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## **Weight Loss and Quality of Life in Patients Surviving 2 Years after Gastric Cancer Resection**

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**Running head:** Quality of life after gastric cancer resection

**Conflicts of interest:** None to be disclosed by any of the authors

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## ABSTRACT

**Background:** Malnutrition is common in patients undergoing gastric cancer resection, leading to weight loss, although little is known about how this impacts on health related quality of life (HRQL) This study aimed to explore the association between HRQL and weight loss in patients 2 years after curative gastric cancer resection.

**Methods:** Consecutive patients undergoing curative gastric cancer resection and surviving at least 2 years without disease recurrence were recruited. Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the specific module for gastric cancer (STO22) before and 2 years postoperatively and associations between HRQL scores and patients with and without  $\geq 10\%$  body weight loss (BWL) were examined.

**Results:** A total of 76 patients were included, of whom 51 (67%) had BWL  $\geq 10\%$ . At 2 years postoperatively, BWL  $\geq 10\%$  was associated with deterioration of all functional aspects of quality of life, with persistent pain (21.6%), diarrhoea (13.7%) and nausea/vomiting (13.7%). By contrast, none of the patients with BWL  $< 10\%$  experienced severe nausea/vomiting, pain or diarrhoea.

**Conclusions:** More than two thirds of patients surviving 2 years after curative gastric cancer resection experienced  $\geq 10\%$  BWL. These patients suffered from more disabling symptoms than those without this extent of weight loss which impaired HRQL.

**Key words:** Gastric cancer; surgery; quality of life; weight loss

## INTRODUCTION

Surgical resection, either alone or in combination with perioperative chemotherapy or adjuvant chemotherapy, or chemoradiation is the main curative treatment for locally advanced gastric cancer (1–3). Malnutrition has been widely recognized in gastric cancer patients because of the disease itself or because of the surgical and oncological treatments (4,5). Gavazzi et al.(5) analysed the nutritional status at the beginning of gastric cancer treatment and reported a body weight loss (BWL)  $\geq 10\%$  of usual weight in 17% of patients, having a negative influence on health-related quality of life (HRQL). Several studies have defined HRQL as an important additional outcome measure in gastric cancer patients undergoing resection, showing differences between surgical techniques (6–8) as well as providing prognostic information (9–11).

A greater than 10% baseline BWL has been considered as a severe nutritional risk indicator in patients with gastrointestinal cancer (12,13). Previous studies have found that patients undergoing total gastrectomy will lose 7%-15% of their body weight, usually within the first year of surgery, and will not return to a pre-operative weight (14–16). The reduction in calorie intake as well as malabsorption are considered the main factors responsible for BWL(14). The extent of postoperative BWL seen postoperatively has been related to a deterioration of HRQL after oesophageal cancer resection (17).

Little is known, however, about long-term HRQL after gastrectomy and especially, how postoperative BWL may affect HRQL. In this study we assessed HRQL in patients surviving at least 2 years after curative gastric cancer resection. It was hypothesised that the magnitude of BWL may be related to HRQL impairment.

## **METHODS**

### ***Study population***

Consecutive patients undergoing curative gastric cancer resection were recruited between October 2004 and May 2014 at Hospital Universitari del Mar (Barcelona, Spain). Total or subtotal gastric resection, depending upon the location and the extent of the tumour, with modified D2 lymphadenectomy was undertaken. A 70 cm Roux-en-Y loop reconstruction was performed in all cases. In the context of clinical trials carried out during the study period, perioperative chemotherapy or adjuvant chemoradiation was offered to a subgroup of patients with clinical stage II/III disease. Tumour stage was defined according to the system of the International Union Against Cancer(18). Postoperative complications were categorised according to a modified Clavien-Dindo classification(19). Sepsis was defined as an infection that had evoked a systemic inflammatory response syndrome (SIRS)(20).

Patients who had survived for at least 2 years, and had completed the HRQL questionnaires were eligible for the study. Excluded were patients who had recurrence, concurrent malignancy, multivisceral resections, cognitive deterioration, and those who declined to complete the study questionnaires. The Ethics Committee of Hospital Universitari del Mar approved the study and written informed consent was obtained from all participants.

