overlap with the QLQ-C30 questionnaire.[21]

In conclusion, although HRQOL declined immediately after nCRT, no effect of nCRT according to CROSS was apparent on postoperative short-term HRQOL compared with surgery alone. In addition to the earlier described improvement in long-term overall and disease-free survival, these results support the view that nCRT according to this effective regimen should be regarded as a standard of care for patients with locally advanced resectable esophageal or esophagogastric junctional cancer.

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Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Trial Design

Details of this multicenter, randomized trial, have been reported previously.[9,10,19] Briefly, patients with locally advanced (clinical stage T1N1M0 or T2–3N0–1M0 according to the 6th edition of the TNM cancer staging)[26], histologically proven squamous cell carcinoma (SCC), adenocarcinoma (AC) or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction (EGJ) were eligible for inclusion. Eligible patients were between 18 and 75 years of age; had adequate pulmonary, hematological, hepatic and renal function; and a WHO performance score of 2 or better. The study protocol was approved by the institutional review boards and all patients provided written informed consent.

Randomization

Patients were randomized 1:1 to each treatment group, with random permuted block sizes of 4 or 6. All patients were stratified according to treatment center, WHO performance score, histological tumor type and clinical lymph node status.

Procedures

Patients assigned to the nCRT group received carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m^2 of body-surface area) intravenously for five cycles on days 1, 8, 15, 22, and 29. Concurrent radiation therapy of 41.4 Gy was given in 23 fractions of 1.8 Gy, 5 days per week. Patients in the surgery alone group received surgery as soon as possible, whereas those in the nCRT plus surgery group preferably had surgery 4 to 6 weeks after completion of nCRT. For carcinomas at or above the level of the carina, a transthoracic esophagectomy with two-field lymphadenectomy was performed. For carcinomas located well below the carina, either a transthoracic esophagectomy with two-field lymphadenectomy or a transhiatal esophagectomy with upper abdominal and lower mediastinal lymphadenectomy was performed, depending on patient characteristics and local preferences. For carcinomas involving the esophagogastric junction, a transhiatal esophagectomy was preferred. During the first year after completion of treatment, follow-up took place every 3 months. In the second year, patients were followed every 6 months and annually thereafter until 5 years after completion of treatment. Additional visits were scheduled if complaints arose before the next visit.[9,10]

Table A1. Mixed Modeling Analysis Including Randomized Grouping for Longitudinal Effects on Physical Functioning

Parameter	Cohen's d*	*P*	95% CI
Baseline scores for nCRT group	0.56	< .001	0.47 to 0.65
Difference for surgery alone	−0.04	.598	−0.18 to 0.10
Comparison with baseline			
1 week post-nCRT	−0.93	< .001	−1.12 to −0.74
3 months postsurgery for nCRT group	−1.09	< .001	−1.29 to −0.90
Difference for surgery alone	0.21	.157	−0.08 to 0.49
6 months postsurgery for nCRT group	−0.70	< .001	−0.89 to −0.52
Difference for surgery alone	0.01	.968	−0.27 to 0.28
9 months postsurgery for nCRT group	−0.53	< .001	−0.72 to −0.35
Difference for surgery alone	−0.15	.287	−0.43 to 0.13
12 months postsurgery for nCRT group	−0.51	< .001	−0.69 to −0.32
Difference for surgery alone	−0.05	.717	−0.34 to 0.23
Comparison with previous measurement			
3 months postsurgery for nCRT group	−0.16	.164	−0.38 to 0.07
6 months postsurgery for nCRT group	0.39	< .001	0.24 to 0.54
Difference for surgery alone	−0.20	.079	−0.43 to 0.02
9 months postsurgery for nCRT group	0.17	.022	0.02 to 0.32
Difference for surgery alone	−0.16	.159	−0.38 to 0.06
12 months postsurgery for nCRT group	0.03	.730	−0.14 to 0.19
Difference for surgery alone	0.10	.430	−0.15 to 0.35

Abbreviation: nCRT, neoadjuvant chemoradiotherapy.
*Cohen's d effect sizes were derived from the beta estimates in the mixed-modeling procedure through standardization of both outcome and predictor variables. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as difference for surgery alone.

Table A2. Mixed Modeling Analysis Including Randomized Grouping for Longitudinal Effects on Global Health Status

Parameter	Cohen's d*	*P*	95% CI
Baseline scores for nCRT group	0.22	.004	0.07 to 0.37
Difference for surgery alone	−0.07	.533	−0.30 to 0.16
Comparison with baseline			
1 week post-nCRT	−0.84	< .001	−1.08 to −0.60
3 months postsurgery for nCRT group	−0.52	< .001	−0.72 to −0.31
Difference for surgery alone	0.11	.467	−0.19 to 0.42
6 months postsurgery for nCRT group	−0.21	.058	−0.42 to 0.01
Difference for surgery alone	−0.04	.801	−0.36 to 0.28
9 months postsurgery for nCRT group	−0.06	.574	−0.29 to 0.16
Difference for surgery alone	−0.05	.776	−0.39 to 0.29
12 months postsurgery for nCRT group	−0.04	.729	−0.27 to 0.19
Difference for surgery alone	0.05	.799	−0.31 to 0.40
Comparison with previous measurement			
3 months postsurgery for nCRT group	0.33	.008	0.09 to 0.57
6 months postsurgery for nCRT group	0.31	.001	0.13 to 0.49
Difference for surgery alone	−0.16	.255	−0.42 to 0.11
9 months postsurgery for nCRT group	0.14	.145	−0.05 to 0.34
Difference for surgery alone	−0.01	.958	−0.30 to 0.28
12 months postsurgery for nCRT group	0.02	.792	−0.15 to 0.20
Difference for surgery alone	0.09	.491	−0.18 to 0.37

Abbreviation: nCRT, neoadjuvant chemoradiotherapy.
*Cohen's d effect sizes were derived from the beta estimates in the mixed-modeling procedure through standardization of both outcome and predictor variables. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as difference for surgery alone.

