**ABSTRACT**

**Purpose:** This study evaluated differences and shifting patterns in the health-related quality of life (HRQoL) of 5-year gastric cancer survivors after either a distal subtotal gastrectomy (DSG) or total gastrectomy (TG).

**Materials and Methods:** We analyzed the prospectively collected HRQoL data of 528 patients who survived 5 years without recurrence using the European Organization for the Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire and the EORTC Quality of Life Questionnaire-Stomach module according to the type of surgery. The purpose was to identify the proportion of patients with deteriorating HRQoL and to assess the clinical significance of these changes.

**Results:** Deteriorating HRQoL was prevalent in both groups, including a large proportion of the DSG group. Decreased overall health status and scores on several function scales were less in the DSG group, while increases on the symptom scales were higher in the TG group. For most of the scales, gaps in HRQoL during the early postoperative period did not merge within the 5 years. Scores on the diarrhea and body image scales revealed “moderate changes” in both groups.

**Conclusions:** During the 5-year period after surgery, the TG group suffered from inferior HRQoL compared to the DSG group. However, a large proportion of the DSG group also suffered HRQoL deterioration. In general, the TG group experienced more HRQoL decline, with diarrhea and body image being the major concerns for both groups. To improve HRQoL after gastrectomy, patients must be better informed about post-gastrectomy symptoms. These symptoms must be vigorously investigated, and medical interventions should be available parallel to nutritional support. Favorable evidence of function-preserving gastrectomy should be established and disseminated to improve the HRQoL of early gastric cancer patients.

**Keywords:** Quality of life; Stomach neoplasms; Gastrectomy
INTRODUCTION

Gastric cancer is one of the leading cancer-related deaths in the world [1]. There are significant regional differences in prevalence, with more than half of all new gastric cancer patients diagnosed in East Asia, including China, Japan, and Korea [1]. Among them, Japan (in the 1960s) and Korea (in 2002) started national screening programs to improve survival rates through early detection. In most countries where national screening programs are not practiced, most newly diagnosed gastric cancer patients are already in advanced stages. The prognosis for patients in advanced stages is poor compared to those who receive initial treatment for early gastric cancer that has an excellent 5-year survival rate of more than 90% [2].

Gastrectomies for gastric cancer are known to negatively impact the patients’ health-related quality of life (HRQoL). A radical gastrectomy for gastric cancer results in deprivation of the anatomic and physiologic functions of the stomach, while extended lymph node dissection results in ligation of major vessels and denervation of the stomach. Therefore, excessive body weight loss, malnutrition, and various post-gastrectomy syndromes contribute to deteriorating HRQoL of the patients. For patients with advanced gastric cancer, the importance of HRQoL is often ignored because of the overwhelming concern about recurrence or cancer-related deaths.

In Korea, national gastric cancer screening starts from the age of forty years and is performed biennially thereafter. After implementation of the program, the proportion of T1 gastric cancer patients who were treated by surgery rose to 61% in 2014 from only 30.4% in 1995 [3]. As in Japan, the rate of long-term survival has been increasing rapidly [4]. Therefore, HRQoL has become an important issue for survivors. Published reports related to HRQoL after gastrectomy have become more frequent; however, the majority have been either cross-sectional studies or studies with patient sample sizes that were too small to be truly representative of the general population [5]. Also, the follow-up periods were too short to estimate long-term HRQoL shifts [6].

In most studies, patient HRQoL after a distal subtotal gastrectomy (DSG) was generally better than after a total gastrectomy (TG). It may be essential to identify both the long-term shifting patterns after gastrectomy and the variations in long-term HRQoL caused by the extent of gastric resection (DSG or TG) using a multidirectional approach. A thorough understanding of the comparative HRQoL changes after both types of gastrectomy may enable us to improve HRQoL through medications, emotional support, and further surgical intervention. However, the long-term results with chronological changes that may indicate actual recovery and adaptation after TG are rare.

Therefore, this prospective cohort study was designed to evaluate the differences and shifting patterns of HRQoL for 5-year gastric cancer survivors after DSG and TG. We compared the HRQoL changes after the 2 types of gastrectomy and the proportion of patients with deteriorated HRQoL to estimate the proportion of survivors who suffer from deteriorating symptoms and the accompanying decline of function after surgery.