All patients were seen at the outpatient clinic by a medical oncologist and a surgeon at 3 months intervals during the first 2 years after surgery; and every 6 months until they completed 5 years postoperatively. After surgery, patients were referred to the Nutrition and Dietetic Outpatient Clinic for nutritional guidance,

although no specific strategy for the provision of oral nutritional supplements was instituted.

### ***Assessment of preoperative and postoperative weight***

Height and weight were measured at the first visit (less than 2 weeks) before the operation. Preoperative BWL was calculated using the formula average weight (kg) minus weight at time of surgery (kg) / average weight (kg) (14). Body mass index (BMI), using the standard formula weight (kg)/height (m<sup>2</sup>), was calculated at baseline and at 6, 12 and 24 months after surgery. The percentage of postoperative weight change was calculated using the formula weight at time of surgery (kg) minus current weight (kg) / weight at time of surgery (kg) at 6 months, 12 months and 2 years postoperatively.

### ***Health-related quality of life***

HRQL was assessed with the validated European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire, EORTC Quality of Life Questionnaire (QLQ-C30) (version 3.0) and the specific module for gastric cancer EORTC QLQ-STO22. Permission from EORTC was obtained in order to use them. EORTC QLQ-C30 is a 30-item questionnaire composed of multi-item scale and single items that reflects the multidimensionality of the quality of life in patients with cancer. It incorporates five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting) and a global health scale. It also includes single items commonly reported by cancer patients (10,21). The validated EORTC QLQ-STO22 contains 22 items structured in five scales (dysphagia, eating restrictions, pain, reflux and anxiety) and three single items (22). Patients were asked to complete the questionnaires by themselves at

home. If patients showed difficulties to understand questionnaires, additional help was provided. Baseline HRQL assessment was performed less than 2 weeks before surgery. Subsequent assessments during the follow-up period were carried out at 6, 12, and 24 months after surgery. When questionnaires were completed or returned, they were checked for missing response. If answers were absent, patients were asked to respond(9,11). If responses were still missing from more than half of the questions within a scale, these questionnaires were excluded from the analyses, according to EORTC recommendations(21,23).

All responses to the EORTC QLQ-C30 and STO-22 questionnaires were linearly transformed into scores from 0 to 100 to standardise the raw score. In the functional scales, high scores represent better quality of life (better function), whereas high scores in symptom scales and items represent worse problems with symptoms(9).

### ***Data Analyses***

Baseline characteristics and HRQL scores were analysed in relation to BWL < 10% or  $\geq$  10% at 2 years. Based on previous studies, a cut-off of 10% was chosen because this percentage of BWL is considered as a severe nutritional risk marker (12–14,16). Mean scores and 95% confidence intervals (CIs) for HRQL were calculated preoperatively and at 2 years after surgery. Changes of 10 or more points on a 0 to 100 scale were considered clinically relevant(9,24). Statistical analyses were performed using *t* test and  $X^2$  test.  $P < 0.05$  was considered statistically significant (two-sided). Responses to symptom scales were dichotomised based on whether the patients reported minimal or severe symptoms, with “not at all” and “a little” categorised as minimal and “quite a bit” or “very much”

categorised as severe (25,26). The SPSS software package (SPSS Inc, Chicago, IL, USA), version 20.0, was used.

## **RESULTS**

### ***Demographics and Cohort Features***

During the study period, 119 patients undergoing curative gastric cancer resection were recruited. Forty-three patients were excluded from the analysis due to reasons depicted in Figure 1. Thus, 76 patients remained for the final analysis. Of these patients, baseline measurement of HRQL was missing in four patients: one underwent emergency gastric resection and the other three patients did not complete them. Preoperative clinical and demographic characteristics in both groups are shown in Table 1. BWL  $\geq$  10% at 2 years was detected in 51 patients (67%) whereas the rest of patients (25 patients) experienced BWL  $<$  10%. No differences were observed between both groups in any variable except for the type of gastrectomy and grade ASA.

