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Health related quality of life following open versus minimally invasive total gastrectomy for cancer: Results from a randomized clinical trial

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ABSTRACT

Introduction: Minimally invasive techniques show improved short-term and comparable long-term outcomes compared to open techniques in the treatment of gastric cancer and improved survival has been seen with the implementation of multimodality treatment. Therefore, focus of research has shifted towards optimizing treatment regimens and improving quality of life.
Materials and methods: A randomized trial was performed in thirteen hospitals in Europe. Patients were randomized between open total gastrectomy (OTG) or minimally invasive total gastrectomy (MITG) after neoadjuvant chemotherapy. This study investigated patient reported outcome measures (PROMs) on health-related quality of life (HRQoL) following OTG or MITG, using the Euro-Qol-5D (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires, modules C30 and STO22. Due to multiple testing a p-value < 0.001 was deemed statistically significant.
Results: Between January 2015 and June 2018, 96 patients were included in this trial. Forty-nine patients were randomized to OTG and 47 to MITG. A response compliance of 80% was achieved for all PROMs. The EQ5D overall health score one year after surgery was 85 (60–90) in the open group and 68 (50–83.8) in the minimally invasive group ($P = 0.049$). The median EORTC-QLQ-C30 overall health score one year

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postoperatively was 83,3 (66,7–83,3) in the open group and 58,3 (35,4–66,7) in the minimally invasive group (P = 0.002). This was not statistically significant.
Conclusion: No differences were observed between open total gastrectomy and minimally invasive total gastrectomy regarding HRQoL data, collected using the EQ-5D, EORTC QLQ-C30 and EORTC-QLQ-STO22 questionnaires.
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1. Introduction

A gradual global adoption of minimally invasive techniques in the treatment of gastric cancer has been observed since Kitano et al. described the first laparoscopic assisted distal gastrectomy in 1994 [1]. Several large Asian studies have shown beneficial short-term and comparable long-term outcomes for minimally invasive techniques in the treatment of gastric cancer [2–4]. Recently reported short-term outcomes of the STOMACH trial showed that minimally invasive total gastrectomy is non-inferior to open total gastrectomy regarding the oncological quality of resection and postoperative complications [5].

With improved survival in gastric cancer patients using multimodality treatment, focus of research has shifted towards optimizing the treatment process and improving quality of life. When evaluating all patients following gastrectomy for cancer, a significant decline in overall health scores is seen in the first months after surgery. Overall health scores return to baseline within a year postoperatively [6]. Since minimally invasive total gastrectomy is non-inferior to open gastrectomy for cancer regarding short-term outcomes and survival, quality of life may be an important determinant to assess optimal treatment for these patients.

Previous studies collected cross-sectional data regarding quality of life in patients who underwent gastrectomy for cancer. Several factors were associated with improved health related quality of life (HRQoL) scores; HRQoL scores were better in patients that underwent smaller resections (i.e. subtotal versus total gastrectomy) and minimally invasive surgery rather than open surgery [7–10]. Data on quality of life in patients who underwent a total gastrectomy, especially in the era of neoadjuvant therapy, is scarce.

Patients in Europe often present with more advanced stages of disease, and the optimal treatment strategy includes peri-operative chemotherapy [11]. No studies were identified reporting HRQoL in patients with gastric cancer receiving minimally invasive total gastrectomy compared to open total gastrectomy or in gastric cancer patients with multimodality treatment.

The aim of this study was to compare health related quality of life following open versus minimally invasive total gastrectomy in patients with advanced gastric cancer treated with neoadjuvant chemotherapy.

2. Methods

2.1. Study design

A multicenter, international, randomized trial between January 2015 and June 2018 was performed in 13 hospitals in six European countries. Patients with resectable adenocarcinoma of the stomach, requiring a total gastrectomy, who completed neoadjuvant chemotherapy, were eligible for inclusion. Patients included had to be above 18 years of age with an American Society of Anesthesiologist classification of 3 or lower.

Eligible patients were randomized between minimally invasive total gastrectomy (MITG) or open total gastrectomy (OTG).

2.2. Procedures

All patients received neoadjuvant chemotherapy in accordance with local protocols.

Gastrectomy was performed after completion of neoadjuvant chemotherapy. Postoperative treatment protocols were similar in both groups. A more detailed description of the protocol and surgical procedures can be found in the study protocol of the STOMACH trial [12].