MATERIALS AND METHODS

Patients
The present analysis included data from patients who underwent curative gastrectomy for pathologically proven gastric cancer between February 2008 and March 2012 at Kyungpook National University Hospital.
National University Hospital and Kyungpook National University Chilgok Hospital. We retrospectively analyzed the prospectively established HRQoL data. Among the 689 patients who had no identified recurrence and had completed all HRQoL questionnaires measured at the preoperative period and at annual regular follow-ups for 5 consecutive years, 161 patients were excluded, of whom 139 patients underwent either minimally invasive or extended surgery, 14 underwent non-curative resection at surgery, and 8 had missing data (Fig. 1). Patients who underwent minimally invasive or extended surgery were excluded from this study because the dissimilar surgical magnitude might have impacted the patients’ HRQoL. This study was approved by the respective institutional review boards of the aforementioned hospitals.

**Surgery and follow-up**

Upper midline incisions were used in both open DSG and TG procedures. In open DSG, the distal two-thirds of the stomach was resected, and an extended lymphadenectomy (D2) was performed. In most of the DSG cases, a Billroth I anastomosis was performed, with the exception of ten cases when a Billroth II anastomosis was chosen as the reconstruction method. In open TG, the whole stomach was resected, D2 was performed, and reconstruction was performed using a Roux-en-Y esophagojejunostomy in all cases.

After discharge, patients visited the outpatient department every 3 months for the first postoperative year and then every six months during the second and third postoperative years. They visited annually in the fourth and fifth postoperative years. In each annual visit, the following were performed: physical examination, chest X-ray, gastroduodenoscopy, an abdomen-pelvis computed tomography scan or ultrasound of the abdomen, tumor markers (CA 19-9, CEA), and additional blood tests for anemia, liver, and renal function analysis.

**HRQoL assessment and interpretation**

The European Organization for the Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) comprises both multi-item and single-item scales, including 5 functional scales, 3 symptom scales, a global health status/QoL scale, and six single items to report other symptoms. The EORTC Quality of Life Questionnaire-Stomach (QLQ-STO22) is a gastric cancer-specific module to assess symptoms associated with gastric cancer treatment. It comprises 5 multi-item and four single-item scales. All completed questionnaires were scored and transformed into a 0–100 scale. Missing values were
processed according to the EORTC QLQ-C30 scoring manual and the EORTC QLQ-STO22 scoring procedure. For overall health status, higher scores represented better HRQoL. For functional scales, high scores represented high or healthy levels of functioning. For symptom scales, high scores represented high levels of symptoms or problems. To measure HRQoL, we used the validated Korean version of the European EORTC QLQ-C30 [7] and QLQ-STO 22 that was checked preoperatively and 5 additional times, once after each regular annual visit. Patients with deteriorating HRQoL were defined as those with decreases in their overall health status and function scale scores and increases in their postoperative symptom scale scores compared to their preoperative scores. All patients completed the questionnaires themselves before interviews with a doctor to exclude the potential influence of the doctor’s opinions on the patients’ responses. Medical consultations were then conducted based on the completed questionnaires to assess symptoms or difficulties in the daily lives of the patients.

To determine the significance of HRQoL changes from the preoperative scores, we adopted the proposal of Osoba and colleagues [8] that classified the amount of change from 0 to less than 5 as “no change,” 5 to less than 10 as “small change,” 10 to less than 20 as “moderate change,” and more than 20 as “large change.”

**Statistical analysis**
Based on the possibility of differences in the preoperative HRQoL data, and regardless of statistical significance, we compared the amount of postoperative change (measured score minus preoperative score). A negative score indicated a decrease in the score and a positive score indicated an increase. All data analyses were performed using SPSS 23.0 (IBM Corp, Armonk, NY, USA). The proportions of patients with categorical variables were compared using chi-square tests. Differences in the means of continuous measurements were tested using Student’s t-tests. Null hypotheses of no difference were rejected when P-values were less than 0.05.

**RESULTS**

The characteristics of the patients are presented in Table 1. Among the 528 patients enrolled in this study, 386 (73.1%) underwent DSG and 142 (26.9%) patients underwent TG. There were no significant differences between the 2 groups for age, gender, body mass index (BMI), and the degree of obesity according to the National Institutes of Health (NIH) clinical guidelines [9]. Pathological staging was done according to the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual [10]. Patients in the TG group showed significantly advanced stages of cancer. As for adjuvant chemotherapy, among 124 patients with stage II cancer or higher, 75 (60.5%) patients were administered adjuvant chemotherapy. In most cases, adjuvant chemotherapy regimens were either S-1 or S-1 plus a platinum agent. There were no differences in the proportion of patients who received adjuvant chemotherapy. Although the data were not presented in this manuscript, the impact of adjuvant chemotherapy on HRQoL was not significant over the 5-year period of the study.

