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Longitudinal Analysis of Quality of Life Recovery After Gastrectomy for Cancer

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Abstract

INTRODUCTION: The purpose of this study was to identify factors associated with quality of life recovery after gastrectomy.

METHODS: Patients anticipated to undergo gastric cancer resection were invited to complete the EORTC-QLQ C30 and STO22 surveys in the preoperative setting and at 0 to 1.5 months (early), >1.5 to 6 months (intermediate), and >6 to 18 months (late) following resection. Quality of life recovery was measured as paired differences between post- and preoperative results. Multivariable linear regression was used to identify factors associated with preoperative quality of life and degree of change following resection.

RESULTS: Across 393 participants, response rates at the intermediate and late postoperative time points were 58% (n = 228) and 71% (n = 277), respectively. Relative to baseline, median global health scale decreased in the early (−15.1 pts, p < 0.001) and the intermediate (−3.6 pts, p = 0.02) time points, but recovered by the late time point (+1.2 pts, p = 0.411). Relative to distal/subtotal gastrectomy, proximal/total gastrectomy was associated with worse recovery in both the early and late time points. Surgical complications were associated with worse early recovery. A minimally-invasive approach was not associated with postoperative recovery. Patients who presented with locally-advanced tumors (T3-T4) had lower preoperative quality of life scores, and more readily recovered to baseline.

CONCLUSIONS: Most patients recover to baseline within 1 year following major gastrectomy, and recovery is easier with more limited resections. Patients with locally-advanced tumors tend to have poorer baseline quality of life which may improve following resection.

INTRODUCTION

In the United States, 27,500 new cases of gastric cancer are diagnosed annually ¹. Although a multimodal approach is indicated for all but the earliest stages of gastric cancer, roughly 50% of stage IB-III cancers are treated with resection alone ². Outcomes of radical gastrectomy have improved over the past 30 years, with mortality decreasing from over 15% to below 5% ³⁻⁶. However, gastrectomy continues to carry long-term health-related quality-of-life (HRQOL) implications. Common post-gastrectomy symptoms include reflux, early satiety, nausea, and pain ⁷.

Several psychometric surveys address upper gastrointestinal symptom profiles. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 with the STO22 gastric module is among the most commonly utilized ^{8,9}. In cross-sectional studies, post-gastrectomy patients score lower across all functional domains and most symptom scales than the general population ¹⁰⁻¹⁴. However, patients' preoperative quality of life must be considered to contextualize the impact of resection. In particular, those with locally-advanced disease may experience relief from pre-existing gastrointestinal symptoms following surgery. Comparison of pre- and postoperative quality of life—which we will call HRQOL recovery—requires a prospective, longitudinal study design. In the West, very few longitudinal HRQOL studies exceed 100 patients, which limits any assessment for associative risk factors ¹⁵⁻¹⁸.

The objective of the present study is to assess risk factors associated with HRQOL recovery after radical resection of gastric cancer. In a previous study, we reported the HRQOL outcomes of 134 gastrectomy patients ¹⁷, but the small sample size limited risk factor analyses. Included in this study is the previously-reported cohort, updated to include our more recent experience. We hypothesized that short-term recovery would be dictated by minimally-invasive approach, surgical complications, and extent of gastric resection. We further anticipated that long-term HRQOL recovery would be primarily determined by the extent of resection and the palliation of symptoms related to the primary tumor.

METHODS

Patients

Patients with gastric cancer (including adenocarcinoma, neuroendocrine tumor, and sarcoma) or a diagnosis of a CDH1 mutation who were anticipated to require partial or total gastrectomy were prospectively enrolled. This study was conducted between April 1, 2001 and November 30, 2018 in a high-volume comprehensive cancer center. Patients were eligible if they were older than 18 years of age and psychologically capable of completing the HRQOL surveys.

Routine institutional practices for gastric cancer were followed. All patients with invasive cancer underwent staging computed tomography. Endoscopic ultrasound was used to assess primary and nodal stage among patients without clear evidence of locally-advanced disease. Locally-advanced patients (i.e., cT3-cT4) and those with evidence of node-positive disease undergo further staging with PET/CT and laparoscopy, followed by induction chemotherapy,

resection and postoperative chemotherapy. Medically fit patients with early, localized gastric cancer proceed directly to resection. Resection may involve distal gastrectomy, subtotal or total gastrectomy with Roux-en-Y esophagojejunostomy, or proximal gastrectomy (PG) with esophagogastrostomy. Patients who underwent a wedge resection were excluded. The choice of open, laparoscopic, or robotic approaches to resection were based on surgeon preference. The study was approved by the institutional review board (protocol #16–692).