### ***HRQL 2 Years after Surgery in relation to weight loss***

Patients with  $\geq$  10% BWL at 2 years after surgery had lower scores in all items of the functional scales of EORTC QLQ-C30 but in none of them there were clinically relevant differences (mean reduction of  $>$  10 points) (Table 2). Of the symptoms reported, patients with  $\geq$  10% BWL at 2 years postoperatively were generally more symptomatic than patients without such percentage of BWL. Clinically relevant differences were identified with pain, diarrhoea, eating restrictions and financial difficulties (Table 2). Results at 2 years after surgery showed that up to one third of patients reported symptoms categorised as severe (“quite a bit” or “very much”) with anxiety (Table 3). Moreover, more than one fifth of these patients

also reported severe problems with fatigue (20.4%), pain (21.6%), eating restrictions (29.4 %), having dry mouth (25.5%) and body image (23.6 %). In addition, 13.7% of patients with  $BWL \geq 10\%$  experienced severe diarrhoea and severe nausea and vomiting (Table 3). By contrast, none of the patients with  $BWL < 10\%$  experienced severe nausea/vomiting, pain or diarrhoea.

### ***HRQL before Surgery in relation to weight loss***

Most of the baseline functional scores were poorer in patients who subsequently experienced more than 10% of BWL compared to those without this extent of BWL (Table 2). However, only differences in role and physical function were clinically relevant (i.e.  $> 10$  points different). Baseline symptoms scores were higher among patients with  $BWL \geq 10\%$ . Clinically relevant differences were only observed in relation to fatigue, pain and constipation. Results at baseline showed that one third of patients with  $\geq 10\%$  BWL reported severe symptoms with anxiety (54.2%), fatigue (36.9%) and constipation (31.2%). Moreover, more than one fifth of these patients also reported severe symptoms with insomnia (25%), dry mouth (25%), appetite loss (22.9%) and pain (20.8%). Severe nausea and vomiting, dyspnoea and financial difficulties were only reported by patients that experienced  $\geq 10\%$  BWL.

## **DISCUSSION**

This prospective study examined the relation between HRQL and BWL in patients surviving 2 years after curative gastric cancer resection. In our study, 67% of patients experienced  $\geq 10\%$  of BWL at 2 years of surgery. The patients with  $\geq 10\%$  BWL after 2 years usually reported more symptoms compared with those patients with less BWL. It is of note that severe symptoms with nausea and

vomiting, pain and diarrhoea were only reported in patients with BWL over 10%. Preoperative measurement of HRQL allowed us to explore HRQL differences between patient groups before surgery. This showed that patients losing at least 10% of weight at 2 years experienced preoperatively more fatigue, pain, and constipation with a significant reduction in role and physical function as compared to patients with a lower percentage of BWL. Moreover, severe symptoms were more frequently reported in patients who experience more BWL at 2 years after surgery. These findings suggest some relation between weight loss and quality of life in long-term survivors after gastric cancer resection and it make us aware of the need for potential early interventions that could minimise this important problem.

A number of studies have described the great impact of gastric resection on HRQL in patients with curable gastric cancer (6,10). It has been shown that HRQL is influenced by the extent of resection (total vs. subtotal or proximal gastrectomy) (4,6) and there is a significant impairment of several aspects of HRQL reported by patients in the immediate postoperative period(6). Whilst studies show that symptoms improve after 6 or 12 months postoperatively, there is also evidence that some symptoms such as fatigue, nausea, pain or diarrhoea remain at 2 years after surgery as we observed in the present study(6,7). Other authors have investigated how baseline HRQL assessment may predict clinical outcomes(9,10). Avery et al. (10) reported worse global health, more nausea and vomiting, pain and fatigue at baseline assessment among those patients dying within 2 years after gastric cancer resection. A difference in the baseline dyspnoea score, measured by HRQL questionnaires, was suggested by Djärv et al. (9) as an independent predictive factor of death, but in this study gastric and oesophageal resection cases were analysed together. There are a few studies reporting the relation between

postoperative malnutrition and HRQL (14,17,27). Although some of them have HRQL baseline assessment, none related HRQL to postoperative BWL. Our study identifies some baseline HRQL items related to long-term greater BWL.

