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Gastrointestinal Symptoms After Resection of Esophagogastric Cancer: A Longitudinal Study on Their Incidence and Impact on Patient-Reported Outcomes

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ABSTRACT

Background. This study assesses the incidence of gastrointestinal symptoms in the first year after resection of esophageal or gastric cancer and its association with health-related quality of life (HRQoL), functioning, work productivity, and daily activities.

Patients and Methods. Patients diagnosed with esophageal or gastric cancer between 2015 and 2021, who underwent a resection, and completed ≥ 2 questionnaires from the time intervals prior to resection and 0–3, 3–6, 6–9, and 9–12 months after resection were included. Multivariable generalized linear mixed models were used to assess changes in gastrointestinal symptoms over time and the impact of the number of gastrointestinal symptoms on HRQoL, functioning, work productivity, and daily activities for patients who underwent an esophagectomy or gastrectomy separately.

Results. The study population consisted of 961 (78.8%) and 259 (21.2%) patients who underwent an esophagectomy and gastrectomy, respectively. For both groups, the majority of gastrointestinal symptoms changed significantly over time. Most clinically relevant differences were observed 0–3 after resection compared with prior to resection and included increased diarrhea, appetite loss, and eating restrictions, and specifically after esophagectomy dry mouth, trouble with coughing, and trouble talking. At 9–12 after resection one or more severe gastrointestinal symptoms were reported by 38.9% after esophagectomy and 33.7% after gastrectomy. A higher number of gastrointestinal symptoms was associated with poorer functioning, lower HRQoL, higher impairment in daily activities, and lower work productivity.

Conclusions. This study shows that gastrointestinal symptoms are frequently observed and burdensome after esophagectomy or gastrectomy, highlighting the importance to address these sequelae for high quality survivorship.

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Esophageal and gastric cancer are common worldwide, with a combined estimated incidence of 1.69 million cases in 2020.[1] The treatment of both cancers is multimodal, but surgical resection remains the cornerstone for curative treatment.[2–4] Esophagectomies and gastrectomies are highly complex but as a result of selection, centralization and improved perioperative care, morbidity, and mortality has decreased considerably in the past decades.[2–7] As survival for patients with esophageal or gastric cancer has improved,[6,7] an increasing number of patients have to deal with the long-term consequences of their disease and treatment.[6,7]

Resection of esophageal and gastric cancer directly impacts patients' ability to ingest and digest food, and may lead to gastrointestinal complaints, characterized by symptoms such as fatigue, abdominal pain, nausea, vomiting, cramping, diarrhea, inability to pass food, regurgitation, and feelings of early satiety.[8–11] Several studies have shown that gastrointestinal symptoms are highly prevalent and often remain present in the long term.[12,13] A cross-sectional study showed that symptom burden did not vary significantly between < 1 year, 1–5 years, and > 5 years after esophagectomy.[12] Over 35% of patients reported heartburn, regurgitation, and a choking feeling during the night, and 90% even reported feelings of early satiety > 5 years after surgery.[12] Studies among patients with cancer of the gastro–esophageal junction have shown that, generally, less gastrointestinal symptoms and higher health-related quality of life (HRQoL) are observed after gastrectomy compared with esophagectomy.[14–17] As previous research has mainly been conducted cross-sectionally, changes in gastrointestinal symptoms over time after esophagectomy or gastrectomy are largely unknown.

Gastrointestinal symptoms have previously been shown to be associated with long-term clinically relevant deteriorations in many aspects of HRQoL,[10–12,18,19] with fatigue, loss of appetite, diarrhea, dumping, abdominal pain, and reflux being negatively associated with HRQoL.[10,11] Besides its influence on HRQoL, qualitative research has shown that many patients experience their eating problems as being a threat to undertaking (social) activities.[20]

Given the lack of longitudinal studies, this study aims to assess the incidence and course of gastrointestinal symptoms over time in the first year after esophagectomy or gastrectomy using data from a prospective observational cohort of esophageal and gastric cancer patients[21] and a nationwide cancer registry. Moreover, the longitudinal association between gastrointestinal symptoms and HRQoL, functioning, work productivity and daily activities are assessed.

PATIENTS AND METHODS

Data Collection

Data from the Prospective Observational Cohort study of Oesophageal-gastric Cancer Patients (POCOP) and the Netherlands Cancer Registry (NCR) were used. POCOP is a nationwide registry that collects clinical data and patient-reported outcomes for scientific research to improve outcomes for patients with esophageal and gastric cancer.[21] Patients receive questionnaires at regular intervals; at enrollment (which can be at any moment during the course of their disease and treatment); at 3, 6, 9, 12, 18, and 24 months; and then annually thereafter. Clinical characteristics of the patients are obtained through linkage with the NCR. The NCR is a population-based registry covering all newly diagnosed malignancies in The Netherlands as notified by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. The study is approved by the privacy review board of the NCR as well as the scientific committee of the Dutch Upper-GI Cancer Group (DUCG).

Study Population

All patients with nonmetastatic esophageal or gastric cancer (cM0) diagnosed between 2015 and 2021, for whom registration in the NCR was complete and who underwent an esophagectomy or (sub)total gastrectomy, were selected. Patients who completed at least two questionnaires for POCOP, without missing data for scales on gastrointestinal symptoms, within the time intervals prior to resection and 0–3, 3–6, 6–9, and 9–12 after resection were included (Fig. 1). For the time interval 0–3, only questionnaires completed after discharge from the hospital were included.