Quality of Life Assessment

Starting at their initial preoperative outpatient consultation, patients were routinely invited to complete the EORTC QLQ-C30 survey and the STO22 gastric module. The EORTC QLQ-C30 is comprised of 30 questions which assess global HRQOL, five functional scales (physical, role, emotional, cognitive, and social), and a variety of cancer-related symptoms⁸. The STO22 gastric cancer module supplement is comprised of 22 questions focusing on gastric-cancer related symptoms such as dysphagia, early satiety, reflux, and taste loss⁹. Each scale is scored from 0–100. Better HRQOL is characterized by higher scores on functional scales and lower scores on symptom scales.

Patients completed the HRQOL surveys during the preoperative visit, and during routine postoperative visits. Postoperative surveys were grouped into three time periods: early (0 to 1.5 months), intermediate (>1.5 to 6 months), and late (>6 to 18 months). The primary objective of the study was to assess recovery from gastrectomy, therefore, only those patients who completed at minimum the preoperative survey and the early postoperative survey were included in analyses.

Statistical Analysis

The primary outcome of this study is the trend in recovery of global HRQOL following surgery. Secondary outcomes include factors associated with HRQOL change between the preoperative, early, and late postoperative periods. Patient characteristics are summarized as median and interquartile range for continuous data and as frequency and percent for categorical data. Recovery between pre- and post-operative states was quantified by within-patient mean differences in results for each functional or symptom scale, with significance determined by paired t-tests. For each HRQOL scale, the minimal important difference (MID) is the smallest change that patients perceive as important. This was defined using the previously-published approach of an effect size greater than 0.5, based on the pooled standard deviation of baseline scores¹⁷. This is comparable to the interpretation of a “moderate difference” in HRQOL¹⁹.

Risk factors for HRQOL recovery were evaluated using uni- and multi-variable linear regression. To minimize type 1 errors due to multiple testing, we restricted regression analyses to seven HRQOL variables: global health status, physical function, role function, fatigue, eating restriction, pain, and dysphagia. These variables were selected based on clinical relevancy and on having response distributions appropriate for linear regression. Similarly, analyses were limited to seven clinical risk factors: age, primary tumor stage, extent of resection, operative approach, major complication (defined as Clavien-Dindo grade 3), neoadjuvant chemotherapy, and adjuvant chemotherapy. Factors associated with

HRQOL with $p < 0.10$ at the univariate level were included in multivariable regression. In these regressions, the beta coefficient (β) represents the degree of change in a quality of life scale attributable to a single predictor variable, adjusting for the effects of all other variables. All analyses were performed using R version 3.6.3²⁰.

RESULTS

During the study period, 663 patients submitted a preoperative baseline HRQOL survey. Three hundred and ninety-three patients (59.3%) completed an early post-operative survey and were included in the study. Early stage cancers (cT1-T2) comprised 47.1% ($n = 185$) of the cohort, and 18.3% ($n = 72$) of operations were performed via a minimally-invasive approach. The major complication rate was 8.1% ($n = 32$). Summary statistics for the study cohort and for excluded patients are shown in Table 1. Patients excluded due to survey attrition (41.7%) had more advanced disease, were more likely to receive chemotherapy, were more likely to have undergone a minimally-invasive operation, [and had a higher complication rate]. Early post-operative surveys were completed at a median of 21 days after surgery (interquartile range, IQR 15 – 27). Among included patients, 228 (58.0%) completed an intermediate-period survey at a median of 4 months (IQR 3.1 – 5.1), and 277 (70.5%) completed a late-period survey at a median of 8.5 months after surgery (IQR 6.8 – 11.6).

Survey results from early, intermediate, and late postoperative periods were compared to preoperative baseline to determine HRQOL recovery. A clinically meaningful difference was defined as $p < 0.05$ and absolute difference greater than MID. On average, patients experienced significant declines during the early postoperative period in global health status, social function, role function, and physical function (Figure 1). In terms of symptoms, early declines were reported in fatigue, dysphagia, pain, and eating restriction (Figure 2). While some statistically significant HRQOL changes from baseline persisted in the intermediate and late postoperative periods, most were not clinically meaningful (i.e., effect size < 0.5). For example, median global health scale decreased in the early (-15.1 pts, $p < 0.001$) time point, but recovered to near baseline at the intermediate time point (-3.6 pts, $p = 0.02$) and fully recovered by the late time point ($+1.2$ pts, $p = 0.411$).