2.3. Study outcomes

Primary short-term outcomes and one-year survival data have previously been reported [5]. This study investigated patient reported outcome measures (PROMs) on health-related quality of life following open or minimally invasive total gastrectomy.

PROMs were obtained preoperatively, five days postoperatively and 3, 6 and 12 months postoperatively. Quality of life was assessed using the Euro-Qol-5D (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires, modules C30 and STO22 [13,14].

2.4. Statistical analysis

The STOMACH trial was designed as a randomized trial. The study was powered on non-inferiority for quality of oncological resection, measured as the number of excised lymph nodes. A total of 96 patient were enrolled in the study. An additional power analysis was performed for this sub-study. When comparing OTG and MITG for non-inferiority in overall health score (VAS) measured with EQ5D at 12 months postoperatively, with a standard deviation of 23.8 and non-inferiority margin of 20, a power of >90% was obtained with 96 included patients.

Statistical analysis was performed using SPSS statistical package, version 26 (IBM software). Outcomes for open and minimally invasive total gastrectomy were compared with continuous variables described as means and standard deviation for normal distributions and medians and interquartile ranges for non-normal distributions. Analysis was performed as intention to treat. Comparison tests were performed with Student's T-test and Mann-Whitney-U tests as appropriate. The measured PROMs assess 29 different scales, measured on 5 different moments, which equals a total of 145 tests per subject. To correct for possible multiple testing bias the Bonferoni correction was applied and a p-value of <0.001 was considered statistically significant for QoL data. Linear mixed models were used to assess for differences in the course of measurements over time.

3. Results

3.1. Demographic and clinical characteristics

A total of 96 patients were included in this trial and randomly assigned to undergo open or minimally invasive total gastrectomy for gastric cancer following neoadjuvant chemotherapy. Forty-nine

patients were randomized to the open group and forty-seven to the minimally invasive group. A flow chart for patient selection is depicted in Fig. 1. The demographic and clinical characteristics of the two groups are depicted in Table 1. Peri-operative results, complications, pathology results and one-year survival were previously published [5]. No differences were seen in one-year survival between the OTG and MITG group. In the OTG group 90.4% and in the MITG group 85.5% was alive one year after surgery (P = 0.701). 87,5% of patients in the MITG group versus 70,3% of patients in the OTG group received adjuvant therapy in the postoperative phase (p < 0.001). After correction, still no differences were observed in survival between open total gastrectomy and minimally invasive total gastrectomy.

3.2. Overall health scores

A response compliance of 80% was achieved for all PROMs. No differences were observed between open and minimally invasive total gastrectomy following neoadjuvant chemotherapy for overall HRQoL scores. Overall health scores were measured in a scale from 0 to 100 with 100 being the best overall health score. The EQ5D overall health score one year after surgery was 85 (60–90) in the open group and 68 (50–83.8) in the minimally invasive group (P = 0.049). The median EORTC-QLQ-C30 overall health score one year postoperatively was 83,3 (66,7–83,3) in the open group and 58,3 (35,4–66,7) in the minimally invasive group (P = 0.002). Generalized linear models revealed no differences in the course of overall health scores over time in both the EQ5D and EORTC-QLQ-C30 overall health score.