Patient, Tumor, and Treatment Characteristics

Information on patient and tumor characteristics and treatment are routinely extracted from the medical records 9–12 months after diagnosis by trained administrators of the NCR. The anatomical site of the tumor is registered according to the International Classification of Disease—Oncology. The Union for International Cancer Control tumor-node metastasis classification is used for stage notification of the primary tumor, according to the edition valid at the time of diagnosis (2015–2016: 7th edition; 2017–2021: 8th edition). Performance status is (re)coded according to the World Health Organization (WHO), as described by Ma et al.[22] Comorbidity is registered according to a modified version of the Charlson Comorbidity Index.

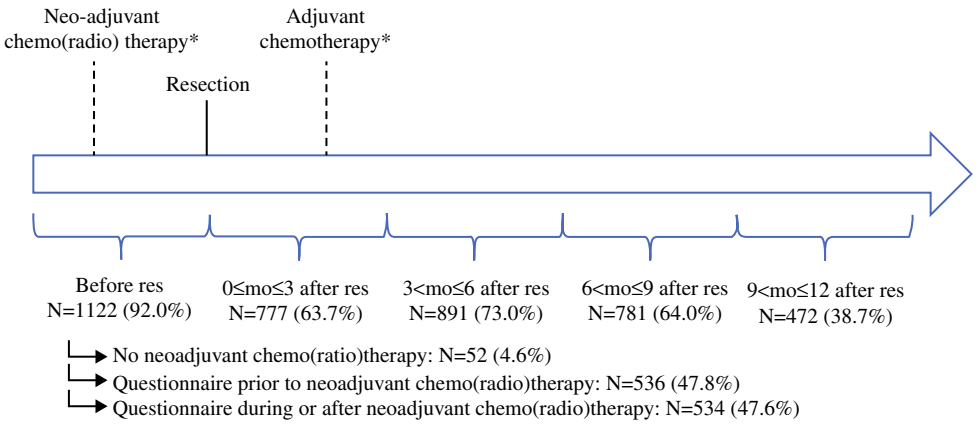

FIG. 1 Overview of the study period and completed questionnaires. *(Neo)Adjuvant chemo(radio)therapy is modeled as time dependent variable in multivariable analysis, where the variable becomes 1 after the start date of (neo)adjuvant therapy. *Mo* months, *res* resection (esophagectomy or gastrectomy)

The following items from the NCR are included in the study: sex, age at diagnosis, ASA classification, number of comorbidities, year of diagnosis, topography, histology, clinical T and N classification, type of resection, type of esophagectomy, type of gastrectomy, (neo)adjuvant chemoradiotherapy, (neo)adjuvant chemotherapy, neoadjuvant radiotherapy, and prolonged hospital stay.

Gastrointestinal Symptoms

Gastrointestinal symptoms were retrieved from scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30[23] (EORTC QLQ-C30) and the EORTC QLQ Oesophageal–Gastric Cancer Module 25[24] (EORTC QLQ-OG25). The EORTC QLQ-C30 is originally developed to evaluate the quality of life of patients in international clinical trials, and has proven to be a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings.[23] The EORTC QLQ-C30 is a 30 item questionnaire that addresses five functioning scales, three symptom scales, six single items, and an overall quality of life item. The EORTC QLQ-OG25 is recommended to supplement the EORTC QLQ-C30 when assessing health-related quality of life in patients with esophageal or gastric cancer.[24] The EORTC QLQ-OG25 consist of six multi-item scales and ten single-item scales.

From the EORTC QLQ-C30 the nausea/vomiting scale (two items) and the single items constipation, diarrhea, and appetite loss were included to assess gastrointestinal symptoms. The following scales from the EORTC QLQ-OG25 were included: dysphagia (three items), eating restrictions (four items), reflux (two items), odynophagia (two items), pain and discomfort (two items), and the following single items: dry mouth; choked when swallowing; and trouble with taste, coughing, swallowing saliva, and talking. An overview of the questions that are used to assess the items and scales included in the analyses is provided in Supplementary Table 1.

HRQoL, Functioning, Work Productivity, and Daily Activities

For HRQoL and functioning, the following scales from the EORTC QLQ-C30 were included: overall quality of life (two items), physical functioning (five items), role functioning (two items), emotional functioning (four items), cognitive functioning (two items), and social functioning (two items) (Supplementary Table 1).

All items of the EORTC QLQ-C30 and OG-25 were scored on a four-point Likert scale ranging between "not at all" to "very much," except the item overall quality of life which ranged from 1 (very poor) to 7 (excellent). All items or scales were linearly transformed to a score ranging between 0 and 100.

To evaluate work productivity and daily activities, the Work Productivity and Activity Impairment Questionnaire–Specific Health Problem was used. The hours missed due to esophagogastric cancer, the hours actually worked, and the degree to which esophagogastric cancer affected productivity while working and regular activities were assessed. These questions were answered on a 0–10-point Likert scale. From these questions, two scales were assessed: percentage of overall work impairment (for employed patients only) and percentage of impairment of daily activities due to esophagogastric cancer.

Statistical Analyses

Baseline characteristics were presented separately for patients who underwent an esophagectomy and gastrectomy. The mean scores on all gastrointestinal symptoms were presented per time interval, stratified according to esophagectomy and gastrectomy. Generalized linear mixed models (GLMMs) were used to analyze the hierarchical structured

data as questionnaire data is nested within patients. GLMMs with unstructured covariance structure were used to assess changes in gastrointestinal symptoms over time and adjusted for age, sex, number of comorbidities, ASA score, clinical T and N stage, histology, type of esophagectomy/gastrectomy, neoadjuvant chemotherapy, neoadjuvant chemoradiation, adjuvant chemotherapy, and prolonged hospital stay (defined as the 75th percentile: > 14 days for esophagectomy and > 9 days for gastrectomy). The last four variables were included as time-dependent variables.