Multivariate regression identified factors associated with postoperative recovery. Early recovery in global health status and nearly all function and symptom scales were better for patients with locally-advanced tumors (cT3-T4) and worse for those who underwent a proximal or total gastrectomy (Table 2). Surgical complications were associated with worse early recovery in physical and role function. In the late phase, patients who underwent proximal or total gastrectomy experienced worse recovery across all HRQOL scales. Patients who underwent resection for locally-advanced tumors reported better long-term symptom recovery than their early-stage counterparts. Minimally-invasive approach was not associated with recovery in either the early or late phase. Full multivariable regression results including all variables for each model is available in **supplemental materials**.

To explore hypotheses regarding the relationship between primary tumor stage and postoperative recovery, HRQOL trends over time were separately depicted for early-stage and locally-advanced subgroups (Figure 3). In the preoperative setting, patients with

locally-advanced disease reported significantly worse global health status, role function, and all four symptom scales. However, by the early postoperative period, functional and symptom scales no longer differed between early-stage and locally-advanced subgroups. By contrast, there were no significant differences in preoperative HRQOL between patients who underwent proximal/total gastrectomy versus those who underwent distal/subtotal gastrectomy (**supplemental materials**).

DISCUSSION

This study exploited a large, longitudinal gastric cancer database to establish temporal trends in HRQOL recovery following gastrectomy. Results showed that gastrectomy has a substantial negative impact on HRQOL. However, most functional and symptomatic impairments recover within 6 months. Beyond this period, HRQOL approximates preoperative levels. Linking these data to clinical variables allowed us to generate hypotheses regarding potential drivers of postoperative recovery, including the extent of resection and the palliation of preexisting symptoms from locally-advanced tumors.

Recovery from gastrectomy balances the negative impact of surgery against the positive impact of cancer treatment. Previous data from our institution showed that more than half of patients who underwent a total gastrectomy reported gastrointestinal impairment beyond one year¹⁷. However, broader measures of HRQOL typically recover more rapidly than individual symptoms. Post-gastrectomy patients may report persistent gastrointestinal symptoms years after surgery, yet global HRQOL ratings are often comparable to the general population¹⁴. Our results regarding global recovery is corroborated by work by Kim et al., which noted that global health scales after gastrectomy may return to baseline within as little as 3 months²¹. This dichotomy between symptoms and global HRQOL represents a challenge to decision-analysis studies that must translate HRQOL into quality-adjusted life years. Over the past decade, several groups have derived utility metrics from the QLQ-C30^{22, 23}; such an approach may shed further light into the disutility associated with gastrectomy.

Subtotal and distal gastrectomy are comparable to total gastrectomy in oncologic outcomes, provided resection margins are appropriate^{24, 25}. Several cross-sectional studies have reported that subtotal or distal gastrectomy is superior to total gastrectomy in terms of symptoms and global HRQOL^{10, 11, 26}. Longitudinal studies with adequate power and follow-up are relatively few. Park et al. followed 275 patients over 2 years with repeated measures using the QLQ-C30 and STO-22, and showed that subtotal gastrectomy outperformed total gastrectomy in long-term upper gastrointestinal symptoms²⁷. Although global health scale and physical function were also consistently higher for the subtotal group, this difference was not significant beyond 3 months due to inadequate sample size. With a larger sample size, the present study confirms that the associations between extent of resection and HRQOL persist in the long term.

The diagnosis of gastric cancer itself carries a disutility which is partially relieved through treatment²⁸. While early stage gastric cancer is often asymptomatic, locally-advanced cancer is often associated with dysphagia, pain, early satiety, and functional impairment

²⁹. In our study cohort, locally-advanced gastric cancer was associated with significantly worse preoperative functional and symptom scores. This corroborates findings from a cohort of 200 gastric cancer patients, in which Suk et al. reported that early stage and academic background were associated with better baseline global health status ³⁰. In our study, relief from these local effects may be responsible for the association between locally-advanced cancer and better postoperative recovery. However, because this retrospective cohort may be susceptible to selection bias and false positives due to multiple testing, these findings should serve to generate hypotheses rather than provide definitive explanations.

