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Quality of Life After Gastrectomy for Adenocarcinoma: A Prospective Cohort Study

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Abstract

Background—Gastrectomy remains a major operation with potential for significant deterioration in patients' health-related quality of life (QOL). This study assessed differences in QOL among patients following distal (DG), proximal (PG) or total (TG) gastrectomy.

Methods—We prospectively enrolled patients undergoing gastrectomy at our institution between 2002 and 2007. Participants completed the EORTC cancer (QLQ-C30) and gastric (QLQ-STO22) questionnaires preoperatively and at five postoperative intervals up to 18 months. We compared changes from baseline in patients based on extent of resection (proximal, distal, or total) using generalized linear models, adjusting for age, stage of disease, and (neo)adjuvant therapy. We converted QOL raw scores to reflect the proportion of patients with clinically significant deterioration based on the minimal important difference (MID).

Results—We included 134 patients: 82 DG, 16 PG, and 36 TG. In the immediate postoperative period, 55% of patients suffered significant impairment in their global QOL. This improved in most patients by six months, although 20-35% continued to have substantially worse QOL than prior to surgery. Patients who underwent PG suffered from significantly more clinical reflux (70% vs 35% (DG), 40% (TG)), nausea/vomiting (60% vs 25%, 30%), and global QOL impairment (60% vs 30%, 30%) than DG or TG patients, whose QOL scores were similar. These differences persisted up to 18 months postoperatively.

Conclusions—Surgeons should discuss expectations of QOL impairment with their patients prior to gastrectomy and reassure them that most symptoms resolve by six months following

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operation. Patients who undergo PG suffer from worse QOL impairment than patients who undergo DG or TG.

Keywords

Gastric cancer; Quality of Life; Proximal Gastrectomy; Distal Gastrectomy; Total Gastrectomy

Introduction

More than 21,000 new cases of gastric cancer are diagnosed annually in the United States¹. The only chance for cure in patients that present with localized gastric adenocarcinoma is surgical resection^{2, 3}. Although the long-term survival of patients with gastric cancer has improved due to earlier diagnosis and advances in multimodality management, significant morbidity associated with gastric resection remains. Patients may suffer from a variety of symptoms including early satiety, loss of appetite, heartburn, dysphagia, nausea and vomiting. These symptoms have a profound impact on patients' health-related quality of life (QOL).

For tumors located in the lower half of the stomach, distal gastrectomy (DG) is the procedure of choice. For tumors in the upper half of the stomach, proximal (PG) or total gastrectomy (TG) is needed to achieve adequate surgical margins. Researchers have attempted to determine the relationship between the extent of gastric resection and the severity of postoperative symptoms, reaching varied conclusions⁴⁻⁹. These studies have suffered from important limitations that make interpretation difficult, most importantly small sample sizes and retrospective study designs. We sought to prospectively explore the impact of surgical resection on QOL following resection of gastric cancer in a large group of patients.

Methods

Patients

We screened all patients with gastric cancer assessed by surgeons at our institution between November 15, 2002 and June 15, 2007 for enrollment in this prospective cohort study. Memorial Sloan-Kettering Cancer Center (MSKCC) is a major comprehensive cancer center with a large program in gastric cancer. Patients were eligible for the study if they were older than 18 years of age, underwent a gastric resection for adenocarcinoma, and were deemed psychologically capable of completing the QOL questionnaires. We excluded patients who were receiving active treatment for a concurrent non-gastric cancer. This study was approved by the institutional review board and all patients signed an informed consent form before beginning the study.

Interventions

Patients were treated according to our institutional practices for patients with gastric cancer. Briefly, patients undergo staging investigations including CT scan, endoscopic ultrasound, and/or laparoscopy. Patients with locally advanced gastric cancer are usually treated with induction chemotherapy followed by resection and postoperative chemotherapy, while

patients with early gastric cancer proceed directly to resection. Patients with metastatic disease undergo resection only for palliation of symptoms.