After processing the missing items according to the EORTC QLQ-C30 scoring manual that suggested less than 2% of patient data would be missing, we found the actual rate of missing values in this study was 1.55%, excluding the hair loss scale. Therefore, the collected data satisfied the criteria set forth in the EORTC QLQ-C30.
There were no significant differences in the preoperative EORTC QLQ-C30 and QLQ-STO22 scores between the DSG and TG groups. Despite this finding, we compared the score changes at each measurement with the preoperative scores to evaluate the post-surgery changes over 5 years.

The HRQoL shift patterns between the 2 groups over 5 postoperative years were roughly classified into 3 patterns according to each scale. In the first pattern, there were no significant differences between the 2 groups over 5 postoperative years (Fig. 2). In the second pattern, there was a significant gap between the groups that increased over time (Fig. 3). In the third pattern, there was a significant difference at the first postoperative year, and this difference lasted throughout the remainder of the 5 postoperative years (Fig. 4).

**Fig. 2** reveals the changes over time in the scales that did not show significant differences between the groups for 5 years after surgery and the percentage of patients with deteriorating HRQoL during that period. In cognitive functioning, there was a rapid and ongoing decline from the first postoperative year through the remainder of the 5 years in both groups. The proportion of patients with declining cognitive functioning showed a slight increase over the 5 years. There were no significant differences in social functioning, general pain, dyspnea, insomnia, financial difficulties, and dry mouth episodes between the groups over the 5 years. Both groups had significantly elevated scores on the diarrhea scale over 5 years.

**Fig. 3** illustrates the changes in scales in which the difference between the 2 groups increased over 5 postoperative years and the percentage of patients with deteriorating HRQoL after surgery.

For overall health status, the scores gradually increased with time after an operation. Although there were no statistical significances, the magnitude of increase was higher in the DSG group. The proportion of patients who reported having deteriorating overall health
Fig. 2. Chronological changes of mean score and proportion of patients with deterioration from the preoperative state, in which, the scale showed the gap between groups had no statistical significance for 5 years. DSG = distal subtotal gastrectomy; TG = total gastrectomy.

*P-value of <0.05, ^p-values of >0.05 and <0.10.

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status decreased slightly, but the gaps between the 2 groups were significant at both the 3- and 5-year postoperative intervals. On the role functioning scale, the DSG group showed less decline in scores while the TG group showed a more rapid decline in the first postoperative year, a small increase for the next 2 years, followed by another decline. The gap between the 2 groups seemed to increase from the 3-year point post-surgery. Regarding the proportion of patients exhibiting deterioration, the DSG group showed a gradual decrease from 38.8% to 30.1% while the TG group showed an increase from 42.8% to 46.4% after the fifth

### Fig. 3. Chronological changes of mean score and proportion of patients with deterioration from the preoperative state, in which, the scale showed the gap between groups had no statistical significance for 5 years.

DSG = distal subtotal gastrectomy; TG = total gastrectomy.

*P-value of <0.05, †P-values of ≥ 0.05 and <0.10.

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Fig. 4. Chronological changes of mean score and proportion of patients with deterioration from the preoperative state, in which, the scale showed the gap between groups has a significant difference for 5 years.

DSG = distal subtotal gastrectomy; TG = total gastrectomy.

*P-value of <0.05, †P-values of ≥0.05 and <0.10.

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Long-Term HRQoL after Gastrectomy

symptom scales; however, the TG group showed a “moderate decrease” in role functioning and a “small decrease” in role functioning and “no change” or a “small increase” on the other cognitive functioning, and a “moderate increase” in diarrhea and body image. For the scales difficulties, a “small increase” in dry mouth, a “small decrease” in physical functioning and social functioning, general pain, insomnia, appetite loss, constipation, and financial difficulties, a “small increase” in dry mouth, a “small decrease” in physical functioning and cognitive functioning, and a “moderate increase” in diarrhea and body image.