Additionally, the presence of gastrointestinal symptoms was dichotomized, similar to a previous study,[13] as follows: the response categories "quite a bit" and "very much" were grouped as severe functional complaint, and the response categories "not at all" and "a little" as no or mild functional complaint. The number of gastrointestinal symptoms present were summed up and categorized as 0, 1, ≥ 2. The proportional distributions of the number of gastrointestinal symptoms were compared between time intervals. Finally, to assess the impact of the number of gastrointestinal symptoms on HRQoL, functioning, the percentage of work impairment, and the percentage of impaired regular activities GLMMs were used again, with adjustment for the same variables as described above. P-values < 0.05 were considered statistically significant. Clinical relevance was based on the evidence-based guidelines for medium clinical relevant differences of the EORTC QLQ-C30[25] and the ten point difference defined by Osoba et al.[26] SAS/STAT® statistical software (version 9.4, SAS Institute, Cary, NC) was used.

RESULTS

Study Population

A total of 1709 patients who underwent an esophagectomy or gastrectomy and who were included in POCOP were selected from the NCR. After exclusions (Fig. 2), the final study population consisted of 1220 patients, of whom 961 (78.8%) underwent an esophagectomy and 259 (21.2%) a gastrectomy. Nearly all patients completed the questionnaire prior to resection (92%). Moreover, 35.5 and 35.9% of patients who underwent an esophagectomy or gastrectomy respectively, completed four questionnaires (Fig. 1 and Table 1). Patient, tumor, and treatment characteristics are presented in Table 1. The mean age of patients who underwent an esophagectomy or gastrectomy was, respectively, 65.2 ± 7.8 and 67.7 ± 9.6 years. In both groups, the majority were male, had an ASA score of II, and no comorbidities. A large majority (90.9%) of patients who underwent an esophagectomy received neoadjuvant chemoradiation, while 64.9% of the patients who underwent a gastrectomy received the neoadjuvant component and 38.6% the adjuvant component of perioperative chemotherapy. Among patients who underwent an esophagectomy, patients who completed two, three, four, or five questionnaires differed with regard to the number of comorbidities (0 comorbidities: 52, 50, 56, 65%; one comorbidity: 29, 33, 31, 20%; two comorbidities: 18, 12, 9, 10%, respectively, $p = 0.015$) and radicality of resection (radical resection: 89, 94, 95, 93%, respectively, $p = 0.023$). No other differences in patient, tumor, or treatment characteristics were present between patients who completed two, three, four, or five questionnaires. Among patients who underwent a gastrectomy, no differences were observed (data not shown).

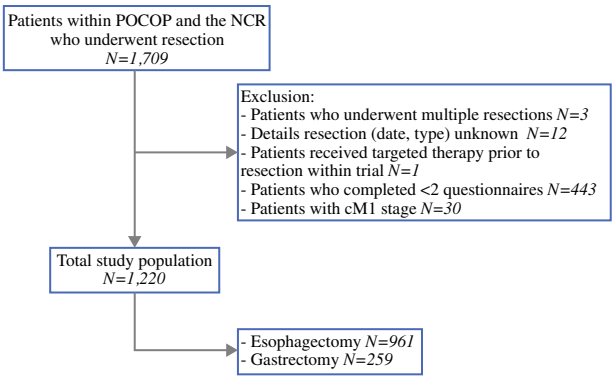

FIG. 2 Flowchart of the selection of the study population. *NCR* Netherlands Cancer Registry, *POCOP* Prospective Observational Cohort study of Oesophageal-gastric Cancer Patients

Gastrointestinal Symptom Scores over Time

The mean scores on all gastrointestinal symptoms per time interval, stratified according to esophagectomy and gastrectomy, are shown in Fig. 3. Clinically relevant higher scores were observed for diarrhea, appetite loss, and eating restrictions 0–3 after esophagectomy and gastrectomy, and for dry mouth, trouble with taste, trouble with coughing, and trouble talking at 0–3 after esophagectomy as compared with before resection. The majority of scores returned to or decreased below the scores reported before resection, except for diarrhea after esophagectomy. On multivariable analyses (Table 2), clinically relevant increases as compared with baseline were observed for diarrhea, appetite loss, and eating restrictions 0–3 after esophagectomy or gastrectomy. Additionally, clinically relevant decreases in dysphagia and odynophagia, and increases in dry mouth, trouble with coughing, and trouble talking were observed after esophagectomy. Moreover, 6–12 months after gastrectomy, clinically relevant decreases in trouble with taste were observed. Most clinically relevant differences were observed 0–3 after esophagectomy or gastrectomy as compared with prior to resection and were no longer different 9–12 after resection as compared with prior to resection.

TABLE 1 Baseline characteristics of patients who underwent an esophagectomy or gastrectomy