Surgical procedures were classified as distal gastrectomy (DG) if they included the distal stomach and pylorus but not the esophagogastric (EG) junction, proximal gastrectomy (PG) if they included the proximal stomach and EG junction but not the distal stomach, and total gastrectomy (TG) if the entire stomach was resected. Patients who had wedge resections were not included in this study. Reconstruction was performed with Billroth II gastrojejunostomy following DG, esophagogastrostomy following PJ, and Roux-en-Y esophagojejunostomy following TG.

Quality of Life Assessment

We assessed QOL with the European Organization for Research and Treatment of Cancer (EORTC) generic cancer (QLQ-C30) and gastric cancer (QLQ-STO22) modules^{10, 11}. The EORTC QLQ-C30 is a reliable and validated measure of the quality of life of cancer patients in multicultural clinical research. The questionnaire is a cancer-specific, self-administered, structured questionnaire that contains 30 questions, 24 of which form nine multi-item scales representing various aspects, or dimensions, of QOL: one global scale, five functional scales (Physical, Role, Emotional, Cognitive and Social), and three symptom scales (Fatigue, Pain and Nausea). The remaining 6 items are mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties).

The gastric cancer module (QLQ-STO22) is a supplement to the QLQ-C30 intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy. The QLQ-STO22 consists of 22 questions which evaluate five multi-item symptoms scales (dysphagia, eating restrictions, pain, reflux and anxiety), and four single item symptoms scales (dry mouth, body image, hair loss and taste loss). For Global QOL and the functional scales, a higher score indicates better QOL, with 100 being perfect. For symptom scales, a lower score indicates better QOL, with 0 being perfect or no symptoms reported.

Patients completed the QLQ-C30 and the STO22 questionnaires preoperatively, postoperatively, and at four other postoperative time intervals: 3, 6, 12, and 18 months after resection.

Statistical Analyses

For each subscale of the QLQ-C30 and QLQ-STO22, we compared changes from baseline in patients based on the type of resection (proximal, distal, or total) using generalized linear models including time of assessment and type of resection. In addition, we computed the area under the QOL-time profile for each patient and used this as a single-number summary for supplemental analysis. To account for informative dropouts we used a pattern-mixture model, stratifying all analyses by the dropout time. We excluded patients with less than two follow-up points from this analysis. We performed adjusted analyses including age, treatment (chemotherapy and/or radiation) and stage of disease in the model. All statistical analyses were performed with SAS version 9.2.

In order to make the statistically significant results more meaningful to clinicians and patients, we converted the QOL scores to reflect the proportion of patients with a clinically significant deterioration in each domain. For each domain of the QLQ-C30 and QLQ-STO22, we calculated the minimal important difference (MID), defined as the smallest change that patients perceive as important¹²⁻¹⁵. Although investigators have identified clinical thresholds specific for the QLQ-C30, no such anchors exist for the QLQ-STO22. We therefore defined the MID for each domain using the conventional approach of an effect size greater than 0.5, which empirically yields nearly identical values to the clinical interpretation of a “moderate difference”^{16, 17}. Since there was no control group in this study we used the pooled standard deviation of the baseline scores for each group to calculate the MID. We determined the proportion of patients in each group that experienced a change in quality-of-life equal to or greater than the MID at each time point.

Results

Four hundred and seventy-five patients were identified as candidates for surgical resection, of whom 209 consented for entry into the study (Figure 1). Of these, 29 patients were unresectable and 10 were excluded for other reasons, leaving 170 patients entered into this study. During the 18-month study period 56 patients (33%) died. Data from two or more post-operative timepoints was available from 134 of the 157 alive patients (85%) and complete questionnaires were collected at all intervals from 86 of the possible 114 patients (75%).

Table 1 presents demographic characteristics of the study participants. Most patients had early stage disease and approximately 50% of patients received some form of adjuvant or neoadjuvant therapy. Distal gastrectomy was most commonly performed, followed by total gastrectomy and proximal gastrectomy.