Two studies have previously described 7-15% of BWL after gastric cancer resection (14,15). Another study has even identified cachexia in half of the patients (9). In agreement with these previous studies, our results show that more than half of the patients experienced at least 10% of BWL after gastric cancer resection. These results highlight the need for more active clinical interventions to counteract malnutrition. Starting nutritional counselling and oral nutritional supplementation before surgery should be considered, and especially increasing nutritional support within 6 months after surgery, when it seems represent the period of greatest weight loss according to our data (data not shown). Although nutritional intervention is recommended in the management of BWL, there is still lack of evidence to support oral nutritional interventions as an individual strategy(28). Furthermore, physiotherapy, psychological assessment and other healthcare support might facilitate improvement in common symptoms reported by patients after gastric cancer resection, such as fatigue, deterioration in emotional function or pain control(29).

In line with our results, previous studies have found a high prevalence of diarrhoea after gastric cancer resection ranging from 20% to 30%(6,7,10,11). In the present study, severe diarrhoea was more common in the group of patients with  $\geq 10\%$  BWL (13% versus 0%). In a recent systematic study of a prospective consecutive series of 45 disease-free patients after esophagectomy or gastrectomy, Henegham et al. (16) found that the incidence of malabsorption at 18 to 24 months postoperatively was 71% in the gastrectomy group. The proportion of patients with

more than 15% weight loss had significantly lower nutritional risk index scores, and a higher incidence of malabsorption compared with those who had less than 15% weight loss at 24 months. Additionally, of those patients with malabsorption, 44% had exocrine pancreatic insufficiency and 38% had evidence of small intestinal bacterial overgrowth. Further studies are required to define a well-established diagnostic and therapeutic strategy for amelioration of malabsorption, including the substitution with pancreatic enzymes and the treatment of bacterial overgrowth, to reduce its incidence and potentially minimise BWL and improve HRQL after gastric resection.

Although our data has been collected accurately, with high compliance even in the baseline assessment, the current study was not powered to perform a multivariate analysis introducing confounders to identify predictive factors for long-term BWL after curative gastric cancer resection. Moreover, It is a single centre study and a multicentre study would provide data that is more generalizable.

In summary, more than 50% of patients surviving 2 years after curative gastric cancer resection experienced  $\geq 10\%$  BWL. These patients suffered from more disabling symptoms than those with  $< 10\%$  BWL, with a relevant negative effect on HRQL. These findings support the need for routine early nutritional support and counselling in gastric cancer patients undergoing curative surgical treatment.

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## **Authors' contribution**

M. Climent: Conception and design, collection of data, assessment of the HRQL, critical review of results and writing of the first draft, and approval of the final draft.

M. Munarriz: Conception and design, collection of data, critical review of results and approval of the final draft.

J. Blazeby: Conception and design, critical review of results and approval of the final draft.

D. Dorcaratto: Conception and design, critical review of results and approval of the final draft.

M.J Carrera: Nutritional follow-up of patients, critical review of results and approval of the final draft.

L. Fontane: Nutritional follow-up of patients, critical review of results and approval of the final draft.

L. Grande: Conception and design, critical review of results and writing of the first draft, and approval of the final draft.