We did not find an association between HRQOL recovery and a minimally-invasive approach. While it is generally accepted that laparoscopic gastrectomy is associated with less blood loss, shorter hospitalization, and quicker return to work, its effect on HRQOL is less clear. In COACT0301, laparoscopic distal gastrectomy outperformed open surgery in global quality of life, physical and emotional function, and symptom profile ^{31, 32}. However, these differences were only present for the first 3 months. This was also a uniform patient population restricted to T1 gastric cancer. Our findings suggest that the impact of a minimally-invasive approach may be dominated by more powerful or confounding variables such as primary tumor stage and extent of resection. For example, patients are more likely to undergo a minimally-invasive gastrectomy if they have earlier-stage disease, which in our cohort was associated with worse recovery. Results of the LOGICA trial, which includes stage II-III patients, should further clarify laparoscopy's impact on HRQOL ³³.

This study has several limitations. Derived from a high-volume cancer center, the cohort's socioeconomic profile may not represent the general population. Participation in the study was voluntary, and comparative analyses showed that the included cohort was enriched for patients with earlier stage disease. Because we found that early stage disease was associated with worse HRQOL recovery, this selection bias implies that the true trajectory of recovery may be even better than what is presented. Because the QLQ-C30 and STO-22 together report on 24 metrics, type 1 error due to repeated testing was possible. To minimize this, we limited testing to 7 metrics and only included risk factors that were consistently reported and clinically meaningful. Finally, the early postoperative surveys were administered at a median of 3 weeks after surgery. This may be too long of an interval to capture early effectors of HRQOL recovery, such as a minimally-invasive approach. Similarly, the timing of the early and intermediate surveys—at 3 weeks and 4 months after surgery, respectively—were such that the HRQOL impact of perioperative chemotherapy could have been missed as well.

CONCLUSIONS

Gastrectomy is associated with a HRQOL detriment that on average recovers within 6 months. While some patients may experience long-term gastrointestinal symptoms, this factor is counteracted by the palliation of preexisting symptoms and an improved disease outlook. Patients with locally-advanced gastric cancer report poorer HRQOL at baseline than early-stage counterparts—a difference that is nullified within 3 months of surgery. The most powerful driver of long-term HRQOL after gastrectomy is the extent of gastric resection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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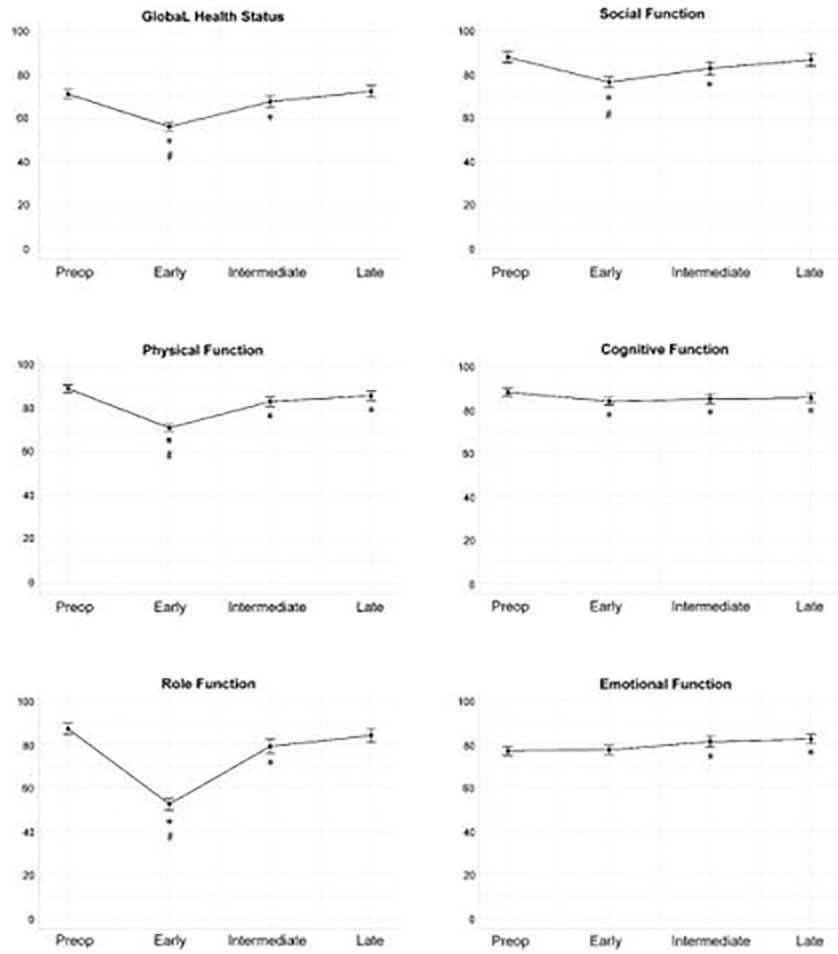


Figure 1 – Trend in global health status and functional scales overtime. Higher scores indicate better quality of life. Significant ($p < 0.05$) differences relative to baseline are marked by (*). Absolute differences greater than the minimal important difference (effect size > 0.5) are marked by (#).