	Esophagectomy ($N=961$)		Gastrectomy ($N=259$)	
	N	%	*N*	%
Age				
< 60 years	203	21.1	47	18.1
60–74 years	668	69.5	148	57.1
≥ 75 years	90	9.4	64	24.7
Sex				
Male	782	81.4	156	60.2
Female	179	18.6	103	39.8
ASA classification				
ASA I	64	6.7	8	3.1
ASA II	602	62.6	150	57.9
ASA III	261	27.2	75	29
Unknown	34	3.5	26	10
Number of comorbidities				
No comorbidity	517	53.8	129	49.8
1 comorbidity	291	30.3	79	30.5
2 or more comorbidities	115	12	26	10
unknown	38	4	25	9.7
Histology				
Squamous cell carcinoma	157	16.3	–	–
Adenocarcinoma—intestinal	577	60	144	55.6
Adenocarcinoma—diffuse	108	11.2	89	34.4
Adenocarcinoma—other	108	11.2	24	9.3
Unknown	11	1.1	2	0.8
cT				
cT1–2	290	30.2	70	27
cT3–4	634	66	166	64.1
cTX	37	3.9	23	8.9
cN				
cN0	422	43.9	141	54.4
cN+	531	55.3	116	44.8
cNX	8	0.8	2	0.8
Type of resection				
Transhiatal esophagectomy	99	10.3		
Transthoracal esophagectomy—Ivor Lewis	600	62.4		
Transthoracal esophagectomy—McKneown	246	25.6		
Transthoracal esophagectomy—unknown type of anastomosis	16	1.7		
Partial gastrectomy			122	47.1
Total gastrectomy			137	52.9
Neoadjuvant chemotherapy				
No	899	93.5	91	35.1
Yes	62	6.5	168	64.9
Neoadjuvant chemoradiotherapy				
No	87	9.1	209	80.7
Yes	874	90.9	50	19.3

Table 1 (continued)

	Esophagectomy ($N=961$)		Gastrectomy ($N=259$)	
	N	%	*N*	%
Adjuvant chemotherapy				
No	918	95.5	159	61.4
Yes	43	4.5	100	38.6
Prolonged hospital stay				
Unknown	56	5.8	16	6.2
No	705	73.4	191	73.7
Yes	200	20.8	52	20.1
Number of completed questionnaires				
2	217	22.6	58	22.4
3	309	32.2	90	34.7
4	341	35.5	93	35.9
5	94	9.8	18	6.9

Estimates for cancer- and treatment-related characteristics are presented separately (Supplementary Table 2a and b) and show clinically relevant increases in trouble with taste after neoadjuvant chemo(radio)therapy and esophagectomy. Neoadjuvant chemoradiotherapy was also associated with dry mouth after esophagectomy. After gastrectomy, neoadjuvant chemo(radio)therapy was associated with trouble with taste, whereas total versus partial gastrectomy was associated with more eating restrictions (Supplementary Table 2b).

Number of Severe Gastrointestinal Symptoms over Time

Before resection, the proportion of patients reporting 0, 1, or ≥ 2 severe gastrointestinal symptoms was 58.9, 17.3, and 23.8% for patients who underwent an esophagectomy, and 53.6, 20.0, and 26.4% for patients who underwent a gastrectomy, respectively. The proportion of patients reporting 0, 1, or ≥ 2 severe gastrointestinal symptoms changed significantly over time (Fig. 4, $p < 0.0001$ for both). At 0–3 after resection compared with before resection, the proportion of patients reporting no severe gastrointestinal symptoms decreased from 58.9 to 28.8% after esophagectomy and from 53.6 to 43.7% after gastrectomy, while the proportion of patients reporting ≥ 2 severe gastrointestinal symptoms increased from 23.8 to 52.1% after esophagectomy and from 26.4 to 42.4% after gastrectomy. Although the proportions slowly returned to the values of prior to resection, the proportion of patients reporting one or more severe gastrointestinal symptoms at 9–12 months remained high, with 38.9 and 33.7% after esophagectomy and gastrectomy, respectively.

Over all time periods, trouble with coughing (21.6%), appetite loss (20.2%), and eating restrictions (14.0%) were the most reported severe gastrointestinal symptoms for patients who underwent an esophagectomy. For patients who underwent a gastrectomy, the most commonly reported severe gastrointestinal symptoms were appetite loss (22.2%), trouble with taste (15.8%), and dry mouth (14.4%). No trend was visible in combinations of gastrointestinal symptoms that often occurred, as almost all combinations were unique (results not shown).

Impact of Gastrointestinal Symptoms on HRQoL, Functioning, Work Productivity, and Daily Activities

The presence of ≥ 2 severe gastrointestinal symptoms was associated with clinically relevant lower scores on emotional functioning, role functioning, cognitive functioning, social functioning, and global QoL (Table 3). One hundred sixty-eight (17.5%) patients who underwent an esophagectomy and 32 (12.4%) patients who underwent a gastrectomy reported to be employed at time of completing the questionnaire. In the gastrectomy group, no analyses with regard to work productivity were performed as the numbers were too small. After esophagectomy, patients with > 2 gastrointestinal symptoms reported a work productivity impairment, which was, on average, 29.3% higher as compared with those without gastrointestinal symptoms ($p < 0.0001$). After esophagectomy, impairment in daily activities was 10.2% higher for patients with one gastrointestinal symptom and 19.4% higher for patients with ≥ 2 gastrointestinal symptoms compared with patients without gastrointestinal symptoms (Table 3, $p < 0.0001$). After gastrectomy, a 17.3 and 21.8% increase in impairment in daily activities was observed in patients with 1 and ≥ 2 gastrointestinal symptoms compared with patients without gastrointestinal symptoms, respectively ($p < 0.0001$).