Table A3. Mixed Modeling Analysis Including Randomized Grouping for Longitudinal Effects on Fatigue

Parameter	Cohen's d*	*P*	95% CI
Baseline scores for nCRT group	−0.63	< .001	−0.76 to −0.49
Difference for surgery alone	0.08	.421	−0.12 to 0.29
Comparison with baseline			
1 week post-nCRT	1.45	< .001	1.23 to 1.67
3 months postsurgery for nCRT group	1.12	< .001	0.91 to 1.32
Difference for surgery alone	−0.23	.137	−0.53 to 0.07
6 months postsurgery for nCRT group	0.74	< .001	0.54 to 0.93
Difference for surgery alone	−0.14	.331	−0.44 to 0.15
9 months postsurgery for nCRT group	0.53	< .001	0.34 to 0.72
Difference for surgery alone	0.05	.754	−0.25 to 0.34
12 months postsurgery for nCRT group	0.49	< .001	0.31 to 0.68
Difference for surgery alone	0.05	.723	−0.23 to 0.33
Comparison with previous measurement			
3 months postsurgery for nCRT group	−0.33	.002	−0.54 to −0.12
6 months postsurgery for nCRT group	−0.38	< .001	−0.54 to −0.22
Difference for surgery alone	0.08	.487	−0.15 to 0.32
9 months postsurgery for nCRT group	−0.21	.010	−0.37 to −0.05
Difference for surgery alone	0.19	.119	−0.05 to 0.43
12 months postsurgery for nCRT group	−0.03	.656	−0.19 to 0.12
Difference for surgery alone	0.00	.970	−0.23 to 0.24

Abbreviation: nCRT, neoadjuvant chemoradiotherapy.
*Cohen's d effect sizes were derived from the beta estimates in the mixed-modeling procedure through standardization of both outcome and predictor variables. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as difference for surgery alone.

Table A4. Mixed Modeling Analysis Including Randomized Grouping for Longitudinal Effects on Emotional Problems

Parameter	Cohen's d*	*P*	95% CI
Baseline scores for nCRT group	−0.09	.262	−0.26 to 0.07
Difference for surgery alone	0.18	.159	−0.07 to 0.43
Comparison with baseline			
1 week post-nCRT	0.32	.001	0.14 to 0.50
3 months postsurgery for nCRT group	0.40	< .001	0.19 to 0.61
Difference for surgery alone	−0.15	.346	−0.46 to 0.16
6 months postsurgery for nCRT group	0.14	.215	−0.08 to 0.36
Difference for surgery alone	−0.15	.362	−0.48 to 0.18
9 months postsurgery for nCRT group	−0.14	.218	−0.37 to 0.09
Difference for surgery alone	0.00	.992	−0.35 to 0.35
12 months postsurgery for nCRT group	−0.14	.210	−0.36 to 0.08
Difference for surgery alone	−0.06	.712	−0.40 to 0.28
Comparison with previous measurement			
3 months postsurgery for nCRT group	0.08	.459	−0.13 to 0.28
6 months postsurgery for nCRT group	−0.26	.006	−0.45 to −0.07
Difference for surgery alone	0.00	.989	−0.28 to 0.27
9 months postsurgery for nCRT group	−0.28	.003	−0.47 to −0.10
Difference for surgery alone	0.15	.295	−0.13 to 0.43
12 months postsurgery for nCRT group	0.00	.982	−0.19 to 0.19
Difference for surgery alone	−0.06	.675	−0.36 to 0.23

Abbreviation: nCRT, neoadjuvant chemoradiotherapy.
*Cohen's d effect sizes were derived from the beta estimates in the mixed-modeling procedure through standardization of both outcome and predictor variables. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as difference for surgery alone.

Table A5. Mixed Modeling Analysis Including Randomized Grouping for Longitudinal Effects on Eating Problems

Parameter	Cohen's d*	*P*	95% CI
Baseline scores for nCRT group	−0.10	.294	−0.28 to 0.09
Difference for surgery alone	0.21	.136	−0.07 to 0.49
Comparison with baseline			
1 week post-nCRT	0.47	.001	0.21 to 0.72
3 months postsurgery for nCRT group	0.43	.001	0.19 to 0.68
Difference for surgery alone	−0.25	.177	−0.61 to 0.11
6 months postsurgery for nCRT group	0.07	.582	−0.17 to 0.30
Difference for surgery alone	−0.15	.403	−0.50 to 0.20
9 months postsurgery for nCRT group	−0.13	.267	−0.37 to 0.10
Difference for surgery alone	−0.19	.283	0.55 to 0.16
12 months postsurgery for nCRT group	−0.21	.086	−0.45 to 0.03
Difference for surgery alone	−0.05	.774	−0.42 to 0.31
Comparison with previous measurement			
3 months postsurgery for nCRT group	−0.03	.816	−0.30 to 0.23
6 months postsurgery for nCRT group	−0.37	< .001	−0.53 to −0.21
Difference for surgery alone	0.10	.422	−0.14 to 0.33
9 months postsurgery for nCRT group	−0.20	.022	−0.37 to −0.03
Difference for surgery alone	−0.04	.741	−0.30 to 0.21
12 months postsurgery for nCRT group	−0.08	.280	−0.22 to 0.07
Difference for surgery alone	0.14	.212	−0.08 to 0.36

Abbreviation: nCRT, neoadjuvant chemoradiotherapy.
*Cohen's d effect sizes were derived from the beta estimates in the mixed-modeling procedure through standardization of both outcome and predictor variables. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as difference for surgery alone.