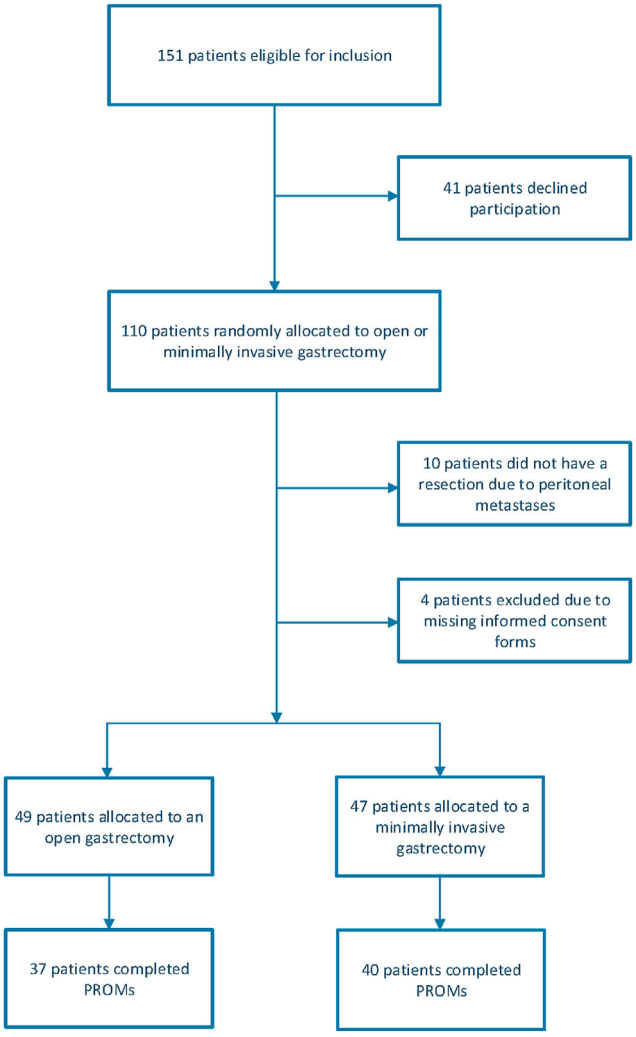


Fig. 1. Flow chart of the included patients.

3.3. EQ5D separate component scores

The remaining EQ5D components, being mobility, self-care, daily activities, pain and anxiety, showed no significant differences between OTG and MITG measured at 5 days postoperatively, 3 months, 6 months and one year postoperatively. Generalized linear models revealed no differences in the course of measurements over time between OTG and MITG. Patients reported the lowest overall HRQoL VAS score five days postoperative (p < 0,0001) compared to preoperative measurements. At three, six and twelve months no differences were observed in VAS score compared to baseline measurements. EQ5D scores are depicted in Fig. 2.

3.4. EORTC QLQ C30 separate domain scores

The EORTC QLQ C30 measures HRQoL with different functional and symptom scales. No statistically significant differences were observed between OTG and MITG for the different functional scales; physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. No differences were observed when comparing OTG and MITG at each different time point, and no differences were observed when assessing the course of measurements over time.

Global health and physical functioning scores were significantly lower at five days postoperative and three months postoperative measurements compared to baseline measurements (p < 0,0001). At six months, postoperative levels were similar to baseline. Role functioning scores were lower five days postoperative compared to baseline measurements, at three months scores were similar to baseline. No differences over time were observed for emotional, social and cognitive functioning scores. Functional scores are depicted in Fig. 3.

EORTC QLQ C30 symptom scales showed no differences between MITG and OTG, generalized linear models also revealed no differences in trends over time between the groups. The symptom scales include; fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties. In both groups pain scores were significantly higher compared to baseline in the direct postoperative phase, and at three months scores returned to baseline values. No statistically significant differences in measurements compared to baseline were observed for other symptom scales. Symptom scores are depicted in Fig. 4.

3.5. EORTC QLQ STO22 separate domain scores

EORTC QLQ STO22 is a gastric cancer specific module that can be added to the generic EORTC QLQ C30 questionnaire. The measured domains include; dysphagia, pain, reflux, dietary restrictions, anxiety, dry mouth, taste and body image. EORTC QLQ STO22 revealed no significant differences in scores between OTG and MITG at separate time moments. Generalized linear models also revealed no differences in trends over time between the groups. Patients reported significantly more dysphagia postoperatively compared to baseline, although scores remained higher compared to baseline measurements, no statistically significant differences were observed from three months onwards. No statistically significant differences in measurements compared to baseline were

Table 1
Baseline characteristics.

Baseline Characteristics						
		Open		**MI**		**p-value**
Total		49		47		
Gender (male, %)		32	65,3%	28	59,6%	0,674
Age (years, mean ± SD)		61,8	10	59,4	12,5	0,298
BMI (kg/m3, mean ± SD)		25,2	4	26,5	4,8	0,139
Weight loss (Yes, %)		23	50,0%	18	40,0%	0,402
ASA classification						
	ASA I	6	12,2%	4	8,5%	0,813[a]
	ASA II	31	63,3%	30	63,8%	
	ASA III	12	24,5%	13	27,7%	
WHO-performance status						
	WHO 0	32	65,3%	29	61,7%	0,582[a]
	WHO 1	13	26,5%	16	34,0%	
	WHO 2	4	8,2%	2	4,3%	
Clinical TNM						
	T1	1	2,0%	2	4,3%	0,730[a]
	T2	8	16,3%	9	19,1%	
	T3	36	73,5%	30	63,8%	
	T4	4	8.2%	6	12,8%	
	N0	17	34,7%	17	36,2%	0,711[a]
	N1	25	51,0%	26	55,3%	
	N2	7	14,2%	4	8,5%	
Neoadjuvant therapy						
	ECC	12	24,5%	9	19,1%	0,690[a]
	ECF	10	20,4%	9	19,1%	
	EOX	13	26,5%	13	27,7%	
	FOLFOX	0		2	4,3%	
	FLOT	10	20,4%	8	17,0%	
	Other	4	8,2%	6	12,8%	