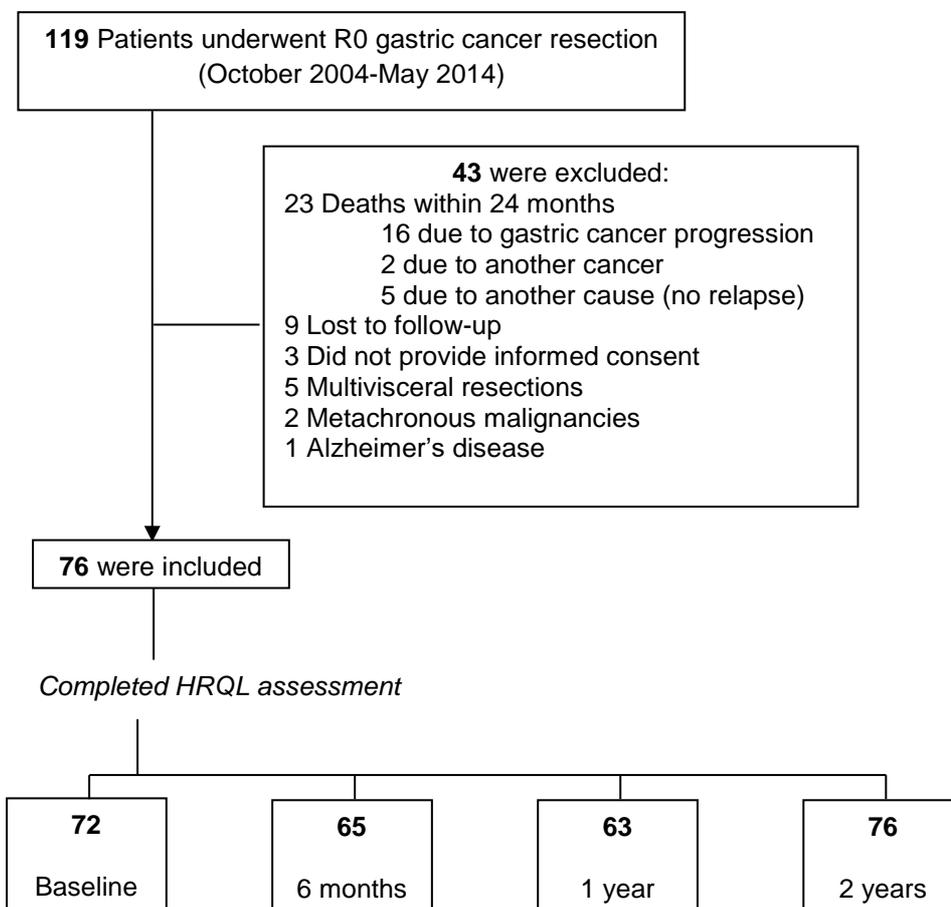
M. Pera: Contribution of design and interpretation of results, critical review of results and writing of the first draft, and approval of the final draft.

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**LEGENDS:**

**Figure 1.** Flow chart of patients included in the study with number of patients who completed the health-related quality of life (HRQL) questionnaires.

Characteristics	Entire group N = 76	Weight Loss < 10% N = 25	Weight Loss ≥10% N = 51	<i>P</i> value
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Sex				
Female	31	11	20	0.69
Male	45	14	31	
Age, years				
< 60	16	6	10	0.65
≥ 60	60	19	41	
ASA, grade				
I - II	43	19	24	<b>0.017</b>
III - IV	33	6	27	
Preoperative weight loss				
< 10 %	62	20	42	0.80
≥ 10	14	5	9	
Preoperative BMI (kg/m <sup>2</sup> )				
< 25	24	8	16	0.95
≥ 25	52	17	35	
Preoperative albumin (g/dL)				
Mean (±SD)	40.1 (±4.5)	40.4 (±4.2)	39.9 (±4.6)	0.67
pT*				
Tis /T1	24	11	13	0.35
T2	15	4	11	
T3	26	6	20	
T4	11	4	7	
pN*				
N0	42	12	30	0.54
N1	16	7	9	
N2/N3	18	6	12	
pTNM*				
0 / I	31	12	19	0.44
II	29	7	22	
III	16	6	10	
Type of operation				
Subtotal gastrectomy	26	14	12	<b>0.005</b>
Total gastrectomy	50	11	39	
Neoadjuvant chemotherapy				
Yes	10	2	8	0.35
No	66	23	43	
Adjuvant therapy				
Yes	16	4	12	0.44
No	60	21	39	
Dindo-Clavien grade				
0 -I	36	12	24	0.93
≥ II	40	13	27	
Sepsis				
Yes	15	3	12	0.23
No	61	22	39	

**Table 1.** Baseline and clinical characteristics of 76 patients who survived at least 2 years after curative gastric cancer resection in relation to weight loss ≥ or < 10% at 2 years

ASA, American Society of Anesthesiologists, BMI: Body mass index. \*According to the 7th edition of the International Union Against Cancer tumor, node metastasis staging system (18). Results are expressed as number of patients unless otherwise stated.