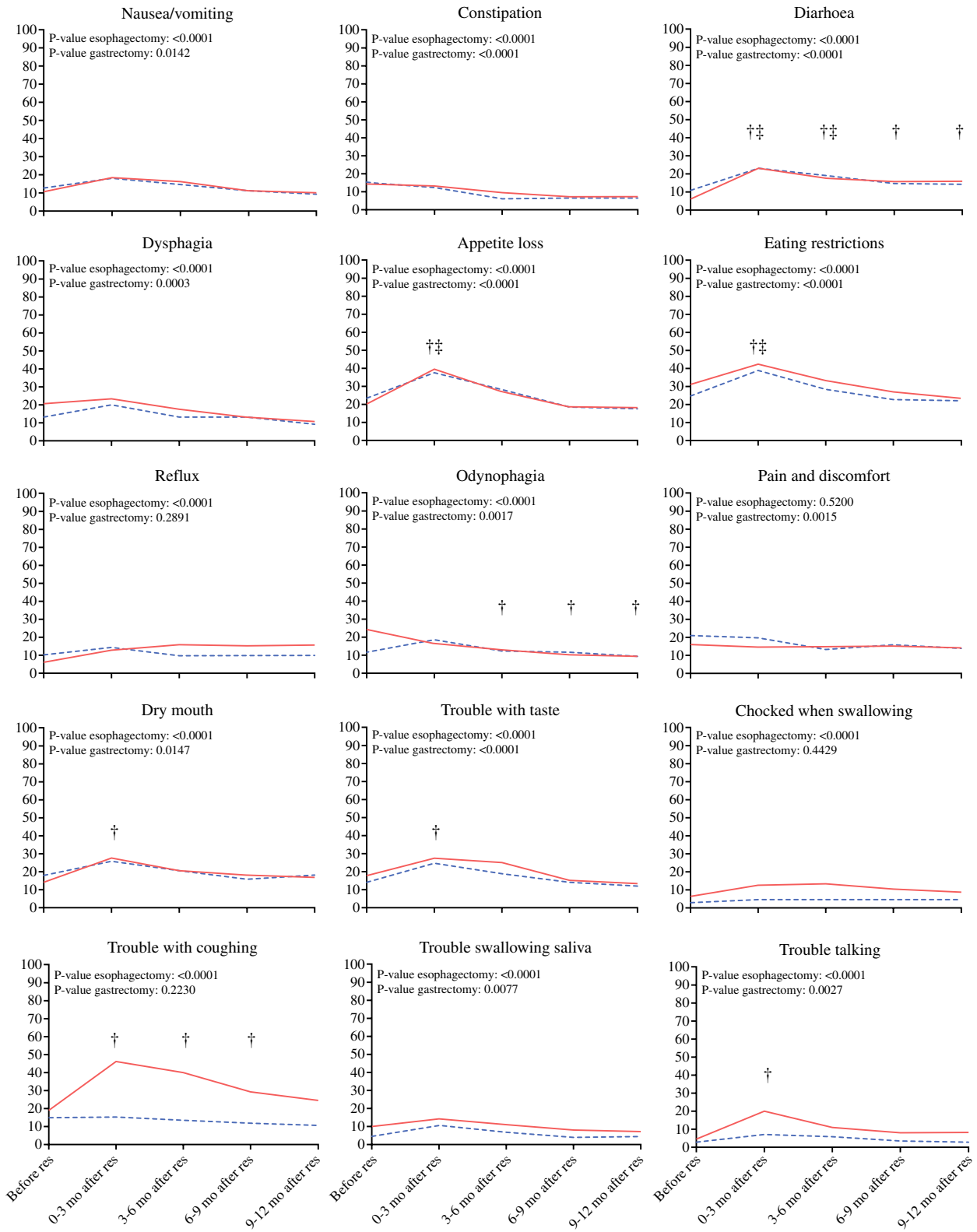

FIG. 3 Mean scores on all gastrointestinal symptoms over time, for patients who underwent an esophagectomy or gastrectomy. Continuous line: esophagectomy, dotted line: gastrectomy *Mo* months, *res* resection (esophagectomy or gastrectomy). *p*-Values indicate significant difference between time intervals. †Clinically relevant difference compared with before esophagectomy, ‡clinically relevant difference compared with before gastrectomy

TABLE 2 Generalized linear mixed models to assess changes in gastrointestinal symptoms over time