In the immediate postoperative period, 50-70% of patients suffered a significant impairment in their global quality of life, physical function, and role function (Figure 2). Symptoms improved in most patients by six months, although 20-35% continued to have substantially worse function in these domains even at 18 months post-operative. Similar trends were observed in patients' complaints of pain and fatigue, while nausea and vomiting was a concern to 35% of patients postoperatively and remained relatively constant over time.

Dysphagia, appetite loss, and eating restrictions were the most common disease-specific symptoms, occurring in 45-55% of patients in the immediate post-operative period (Figure 3). These symptoms improved by six months in most patients but persisted in approximately 20-30% of patients.

In multivariable analyses, statistically significant differences were seen based on extent of gastrectomy in global QOL, reflux, diarrhea, and nausea/vomiting (Table 2). Patients who underwent PG suffered from significantly more reflux (70% vs 35% (DG), 40% (TG)), nausea/vomiting (60% vs 25%, 30%), and global QOL impairment (60% vs 30%, 30%) than DG or TG patients, whose QOL scores were similar (Figure 4). These differences persisted from the immediate postoperative period to 18 months from operation. In contrast, more

patients who had TG complained of diarrhea than patients who underwent DG or PG (40% vs 25%, 20%).

Discussion

This prospective study including 134 patients undergoing gastric resection for adenocarcinoma identifies many findings that surgeons can apply to clinical care. As part of the informed consent process, surgeons should discuss with patients how they might reasonably expect to feel in the postoperative period. Conventionally this has been done using vague, qualitative terms. This study provides quantitative measures of QOL that surgeons and patients can easily understand and incorporate into the decision-making process.

In the immediate post-operative period, the majority of patients suffer from important impairment in global QOL. At the time of the first follow-up visit, 60-70% of patients can expect to feel fatigued, with worse overall function and QOL than preoperatively. Surgeons can reassure patients that most will return to baseline function by approximately six months postoperatively, although about a third of patients will continue to have important functional impairment. In contrast, only a third of patients will ever suffer symptoms like reflux, nausea, and dry mouth, although these symptoms will generally persist through follow-up.

The differing QOL between patients based on extent of gastrectomy may help surgeons select the optimal resection for some patients. For patients with tumors localized in the distal stomach, distal gastrectomy allows resection of gross disease. For patients with proximal tumors, resection with clear margins may be achieved with proximal or total gastrectomy. For patients with extensive malignancies, subtotal or total gastrectomy may be needed to achieve clear margins. Although these operative approaches appear to be oncologically equivalent for appropriate tumors¹⁸, the impact of each approach on QOL differs and should help to direct surgical practice. In this analysis, the QOL following total gastrectomy was almost identical in all domains to the QOL following distal gastrectomy. In contrast, patients who underwent proximal gastrectomy suffered from significantly more reflux, nausea/vomiting, and a worse overall QOL. The improved global QOL of patients who underwent total gastrectomy compared with patients who had proximal gastrectomy suggests that proximal gastrectomy may not be the optimal procedure for most patients with tumors localized to the proximal stomach.

Several past studies have examined QOL following gastric resection; most have important limitations. The largest studies to date have been cross-sectional, assessing QOL in patients from six months to five years following gastric resection^{5, 6, 8, 9}. These well-powered studies concluded that some patients have impaired QOL after curative gastrectomy. Further, the analyses revealed associations between extent of gastric resection (distal compared to total) and QOL on several domains. While these studies provide important insights into the overall well-being in patients following gastrectomy, they are limited by the lack of baseline QOL assessment. As such, they do not differentiate the extent to which QOL was impaired by the operation as opposed to the underlying disease process. Furthermore, none of these studies

reported the QOL data relative to clinically-meaningful anchors so it is difficult for clinicians to discuss the implications of these results with their patients.