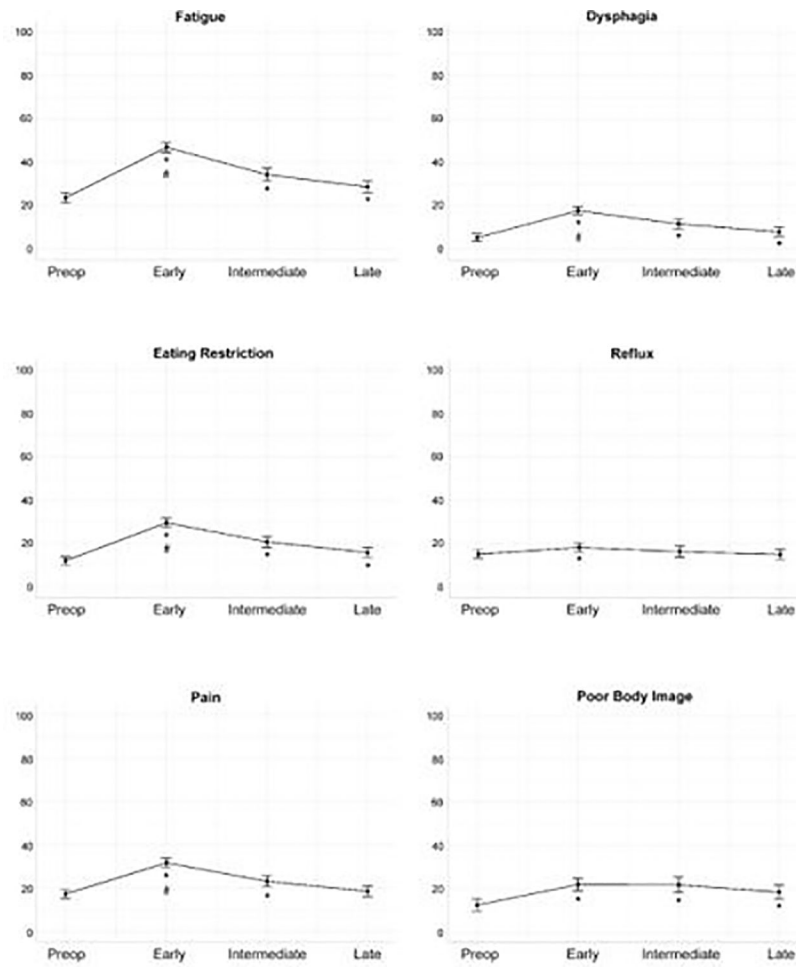


Figure 2 –. Trend in symptom scales overtime. Higher scores indicate poorer quality of life. Significant ($p < 0.05$) differences relative to baseline are marked by (*). Absolute differences greater than the minimal important difference (effect size > 0.5) are marked by (#).