**Table 2.** EORTC QLQ-C30 and QLQ-STO-22 scales/items before and 2 years after gastric cancer resection in relation to weight loss  $\geq$  or  $<$  10% at 2 years.

EORTC QLQ C-30 scales/items	Before Surgery N= 72			2 Years After Surgery N= 76		
	Weight loss < 10% N=24	Weight loss $\geq$ 10% N=48	MSD	Weight loss < 10% N=25	Weight loss $\geq$ 10% N=51	MSD
Functional scales*						
Global health	74.6 (66 to 83)	65.6 (58 to 72)	-9	71.7 (64 to 80)	64.7 (60 to 71)	-7
Physical function	91.4 (86 to 96)	81 (76 to 88)	<b>-10.4</b>	87.2 (81 to 94)	79.9 (76 to 87)	-7.3
Role function	93.7 (88 to 99)	77.4 (69 to 89)	<b>- 16.3</b>	90 (84 to 96)	82 (78 to 90)	-8
Emotional function	76 (67 to 84)	68.9 (64 to 77)	-7.1	76.7 (66 to 87)	74.4 (70 to 83)	-2.3
Cognitive function	84 (77 to 91)	85.4 (80 to 92)	1.4	83.3 (75 to 91)	78.1 (74 to 87)	-5.2
Social function	90.3 (84 to 97)	86.4 (80 to 93)	-3.9	91.3 (83 to 99)	85.3 (80 to 93)	-6
Symptom scales/items**						
Fatigue	16.7 (8 to 25)	36.9 (26 to 43)	<b>20</b>	21.8 (12 to 31)	31.1 (24 to 35)	9.3
Nausea and vomiting	4.2 (0 to 8)	7.9 (2 to 10)	3.7	8 (2 to 14)	16.3 (6 to 20)	8.3
Pain	9.7 (3 to 16)	26 (16 to 31)	<b>16.3</b>	6 (1 to 11)	23.2 (14 to 29)	<b>17.2</b>
Dyspnoea	0	7.6 (0 to 14)	7.6	5.3 (0 to 10)	6.5 (2 to 12)	1.2
Insomnia	22.2 (9 to 36)	29.9 (19 to 39)	7.7	26.7 (12 to 41)	24.2 (14 to 31)	-2.5
Appetite loss	20.8 (8 to 33)	26.4 (14 to 34)	5.6	20 (7 to 32)	20 (10 to 24)	-
Constipation	22.2 (9 to 35)	33.3 (23 to 42)	<b>11.1</b>	14.7 (4 to 25)	8.8 (2 to 15)	-5.9
Diarrhoea	6.9 (-1 to 15)	7.6 (1 to 13)	0.7	10.6 (4 to 17)	20.6 (11 to 27)	<b>10</b>
Financial difficulties	5.5 (0 to 11)	12.3 (4 to 20)	6.8	6.7 (0 to 13)	18.7 (8 to 26)	<b>12</b>
EORTC QLQ-STO-22 scales/items**						
Dysphagia	5.5 (0 to 12)	9.9 (4 to 12)	4.4	6.9 (-2 to 16)	14.2 (9 to 18)	7.2
Pain	12.8 (4 to 23)	20.4 (12 to 26)	7.6	8.7 (1 to 16)	23.1 (15 to 31)	<b>14.4</b>
Reflux symptoms	11.8 (2 to 24)	9 (6 to 13)	2.8	11.3 (4 to 19)	14.4 (8 to 18)	3.1
Eating restrictions	8.7 (2 to 16)	16.3 (9 to 22)	7.6	14.4 (8 to 25)	26.1 (18 to 34)	<b>11.7</b>
Anxiety	44.4 (32 to 52)	45.2 (37 to 51)	0.8	25 (12 to 31)	33.8 (24 to 40)	8.8
Having dry mouth	25 (11 to 42)	34.7 (23 to 43)	9.7	27.1 (13 to 47)	34 (21 to 41)	6.9
Taste	6.9 (-2 to 18)	11.8 (3 to 18)	4.9	10.7 (-2 to 18)	18.9 (12 to 34)	8.2
Body image	13.8 (3 to 30)	15.3 (4 to 21)	1.5	17.3 (5 to 31)	23.5 (4 to 21)	6.2
Hair loss	6 (-1 to 15)	12.7 (0 to 14)	6.7	13.9 (0 to 23)	6.8 (0 to 14)	-7.1