		Esophagectomy				Gastrectomy			
		Beta	SE	*P*-value	Clin relev.	Beta	SE	*P*-value	ClinRelev.
Nausea/vomiting	0–3 after versus pre-res	5.7798	1.1677	< 0.0001		3.1451	2.7263	0.2499	
	3–6 after versus pre-res	3.8541	1.0706	0.0003		−0.4709	2.568	0.8547	
	6–9 after versus pre-res	−0.6767	0.9988	0.4982		−2.7441	2.5477	0.2826	
	9–12 after versus pre-res	−2.0974	1.0611	0.0484		−4.9791	2.5093	0.0484	
Constipation	0–3 after versus pre-res	−3.6542	1.3173	0.0057		−5.5024	2.3404	0.0196	
	3–6 after versus pre-res	−7.8107	1.2278	< 0.0001		−10.1501	2.1835	< 0.0001	
	6–9 after versus pre-res	−9.4836	1.1801	< 0.0001		−9.467	2.3273	< 0.0001	
	9–12 after versus pre-res	−10.1947	1.3205	< 0.0001		−9.2377	2.2364	< 0.0001	
Diarhoea	0–3 after versus pre-res	17.2005	1.3066	< 0.0001	**	8.2871	2.969	0.0057	**
	3–6 after versus pre-res	11.9585	1.2372	< 0.0001	**	5.085	3.0129	0.0928	
	6–9 after versus pre-res	9.4658	1.2054	< 0.0001	**	0.681	2.6704	0.7989	
	9–12 after versus pre-res	8.7455	1.3412	< 0.0001	**	−0.4673	2.8577	0.8702	
Appetite loss	0–3 after versus pre-res	15.5517	1.7414	< 0.0001	**	14.9687	3.7027	< 0.0001	**
	3–6 after versus pre-res	2.2855	1.6153	0.1575		6.0988	3.7348	0.1039	
	6–9 after versus pre-res	−5.8757	1.5358	0.0001		−3.235	3.6625	0.378	
	9–12 after versus pre-res	−5.7924	1.6453	0.0005		−4.0841	3.5878	0.2562	
Dysphagia	0–3 after versus pre-res	2.455	1.344	0.0681		6.7216	2.5227	0.0083	
	3–6 after versus pre-res	−4.7432	1.268	0.0002		−0.9755	2.2858	0.67	
	6–9 after versus pre-res	−8.3807	1.2153	< 0.0001		−0.1112	2.3687	0.9626	
	9–12 after versus pre-res	−10.7357	1.2761	< 0.0001	**	−4.2601	2.2691	0.0617	
Eating restrictions	0–3 after versus pre-res	10.312	1.5384	< 0.0001	**	14.9304	3.282	< 0.0001	**
	3–6 after versus pre-res	0.3326	1.4976	0.8243		4.0445	3.1751	0.204	
	6–9 after versus pre-res	−5.3493	1.4487	0.0002		0.05986	3.183	0.985	
	9–12 after versus pre-res	−8.5958	1.5623	< 0.0001		−1.5149	3.2048	0.6369	
Reflux	0–3 after versus pre-res	6.3378	1.1338	< 0.0001		4.2151	2.8215	0.1366	
	3–6 after versus pre-res	8.7099	1.1084	< 0.0001		0.8551	2.6902	0.7509	
	6–9 after versus pre-res	8.2111	1.1206	< 0.0001		−0.02766	2.6464	0.9917	
	9–12 after versus pre-res	9.0993	1.2414	< 0.0001		−1.02	2.6023	0.6955	
Odynophagia	0–3 after versus pre-res	−8.0505	1.3292	< 0.0001		9.0042	2.6135	0.0007	
	3–6 after versus pre-res	−11.6016	1.3102	< 0.0001	**	3.0628	2.2619	0.1771	
	6–9 after versus pre-res	−13.8233	1.2417	< 0.0001	**	2.684	2.3008	0.2446	
	9–12 after versus pre-res	−15.0295	1.3233	< 0.0001	**	0.1629	2.3472	0.9447	
Pain and discomfort	0–3 after versus pre-res	−1.8166	1.2613	0.1501		−3.0005	2.761	0.2783	
	3–6 after versus pre-res	−1.1481	1.2455	0.3569		−8.6511	2.5164	0.0007	
	6–9 after versus pre-res	−1.0193	1.2455	0.4133		−7.3244	2.6713	0.0066	
	9–12 after versus pre-res	−2.0823	1.363	0.1269		−8.6016	2.7713	0.0022	
Dry mouth	0–3 after versus pre-res	10.4553	1.5151	< 0.0001	**	−0.1537	3.1095	0.9606	
	3–6 after versus pre-res	2.0728	1.3748	0.132		−1.5835	3.1785	0.6188	
	6–9 after versus pre-res	−0.1323	1.3756	0.9234		−7.8534	2.9374	0.0081	
	9–12 after versus pre-res	−1.2719	1.5212	0.4033		−5.5905	3.2554	0.0873	
Trouble with taste	0–3 after versus pre-res	4.251	1.6	0.008		2.2832	3.64	0.5311	
	3–6 after versus pre-res	−2.1438	1.5162	0.1577		−2.9028	3.6214	0.4236	
	6–9 after versus pre-res	−6.4052	1.465	< 0.0001		−11.5548	3.4687	0.001	**
	9–12 after versus pre-res	−7.8572	1.5198	< 0.0001		−12.7946	3.3649	0.0002	**
Trouble swallowing saliva	0–3 after versus pre-res	3.2556	1.3473	0.0159		5.5818	2.3979	0.0208	
	3–6 after versus pre-res	−0.8668	1.271	0.4954		1.6746	2.0909	0.424	
	6–9 after versus pre-res	−3.1425	1.2429	0.0116		−1.5988	2.003	0.4256	
	9–12 after versus pre-res	−3.7688	1.3322	0.0048		0.5546	2.3559	0.8141	

Table 2 (continued)

		Esophagectomy				Gastrectomy			
		Beta	SE	*P*-value	Clin relev.	Beta	SE	*P*-value	ClinRelev.
Choked when swallowing	0–3 after versus pre-res	6.2444	1.0901	< 0.0001		0.004542	1.2899	0.9972	
	3–6 after versus pre-res	6.9162	1.0609	< 0.0001		0.7167	1.4083	0.6113	
	6–9 after versus pre-res	3.6578	0.9992	0.0003		0.05126	1.3513	0.9698	
	9–12 after versus pre-res	2.9824	1.1168	0.0077		−0.02473	1.4276	0.9862	
Trouble with coughing	0–3 after versus pre-res	27.1871	1.5364	< 0.0001	**	0.715	2.4651	0.7721	
	3–6 after versus pre-res	17.8011	1.46	< 0.0001	**	−2.1363	2.3623	0.3668	
	6–9 after versus pre-res	8.718	1.4101	< 0.0001		−3.5428	2.3374	0.131	
	9–12 after versus pre-res	4.2158	10.545	0.0065		−6.0568	2.808	0.0321	
Trouble talking	0–3 after versus pre-res	14.8702	1.2934	< 0.0001	**	3.5914	1.4652	0.015	
	3–6 after versus pre-res	4.8622	1.0275	< 0.0001		3.4774	1.4749	0.0192	
	6–9 after versus pre-res	2.681	0.9819	0.0065		0.7874	1.2446	0.5276	
	9–12 after versus pre-res	2.9038	1.1077	0.0089		−0.2838	1.162	0.8073	