Table 2 shows the determination of clinical significance of the postoperative HRQoL changes at 5-year intervals. Both groups in common showed “no change” in emotional functioning, social functioning, general pain, insomnia, appetite loss, constipation, and financial difficulties, a “small increase” in dry mouth, a “small decrease” in physical functioning and cognitive functioning, and a “moderate increase” in diarrhea and body image. For the scales of role functioning, fatigue, and eating restriction, the DSG group showed a “small decrease” in role functioning and “no change” or a “small increase” on the other symptom scales; however, the TG group showed a “moderate decrease” in role functioning and a “moderate increase” on the aforementioned symptom scales. Regarding overall health status, the DSG group showed a “small increase” while the TG group showed “no change.”
Some authors have previously reported that long-term survivors after TG generally do as well as the normal population control groups in their studies using SF-36 and 15D questionnaires [11]. Others insisted that there were no differences in overall patient QoL after TG or DSG except for diminished results on the eating restriction and dysphagia scales [12]. However, the DSG group in this study showed either larger increases or less decreases than the TG group in overall health status and on most of the function scales. For most of the symptom scales of the EORTC QLQ-C30, no significant differences existed between the groups except for significantly elevated scores on the fatigue and nausea/vomiting scales in the TG group. Contrarily, there were significant differences between the groups on most of the symptom scales of the QLQ-STO22 with the exception of dry mouth and hair loss. Therefore, this study aligned with similar results from previous reports that showed declining HRQoL after TG [13-16]. In a study showing a serial comparison of HRQoL after DSG and TG over 2 years, the authors classified deviant QoL patterns into 3 types: 1) with consistent gaps throughout, 2) without significant differences, and 3) with a brief QoL gap followed by rapid convergence [14]. In the present study, we found similar patterns with the first 2 types but did not find a brief QoL gap followed by rapid convergence. Instead, in some scales—including role functioning, emotional functioning, and the nausea/vomiting scales—the gap seemed to increase after 2 or 3 postoperative years. Fortunately, a study that compared HRQoL of

| Scale  | Groups | Change | Significance |
|--------|--------|--------|--------------|
| QL2    | DSG    | +7.36  | ↑            |
|        | TG     | +3.63  | =            |
| PF2    | DSG    | −5.51  | ↓            |
|        | TG     | −8.84  | ↓            |
| RF2    | DSG    | −6.28  | ↓            |
|        | TG     | −14.05 | ↓↓           |
| CF     | DSG    | −5.57  | ↓            |
|        | TG     | −7.18  | ↓            |
| FA     | DSG    | +4.98  | =            |
|        | TG     | +12.5  | ↑↑           |
| NV     | DSG    | +2.37  | =            |
|        | TG     | +7.28  | ↑            |
| DI     | DSG    | +11.26 | ↑↑           |
|        | TG     | +13.71 | ↑↑           |
| STODYS | DSG    | +3.88  | =            |
|        | TG     | +8.88  | ↑            |
| STOPAIN| DSG    | −0.04  | =            |
|        | TG     | +6.12  | ↑            |
| STORFX | DSG    | +2.26  | =            |
|        | TG     | +9.86  | ↑            |
| STOEAT | DSG    | +5.66  | ↑            |
|        | TG     | +12.49 | ↑↑           |
| STOANX | DSG    | +2.93  | =            |
|        | TG     | +7.43  | ↑            |
| STODM  | DSG    | +5.36  | ↑            |
|        | TG     | +7.14  | ↑            |
| STOTA  | DSG    | +2.19  | =            |
|        | TG     | +6.62  | ↑            |
| STOBI  | DSG    | +10.09 | ↑↑           |
|        | TG     | +19.25 | ↑↑           |

*: = signifies no change (0–5); ↑ or ↓ signify small changes (5–10); ↑↑ or ↓↓ signify moderate changes (10–20). Words written in bold type indicate scales showing moderate changes. HRQoL = health-related quality of life; DSG = distal subtotal gastrectomy; TG = total gastrectomy.
patients after TG who survived 5 years with HRQoL of patients after TG who survived more than 5 years reported improved HRQoL for patients who had survived beyond 5 years [17].

One study revealed that most of the patients after DSG experienced fair to good HRQoL [18]. Although the patient grouping was different, our study showed that a large proportion of patients had declining HRQoL after DSG based on any of several factors—including diarrhea (39%), dysphagia (37%), stomach area pain (34.8%), reflux (35.2%), eating restriction (44.2%), anxiety (45.1%), and body image (36.1%)—compared to their preoperative state. Therefore, this suggests that the HRQoL of patients after DSG in this study was not very good but they still experienced less decline than TG patients.