Results are expressed as mean (95% CI). Abbreviation: EORTC QLQ, European Organization for Research and treatment of cancer Quality of Life Questionnaire –C30 and STO22; \*Higher score represent better function; \*\* Higher score represent more symptoms. MSD: Mean score difference.

**Table 3.** Percentage of patients reporting “quite a bit” or “very much” with regard to symptoms before and 2 years after gastric cancer resection in relation to weight loss  $\geq$  or  $<$  10% at 2 years

	Before Surgery N= 72				2 Years After Surgery N=76			
	Weight loss < 10% N= 24		Weight loss $\geq$ 10% N= 48		Weight loss < 10% N=25		Weight loss $\geq$ 10% N= 51	
<b>QLQ-C30</b>								
Fatigue	12.5	(4 to 31)	36.9	(23 to 49)	20	(9 to 39)	20.4	(11 to 32)
Nausea and vomiting	-		10.4	(1 to 22)	-		13.7	(7 to 26)
Pain	4.1	(1 to 20)	20.8	(12 to 34)	-		21.6	(12 to 35)
Dyspnoea	-		6.2	(2 to 17)	-		2	(1 to 10)
Insomnia	16.7	(7 to 36)	25	(15 to 39)	24	(11 to 43)	19.6	(11 to 32)
Appetite loss	16.7	(7 to 36)	22.9	(13 to 36)	20	(9 to 39)	14	(7 to 26)
Constipation	12.5	(4 to 31)	31.2	(20 to 45)	8	(2 to 25)	6.1	(2 to 16)
Diarrhoea	8.3	(2 to 26)	6.2	(2 to 17)	-		13.7	(7 to 26)
Financial difficulty	-		10.9	(4 to 22)	4	(1 to 19)	16	(8 to 28)
<b>QLQ-STO22</b>								
Dysphagia	25	(12 to 45)	8.5	(3 to 19)	8	(2 to 25)	11.8	(5 to 23)
Pain	17.4	(7 to 36)	18.7	(10 to 32)	4	(1 to 19)	18	(10 to 30)
Reflux symptoms	21.7	(9 to 40)	6.2	(2 to 17)	12	(4 to 30)	12	(5 to 23)
Eating restrictions	29.1	(15 to 49)	12.5	(6 to 25)	24	(11 to 43)	29.4	(19 to 43)
Anxiety	70.8	(51 to 85)	54.2	(40 to 67)	32	(17 to 52)	33	(22 to 47)
Having dry mouth	37.5	(21 to 57)	25	(15 to 39)	24	(11 to 43)	25.5	(15 to 39)
Taste	20.8	(9 to 40)	4.2	(1 to 14)	12	(4 to 30)	11.8	(5 to 23)
Body image	20.8	(9 to 40)	10.4	(4 to 22)	8	(2 to 25)	23.6	(23 to 36)
Hair loss	13.6	(4 to 31)	19.1	(10 to 32)	17	(6 to 34)	10	(4 to 20)

Results are expressed as percentages (95% CIs). Abbreviation: EORTC QLQ, European Organization for Research and treatment of cancer Quality of Life Questionnaire –C30 and STO22; CI confidence interval. \* Higher scores represent greater proportion of individuals reporting (3) “quite a bit” or (4) “very much” with regard to symptoms (severe symptoms).