SE standard error, *Clin. Relev.* clinically relevant difference, *Mo* months, *res* resection (esophagectomy or gastrectomy). *Analysis adjusted for age, comorbidity, histology, cT, cN, ASA, type of resection, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and prolonged hospital stay. **Clinically relevant difference. Estimates for type of resection, neoadjuvant chemo(radio)therapy, adjuvant chemotherapy, and prolonged hospital stay are presented separately in Supplementary Table 2

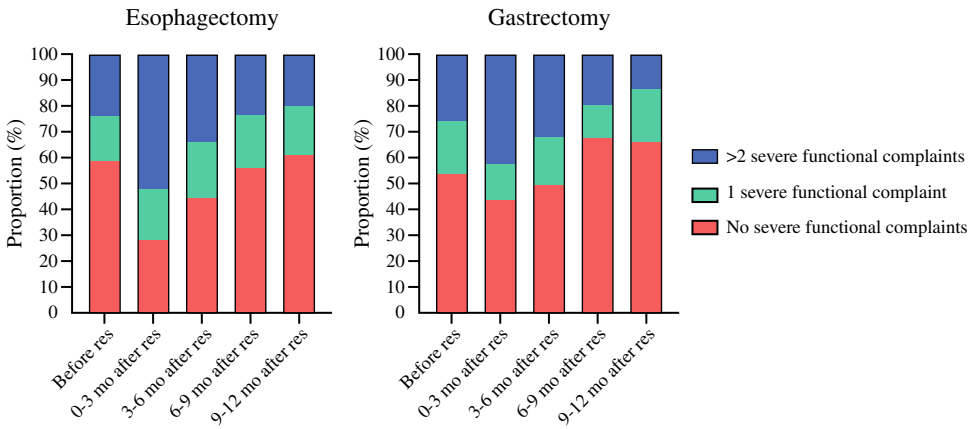

FIG. 4 Number of severe gastrointestinal symptoms over time, for patients who underwent an esophagectomy or gastrectomy. Red bar: no severe functional complaints, green bar: 1 severe functional complaint; blue bar: ≥ 2 severe functional complaints. *Mo* months, *res* resection (esophagectomy or gastrectomy)

DISCUSSION

This study shows that gastrointestinal symptoms changed significantly over time, with highest scores at 0–3 after esophagectomy or gastrectomy, while at 9–12 after resection, scores were comparable to baseline scores, indicating a natural recovery process after major surgery. However, some gastrointestinal symptom scores remained high up to 1 year after resection, with the most frequently reported gastrointestinal symptoms after esophagectomy being trouble with coughing, appetite loss, and eating restrictions, and after gastrectomy appetite loss, trouble with taste, and dry mouth. The proportion of patients that reported one or more severe gastrointestinal symptoms remained high 9–12 after esophagectomy and gastrectomy, at 38.9 and 33.7%, respectively. Finally, two or more gastrointestinal symptoms were associated with clinically relevant deteriorations in HRQoL, functioning, work productivity, and impairment in daily activities.

The current study shows that the presence of gastrointestinal symptoms reached a peak at 0–3 after esophagectomy or gastrectomy but remained present during the total first year after esophagectomy and gastrectomy with scores at 9–12 comparable to before resection, independent of (neo) adjuvant treatment. Where the symptoms before esophagectomy or gastrectomy are caused by the tumor, the symptoms that remain comparable to baseline are likely attributable to anatomical changes after resection. Additionally, malabsorption syndromes including exocrine pancreatic insufficiency (EPI), small intestinal bacterial overgrowth (SIBO), and bile acid malabsorption (BAM), which are known to be prevalent after an esophagectomy[27] or gastrectomy,[28,29] could also

TABLE 3 Generalized linear mixed models to assess the impact of the number of severe gastrointestinal symptoms on HRQoL, functioning, work productivity, daily activities, and weight loss

	Esophagectomy						Gastrectomy					
	1 versus 0 gastrointestinal symptoms			≥ 2 versus 0 gastrointestinal symptoms			1 versus 0 gastrointestinal symptoms			≥ 2 versus 0 gastrointestinal symptoms		
	Beta	SE	*P*-value	Beta	SE	*P*-value	Beta	SE	*P*-value	Beta	SE	*P*-value
HRQoL												
Physical functioning	−3.9922	0.6207	< 0.0001	−11.9138	0.6147	< 0.0001	−4.9486	1.1893	< 0.0001	−10.9075	1.1795	< 0.0001
Emotional functioning	−4.9297	0.6913	< 0.0001	−12.3744	0.6703	< 0.0001**	−5.2436	1.2686	< 0.0001	−10.903	1.2446	< 0.0001**
Role functioning	−8.2424	1.039	< 0.0001	−21.9941	0.9991	< 0.0001**	−11.979	1.9525	< 0.0001	−22.4011	1.9096	< 0.0001**
Cognitive functioning	−4.4953	0.7017	< 0.0001	−9.4827	0.6824	< 0.0001**	−2.1283	1.3093	0.1054	−9.9979	1.2572	< 0.0001**
Social functioning	−6.5292	0.919	< 0.0001	−18.6335	0.8744	< 0.0001**	−9.2711	1.7962	< 0.0001	−17.7194	1.7443	< 0.0001**
Global quality of life	−6.8175	0.6669	< 0.0001	−15.873	0.6404	< 0.0001**	−5.2135	1.2387	< 0.0001	−16.2103	1.1943	< 0.0001**
Work productivity												
Work impairment*	6.2675	4.3858	0.1551	29.3014	4.8402	< 0.0001	NA			NA		
Daily activity impairment	10.1999	1.4005	< 0.0001	19.4384	1.3039	< 0.0001	17.2679	2.7647	< 0.0001	21.8314	2.5124	< 0.0001

SE standard error, *HRQoL* health-related quality of life. Analysis adjusted for age, comorbidity, histology, clinical T, clinical N, ASA, type of resection, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and prolonged hospital stay. *$n = 168$ for esophagectomy. NA: not applicable, the number of currently employed patients who underwent a gastrectomy was too small ($N = 32$). **clinically relevant difference

cause the symptoms. In extension, a previous study showed that the digestive symptom burden in the first year was similar to the burden after 1–5 years,[12] indicating that gastrointestinal symptoms do not represent a temporary problem.