[a] Additional testing within groups with Bonferroni correction showed no differences between groups.



Fig. 2. EQ5D scores with p-value at each measurement in time.



Fig. 3. EORTC QLQ C30 functional scale scores with p-value at each measurement in time.

observed for other STO22 scales. The STO22 scores are depicted in Fig. 5.

4. Discussion

This study investigated health related quality of life in open versus minimally invasive total gastrectomy in patients with advanced gastric cancer. No differences in health-related quality of life scores were observed between open total gastrectomy and minimally invasive total gastrectomy following neoadjuvant chemotherapy in patients with advanced gastric cancer. HRQoL data was assessed using the EQ-5D, EORTC QLQ-C30 and EORTC-QLQ-STO22 questionnaires. Postoperative chemotherapy was found to be a potential confounder, as more patients in the MITG group received postoperative chemotherapy. After correction for postoperative chemotherapy, and in subgroup analysis, no differences in HRQoL scores were observed between OTG and MITG. It should be noted that baseline quality of life was assessed at different moments in the preoperative phase, all patients were included after completion of neoadjuvant chemotherapy. It may be possible that baseline quality of life was already influenced by neoadjuvant chemotherapy.

Overall data revealed that global health (both EQ-5D VAS and EORTC global health score) and physical functioning decreased after surgery in order to return to baseline at six months postoperatively. As expected, pain and dysphagia scores were higher postoperatively and also returned to baseline at six months. These results are in line with a recent meta-analysis by van den Boorn et al. that showed that the largest decline in global health status was seen in the first month after gastrectomy and twelve months after surgery global health status returned to baseline [15].

In the few published studies on HRQoL following gastrectomy for cancer: varying results were reported. One study compared quality of life data in open versus minimally invasive distal gastrectomy. The results were in favor of a minimally invasive approach regarding short-term data. Long-term outcomes revealed no differences between the two approaches [10,16].

Another cross-sectional study revealed improved HRQoL in gastric cancer patients operated with minimally invasive techniques. It should be noted that the study included both distal and total gastrectomies, whereas total gastrectomy is associated with overall worse HRQoL outcomes in comparison to subtotal or distal gastrectomy [8,9]. Alongside, more than a third of patients did not receive neoadjuvant therapy, which might affect HRQoL data. Also, patients were at different time points in follow-up during measurements [7]. Improved perioperative guidance in the multimodality treatment of patients with advanced gastric cancer might diminish differences in HRQoL between open and minimally invasive techniques.

Regarding peri-operative chemotherapy; A previous study reported around 90% of patients complete preoperative chemotherapy treatment. Postoperatively, 52 to 60% start chemotherapy treatment but only 37 to 46% of patients complete both pre- and postoperative chemotherapy treatment [17]. In this trial 77,9% of patient continued with postoperative chemotherapy regimens (70,3% following OTG versus 87.5% following MITG, $P < 0.001$). Regardless of more patients continuing with postoperative chemotherapy in the MITG group, quality of life was still similar in both groups.



Fig. 4. EORTC QLQ C30 symptom scale scores with p-value at each measurement in time.

A recent review investigated different HRQoL tools and the effect of different gastric cancer operative techniques on HRQoL. A minimally invasive approach, limited extent of resection and pouch reconstruction were associated with improved quality of life [18]. When choosing the appropriate surgical procedure for a patient this can be considered (i.e. distal gastrectomy if oncologically feasible as opposed to total gastrectomy). Although quality of life first decreases after surgery, global quality of life appears not to be permanently impaired.

A limitation of this study was that quality of life was not a primary outcome in this trial, which might have led to an underpowered analysis of these results. A Bonferroni correction was applied for multiple testing bias. The response rate was 80%, missing data might affect outcomes. Nonetheless the results add to our knowledge on quality of life in patients with advanced gastric cancer with multimodality treatment.