Two recent studies have prospectively assessed QOL in patients before and after gastrectomy for cancer using the EORTC modules. Kobayashi and colleagues reported results from 98 patients who had no evidence of recurrence one year after gastrectomy⁷. Similar to our results, the authors concluded that QOL worsened in the immediate post-operative period but returned close to baseline by approximately six months following operation. The majority of procedures in this study were distal gastrectomy with only eight patients undergoing total gastrectomy, so the authors were unable to make strong conclusions regarding the impact of extent of resection on QOL. In a similar study, Avery and colleagues followed 58 patients who underwent total or subtotal gastrectomy for two years following operation⁴. Similar to our findings, their patients had significant deterioration in QOL in the early post-operative period that returned to baseline in most by six months. The authors did not explore the impact of extent of resection on QOL due to the limited sample size. The current study builds on this prior work by prospectively assessing QOL in a large group of patients undergoing a variety of gastric resections.

This study has several strengths. We enrolled consecutive patients undergoing gastric resection at our institution and prospectively collected quality of life data. This allows us to be confident that the results of this study are representative of all patients undergoing gastrectomy at our institution and are generalizable to other institutions that care for similar patients. The inclusion of preoperative QOL data on all patients and the postoperative assessments at fixed times permits comparison between patients, accounting for baseline differences in QOL. Furthermore, because all operations were performed by the same small group of surgeons at one institution, it is likely that the differences observed were due to the surgical procedures themselves, rather than differences between surgeons or institutional practices. Importantly, the baseline QOL in these patients was assessed immediately preoperatively – it is likely that many patients already had some impairment from their true, healthy “baseline” as a result of the gastric cancer itself or treatment with neoadjuvant therapy. Therefore, although most patients returned to their preoperative baseline it is possible that many continued to suffer from important impairment in their QOL.

This study is further strengthened by the use of clinically relevant anchors to interpret the data. In a systematic review of all randomized trials in the field of gastric cancer surgery that reported QOL, all studies reported the results using raw scores and interpreted statistically significant differences as clinically relevant¹⁹. Few patients or surgeons would be able to discern the extent to which an absolute difference in a QOL measure represents a trivial difference, a small but important difference or a large difference. As a result, trials that report these raw values are likely to be ignored, or worse, misinterpreted by patients and clinicians. In contrast, we have converted the raw scores into easily interpretable proportions using accepted techniques based upon the MID^{12, 14}. Future studies in gastric cancer surgery and beyond should be encouraged to also present their data in ways that are clinically intuitive.

Our study is most limited by missing data. Although we followed patients rigorously, 14% of patients were excluded due to insufficient data and a further 2% were included but had incomplete data. Most of these patients continued to be cared for at our center, but chose not to complete the QOL assessments because they found them too burdensome. An additional 33% died during the course of follow-up. We explored several options for controlling for missing data, including various techniques of imputation. Ultimately, we felt that all of these methods suffered from important inherent limitations and the most transparent method of analysis was excluding missing data points from the analysis. It is possible, and perhaps likely that data was missing in a non-systematic fashion. For example, patients who died during the study period likely suffered from a worse quality of life in the months preceding death relative to patients who did not die during the study period. Unfortunately this limitation is inherent in all studies of quality of life, and it is a particular problem in disease conditions with a significant mortality rate such as gastric cancer. In this study the mortality rate was similar between the different procedures, making it less likely that data missing due to deaths biased the results.

While this study identifies important deficiencies in QOL after gastrectomy, the exact etiology of the impairment is not completely clear. It is likely related to a combination of the underlying disease, normal postoperative recovery and the effect of complications. The extent to which each of these factors contributed to QOL in these patients is unknown. Given the rate of significant complications following gastrectomy (approximately 15%), this study lacked the power to identify a link between complications and QOL impairment; further research is needed to determine the factors that lead to poor QOL in this patient population³.