A previous study found reduced scores in the first weeks after gastrectomy, but similar or improved scores after 1 year.[30] After total gastrectomy, scores on physical functioning, emotional functioning, and functional health were worse compared with gastrectomy.[30] Regarding gastrointestinal symptoms, patients reported more dysphagia and eating restrictions after total versus partial gastrectomy.[31] These results were similar to our results, although the difference in dysphagia did not reach the threshold for clinical relevance in the current study. Additionally, another study with similar results for patients with esophageal or gastro–esophageal junction cancer who underwent an esophagectomy also showed that postoperative complications were not associated with decreased short- or long-term HRQoL.[32] Finally, although we observed more issues with taste after neoadjuvant chemoradiotherapy, the CROSS trial found that neoadjuvant chemoradiotherapy had no effect on postoperative HRQoL compared with surgery alone.[33] Impairments in HRQoL are likely attributable to gastrointestinal symptoms, which underlines the importance of early recognition and management of gastrointestinal symptoms.

In line with our findings, a systematic review also found that increased gastrointestinal symptom frequency and severity following gastrectomy negatively impacted HRQoL.[30] For patients who underwent an esophagectomy, digestive symptoms were found to have a strong influence on all domains of HRQoL except physical functioning,[12] similar to our results. Emotional and social functioning were mostly affected,[12] while in our study, role and social functioning were mostly affected.

Gastrointestinal symptoms were also associated with impairments in daily life, which is in line with a qualitative study among patients that found that different gastrointestinal symptoms such as eating difficulties and diarrhea fundamentally change and threaten patients' social relationships and activities in the first year after esophageal cancer surgery.[20] Furthermore, gastrointestinal symptoms were previously shown to have prognostic value for overall survival. The presence of two different symptom clusters 6 months after surgical treatment of esophageal cancer have been shown to be negatively associated with 5 year survival, with an approximately 40% increased risk of mortality, even after adjusting for other known prognostic factors.[34] The first cluster was characterized by symptoms such as dry mouth, problems with taste, coughing, and reflux. The second cluster entailed symptoms related to eating, such as appetite loss, dysphagia, eating difficulties, and nausea/vomiting. Assessing the association between gastrointestinal symptoms and overall survival was not in the scope of this study.

Although follow-up care every 3 months during the first year after esophagectomy or gastrectomy is aimed at gastrointestinal symptoms, their management and treatment is not standardized in The Netherlands. Guidelines for the treatment of gastrointestinal symptoms have been developed previously, including, with the exception of eating restrictions, the most frequently reported severe gastrointestinal symptoms in our study (trouble with coughing, appetite loss, trouble with taste, and dry mouth).[35,36] Patients are concerned about a large number of symptoms after resection for esophageal or gastric cancer, with heartburn and early satiety as the most frequently reported symptoms deemed important to their quality of life.[37] Recently, management of gastrointestinal symptoms was protocolized by one expert hospital to offer an unambiguously method for the diagnosis and treatment of each symptom.[38] This is a multidisciplinary protocol developed by specialized nurses and specialists from the departments of surgery, gastroenterology, anesthesiology, dietetics, pharmacy, and internal medicine. To offer the protocol a structural place in the care pathway and discuss it multidisciplinary, a monthly multidisciplinary team meeting is organized. Patients with severe gastrointestinal symptoms are discussed during this meeting. Additionally, medical information from these patients are prospectively collected with the aim of evaluating the treatments and optimizing the protocol if necessary.[38] Furthermore, specific consultation hours for patients with gastrointestinal symptoms were introduced in some hospitals in The Netherlands. The results from the current study underline the importance of these initiatives, which might benefit from further standardization to provide optimal care for all patients. Moreover, future initiatives should focus on real-time feedback of patient-reported outcomes in clinical practice to ascertain timely discussion of and, if needed, intervention on gastrointestinal symptoms.

Our results add relevant information to the limited literature on this topic. A specific strength of this study is its longitudinal design that allowed us to investigate changes in gastrointestinal symptoms over time. This study also has some limitations: we could not fully correct for postoperative complications, instead we used prolonged hospital stay as a proxy for postoperative complications. In addition, we had no information on EPI, SIBO, and BAM. Moreover, some selection bias might have occurred as patients who respond to questionnaires are in general younger, less frail, and have a better prognosis,[39] which possibly results in an underestimation of the currently reported gastrointestinal symptoms and outcomes. Similarly, this applies to the response rate over time, as younger and less frail patients are more likely to continue questionnaire completion over time. Finally, information on cancer recurrence was unknown, thus whether persistent symptoms were indicative of recurrence is also unknown.

In conclusion, gastrointestinal symptoms are frequently reported after esophagectomy and gastrectomy, and several symptoms last in the first year after resection. Moreover, having gastrointestinal symptoms severely impacts HRQoL, functioning, productivity in work, and daily activities. These results highlight their importance for high-quality survivorship. Currently, a standardized protocol on treatment of gastrointestinal symptoms is being evaluated in one hospital in The Netherlands, which will contribute to future research focusing on the improvement of gastrointestinal symptoms after esophagectomy and gastrectomy.

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