Aside from the HRQoL differences between the groups, it is also important to determine the clinical significance of these post-surgery changes. We used the classification suggested by Osoba and colleagues [8], one of the most frequently used tools for the determination of the clinical significance of HRQoL changes. On most HRQoL scales, except for diarrhea and body image, the DSG group showed “no change” or a “small change” (increase or decrease). In the TG group, the magnitude of change was larger than that of DSG, including an identified moderate decrease on the role function scale and moderate increases on the fatigue, diarrhea, eating restriction, and body image scales. It is clear that diarrhea and body image are common major concerns for patients after both DSG and TG, and patients after TG have more significant HRQoL deterioration.

Diarrhea is one of the most common symptoms of post-gastrectomy maldigestion syndrome that is also characterized by flatulence, weight loss, and fatty stools. Possible effects of maldigestion syndrome are reduced food intake, small-bowel bacterial overgrowth, rapid small-bowel transit, and exocrine pancreatic enzyme insufficiency [19]. Although the body weight loss data were not presented in this study, weight loss was found to be significantly higher in the TG group compared to the DSG group [20]. Therefore, body image dissatisfaction seemed more attributable to postoperative body weight loss rather than the presence of an operative wound scar because all of the patients who underwent open surgery had similar scars.

The presence of a larger magnitude of change on the QLQ-STO22 symptom scales in the TG group seemed to be influenced by the absence of a remnant stomach. The presence of a remnant stomach and the esophagogastric junction after DSG usually enables accommodation of food, smooth transfer of food from the esophagus into the stomach, and the prevention of reflux to the esophagus. On the contrary, patients after TG have an anastomotic ring at the distal part of the esophagus that may cause difficulties when swallowing, eating restrictions, and reflux.

There have been many trials to improve patients’ HRQoL after gastrectomy by function-preserving gastrectomy and/or by education.

Regarding function-preserving gastrectomy for early gastric cancer, in a nationwide Japanese study, pylorus-preserving gastrectomy achieved better outcomes on the diarrhea and dumping subscales as well as the frequency of additional meals [21]. Proximal gastrectomy (PG) was not widely performed because of higher incidences of postoperative complications, such as anastomotic stricture and reflux esophagitis [22]. Recent modifications of reconstruction in PG—including jejunal interposition, double-tract reconstruction, and
valvuloplasty esophagojejunostomy—have been shown to reduce complications like reflux and to improve HRQoL after TG [23-25]. For advanced gastric cancer patients, modified surgery to reduce the extent of lymph node dissection or to leave more of the remnant stomach is not permitted as a general practice [26,27]. Therefore, frequent reassessment of patients’ symptoms and medical interventions with nutritional support are important to prevent HRQoL deterioration after surgery in these cases.

One study has shown that extensive nutritional training has improved the immediate postoperative nutritional status of gastrectomy patients as well as their self-efficacy and meal satisfaction, thereby suggesting a promising role of nutritional education for postsurgery patients [28]. The HRQoL of patients with decreased BMI after TG was significantly worse than that of patients with maintained or increased BMI [29]. Therefore, nutritional support and training should be integrated into postoperative follow-up programs as well as comprehensive medical interventions.

Quality of life depends on subjective evaluations that reflect the ratio between expectations and the present status of an individual. An overly optimistic and thus erroneous expectation of surgery might result in postoperative disappointment that may in turn lead to further deterioration of the patient’s HRQoL [30]. Before surgery, patients with gastric cancer should be thoroughly informed of the expected postoperative symptoms and all potential decreases in systemic functions. After surgery, patients must be trained how to cope with postoperative symptoms through self-management and medical interventions together with the provision of information and guidance regarding nutrition and exercise.

We acknowledge the following limitations: 1) this retrospective study could not be free from selection bias based on the significant difference in the pathological stages of the 2 groups; 2) the DSG group was 2.5 times larger than the TG group; 3) this study did not consider any administered measures to improve the patients’ HRQoL; and 4) preoperative HRQoL cannot represent premorbid HRQoL. Despite these limitations, we believe that this study provides important information regarding long-term serial shifts in HRQoL after 2 types of gastrectomy based on a large sample of patients.

To conclude, a significant number of patients after either TG or DSG for gastric cancer exhibited deteriorated HRQoL compared to their preoperative states, and the diminished HRQoL for patients after TG was worse after 5 years. Therefore, one recommendation is to favor DSG over TG when oncological principles are strictly observed. Further investigations should follow, particularly those related to function-preserving gastrectomy, nutritional support and education, and education for self-management to improve postoperative HRQoL after gastrectomy, especially after TG.

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