In summary, 60-70% of patients experience clinically significant deterioration in QOL shortly after gastrectomy. Function and symptoms return to baseline by approximately six months postoperatively in most patients, although about a third of patients will continue to have clinically important impairment. Patients who undergo proximal gastrectomy suffer from worse reflux, nausea/vomiting, and global QOL compared to patients who have distal or total gastrectomy. Surgeons should discuss expectations regarding symptoms and QOL with their patients before gastrectomy. Alternatives to standard proximal gastrectomy should be considered for patients with tumors of the proximal stomach.

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Appendix

Appendix. Quality of life of patients on other EORTC QLQ-C30 and STO-22 domains following gastric resection. Plots represent the percent of patients with clinically important worsening of each domain compared with preoperatively (i.e. preoperative = 0%).

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Figure 1.
Flowchart of patients included in study.

Figure 2.

Quality of life of patients on selected EORTC QLQ-C30 domains following gastric resection. Plots represent the percent of patients with clinically important worsening of each domain compared with preoperatively (i.e. preoperative = 0%). Plots of other domains are presented in Appendix.

Figure 3.

Quality of life of patients on selected EORTC STO-22 domains following gastric resection. Plots represent the percent of patients with clinically important worsening of each domain compared with preoperatively (i.e. preoperative = 0%). Plots of other domains are presented in Appendix.

Figure 4.

Quality of life of patients following proximal, distal, or total gastric resection. Plots are displayed for domains where statistical differences were seen based on extent of gastric resection. Plots represent the percent of patients with clinically important worsening of each domain compared with preoperatively (i.e. preoperative = 0%).

Table 1

Characteristics of patients

	All patients Enrolled N=170 (%)	Included in Analysis N=134 (%)
Age [Median (IQ Range)]	68 (55-75)	68 (54-74)
Gender		
Male	105 (62)	79 (59)
Female	65 (38)	55 (41)
Stage		
I	63 (37)	53 (40)
II	35 (21)	31 (23)
III	47 (28)	36 (27)
IV	25 (15)	14 (10)
Chemotherapy		
Preoperative	31 (18)	25 (19)
Postoperative	18 (11)	15 (11)
Both	14 (8)	12 (9)
None	107 (63)	82 (61)
Chemoradiation		
Preoperative	13 (8)	10 (7)
Postoperative	26 (15)	24 (18)
Both	0 (0)	0 (0)
None	131 (77)	100 (75)
Operation		
Distal	101 (59)	82 (61)
Proximal	20 (12)	16 (12)
Total	49 (29)	36 (27)

Table 2

Comparison of Quality of Life between patients who underwent proximal, distal, or total gastrectomy; adjusted for age, stage of disease, and receipt of chemotherapy or radiation. Significant differences ($p < 0.05$) are shaded. Pairwise comparisons are only displayed for domains with a significant finding on overall comparison.

DOMAIN	Overall comparison (p value)	Pairwise Comparisons (p value)		
		Proximal Vs. Distal	Distal Vs. Total	Proximal Vs. Total
Global Quality of Life	0.005	0.015	0.873	0.021
Functional Domains				
Role Functioning	0.086	-	-	-
Cognitive Functioning	0.479	-	-	-
Emotional Functioning	0.997	-	-	-
Physical Functioning	0.194	-	-	-
Social Functioning	0.878	-	-	-
Symptom Domains				
Dysphagia	0.220	-	-	-
Dry Mouth	0.837	-	-	-
Eating Restrictions	0.104	-	-	-
Hair Loss	0.230	-	-	-
Pain (general)	0.918	-	-	-
Reflux	0.019	0.005	0.512	0.034
Taste	0.293	-	-	-
Appetite Loss	0.177	-	-	-
Constipation	0.222	-	-	-
Diarrhea	0.039	0.986	0.013	0.095
Dyspnea	0.912	-	-	-
Nausea/Vomiting	0.003	<0.001	0.515	0.008
Pain (stomach)	0.209	-	-	-
Insomnia	0.436	-	-	-
Fatigue	0.510	-	-	-
Anxiety	0.123	-	-	-
Body Image	0.432	-	-	-
Financial concerns	0.324	-	-	-