5. Conclusion

No differences were observed between open total gastrectomy and minimally invasive total gastrectomy regarding HRQoL data, collected using the EQ-5D, EORTC QLQ-C30 and EORTC-QLQ-STO22

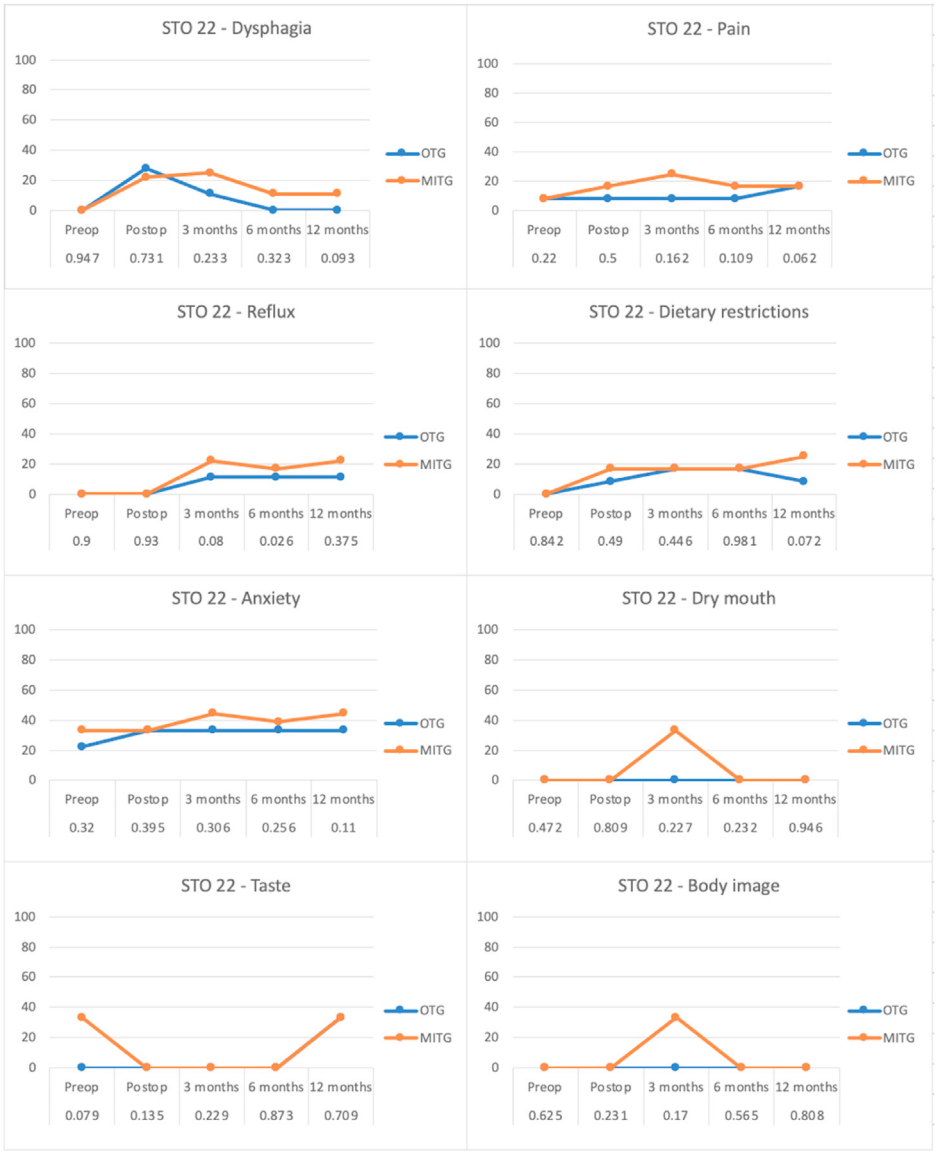


Fig. 5. EORTC QLQ STO 22 scores with p-value at each measurement in time.

questionnaires. These results may be explained by improved perioperative and multidisciplinary care pathways. Taking into account the previously published data, which depicted no differences between OTG and MITG regarding quality of resection, perioperative complications and one-year survival, this study has shown that, next to being non inferior to OTG, MITG has a comparable impact on the quality of life. Leaving the choice between open or minimally invasive total gastrectomy at the discretion of the surgeon and patient.

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