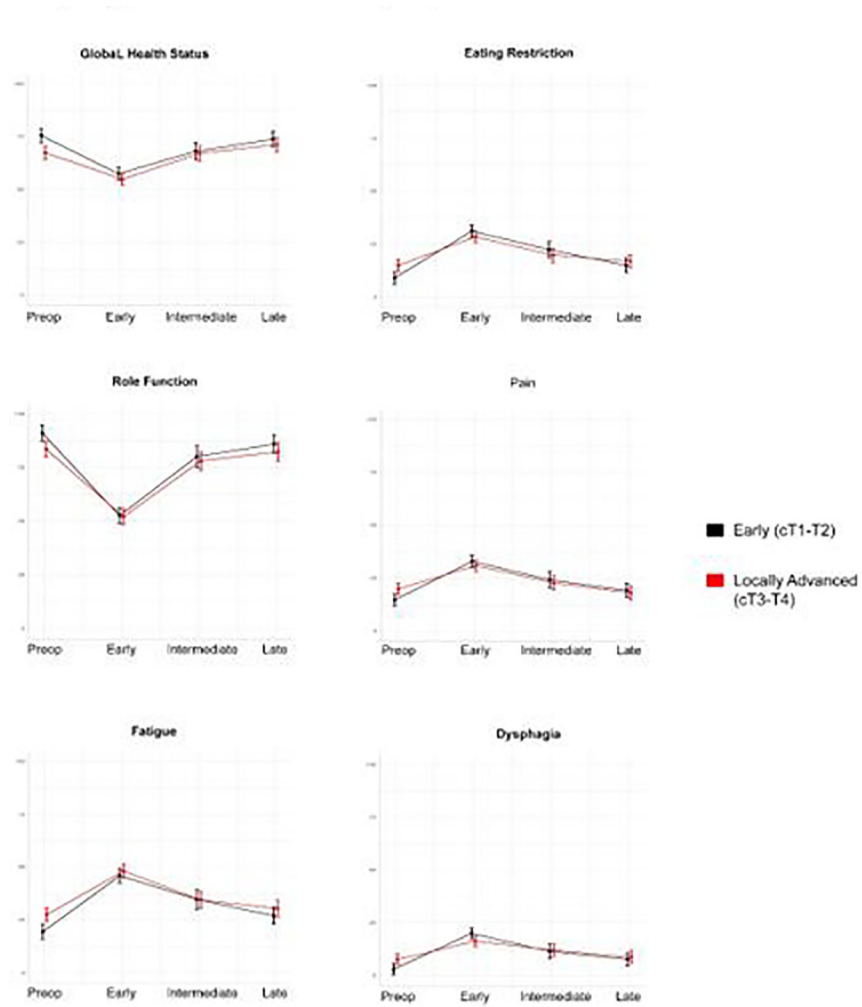


Figure 3 –. Trend in global health status, role function, and symptom scales over time, stratified by early (cT1-T2, black) and locally advanced (cT3-T4, red) primary tumor stage. Confidence intervals (95%) are shown for each subgroup.

Table 1 –

Patient Characteristics

	Included Patients (N = 393)	Excluded Patients (N = 270)	p-value
Age (SD)	63.3 (14.1)	64.6 (14.3)	0.3
Female	164 (41.7%)	102 (41.5%)	>0.9
BMI (SD)	26.8 (5.6)	26.9 (5.1)	0.8
Stage			
Early (cT1–2)	185 (47.1%)	76 (33.9%)	0.002
Locally advanced (cT3–4)	208 (52.9%)	148 (66.1%)	
Neoadjuvant Chemo Adjuvant Chemo	157 (39.9%) 129 (32.8%)	124 (50.4%) 147 (59.8%)	0.012 <0.001
Extent of Resection			
Subtotal/distal	241 (61.3%)	129 (52.4%)	0.033
Total/proximal	152 (38.7%)	117 (47.6%)	
Surgical Approach			
Open	321 (81.7%)	170 (69.1%)	<0.001
Minimally invasive	72 (18.3%)	76 (30.9%)	
Complications (G3+)	32 (8.1%)	50 (18.5%)	<0.001

SD – standard deviation

Table 2 –

Factors Associated with Postoperative Recovery

Quality of Life Scale	Association with Early Recovery	β	p-value	Association with Late Recovery	β	p-value
Global health status ^a	Locally-advanced	+6.7	0.013	PG/TG	-8.6	0.005
	PG/TG	-9.4	<0.001			
Physical function ^a	Major complication	-12.5	<0.001	PG/TG	-5.2	0.012
	BMI > 30	+5.6	0.016			
Role function ^a	Locally-advanced	+7.6	0.031	PG/TG	-10.1	0.002
	Age > 65	+11.5	0.001			
	Major complication	-14.5	0.024			
Fatigue ^b	Locally-advanced	-5.9	0.039	PG/TG	+10.4	0.003
Eating restriction ^b	Locally-advanced	-8.9	<0.001	Locally-advanced	-6.7	0.014
	PG/TG	+8.6	0.001	PG/TG	+10.1	<0.001
Pain ^b	Locally-advanced	-6.6	0.020	Locally-advanced	-8.1	0.005
				PG/TG	+8.9	0.002
Dysphagia ^b	Locally-advanced	-8.4	<0.001	Locally-advanced	-5.2	0.040
	PG/TG	+9.7	<0.001	PG/TG	+9.5	<0.001

^aPositive effect indicates better recovery^bNegative effect indicates better recovery