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Long-Term Quality of Life Following Endoscopic Therapy Compared to Esophagectomy for Neoplastic Barrett's Esophagus

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Abstract

Introduction—Endoscopic therapy (ET) and esophagectomy result in similar survival for Barrett's esophagus (BE) with high-grade dysplasia (HGD) or T1a esophageal adenocarcinoma (EAC), but the long-term quality of life (QOL) has not been compared.

Aims—We aimed to compare long-term QOL between patients who had undergone ET versus esophagectomy.

Methods—Patients were included if they underwent ET or esophagectomy at the University of Michigan since 2000 for the treatment of HGD or T1a EAC. Two validated survey QOL questionnaires were mailed to the patients. We compared QOL between and within groups (ET = 91, esophagectomy = 62), adjusting for covariates.

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Results—The median time since initial intervention was 6.8 years. Compared to esophagectomy, ET patients tended to be older, had a lower prevalence of EAC, and had a shorter duration since therapy. ET patients had worse adjusted physical and role functioning than esophagectomy patients. However, the adjusted odds ratio (OR) of having symptoms was significantly less with ET for diarrhea (0.287; 95% confidence interval [CI] = 0.114, 0.724), trouble eating (0.207; 0.0766, 0.562), choking (0.325; 0.119, 0.888), coughing (0.291; 0.114, 0.746), and speech difficulty (0.306; 0.0959, 0.978). Amongst the ET patients, we found that the number of therapy sessions and need for dilation were associated with worse outcomes.

Discussion—Multiple measures of symptom status were better with ET compared to esophagectomy following treatment of BE with HGD or T1a EAC. We observed worse long-term physical and role functioning in ET patients which could reflect unmeasured baseline functional status rather than a causal effect of ET.

Keywords

Endoscopic mucosal resection; Radiofrequency ablation; Quality of life

Introduction

Barrett's esophagus (BE) is defined as the replacement of normal esophageal squamous epithelium with columnar mucosa and histological evidence of intestinal metaplasia [1]. It is a known precursor to the development of esophageal adenocarcinoma (EAC) and it is believed that patients with BE develop EAC in a pathway through dysplasia [1–3]. The risk of EAC is highest among patients with high-grade dysplasia (HGD) [1]. Patients who develop HGD or early EAC can undergo endoscopic therapy (ET) (including radiofrequency ablation (RFA), endoscopic mucosal resection (EMR), and/or cryotherapy) or esophagectomy as curative treatment [2].

Over the past 20 years, ET techniques have become the preferred treatment strategy for HGD and early EAC given the morbidity and mortality associated with esophagectomy [4]. The overall incidence of postoperative complications after esophagectomy are varied and can range anywhere between 20 and 80% depending on the age, comorbid disease, and surgical procedural volume at the center [5–7]. In contrast, ET techniques, such as EMR, RFA, and cryotherapy, provide success rates that are comparable to esophagectomy but with fewer complications. In one systematic review, complete eradication of HGD or early EAC occurred in 95% of patients undergoing EMR and in 92% of patients undergoing RFA [8]. Serious complications of ET are rare but can include bleeding, perforation, and stricture formation [9, 10]. ET generally requires multiple treatments with surveillance endoscopies after eradication is achieved. However, despite this, EMR/RFA is more cost-effective than esophagectomy for patients with HGD and T1a EAC across all age groups, and ET has become the standard of care for T1a cancers [4, 11]. For T1b EAC, whether to perform esophagectomy or attempt ET is less clear, and depends on patient age and comorbidities, as ET is less effective in T1b than in T1a EAC [11]. Another factor that should be considered in that decision is the long-term quality of life with esophagectomy or ET.

Though the cancer outcomes and complications of ET and esophagectomy have been described, the long-term health related quality of life (HR-QOL) has been inadequately compared between the two strategies. Among patients who have undergone an esophagectomy, gastrointestinal symptoms such as dysphagia, reflux, dumping syndrome, and delayed gastric emptying are common with < 20% of patients reporting normal digestive function after esophagectomy [12, 13]. Furthermore, poor HR-QOL scores both before surgery and 6 months postoperative were found to be predictive of survival, with poor function and symptoms predictive of increased mortality [14–16]. A diagnosis of Barrett's esophagus itself is associated with decreased HR-QOL. A systematic review on the HR-QOL of patients with BE found that patients feel psychologically burdened by the threat of developing EAC, which negatively affects their overall QOL [17]. Among BE patients with dysplasia randomized to RFA treatment versus sham treatment in the AIM dysplasia trial, RFA was associated with improvement in disease-specific HR-QOL as compared to patients randomized to the sham treatment arm, mainly due to the perceived decrease in the risk of cancer [18]. Similarly, a recent study showed that patients treated with low-grade dysplasia (LGD) who received ablation had fewer concerns and less threatening view of their condition compared to those undergoing endoscopic surveillance [19]. To date, we are unaware of any studies directly comparing long-term HR-QOL in patients undergoing endoscopic therapy versus those undergoing esophagectomy.

We hypothesized that the HR-QOL of BE patients who have undergone ET is better than in patients who have undergone esophagectomy. We also hypothesized that among ET patients, HR-QOL of BE patients is negatively affected by complications, such as stricture formation and with the number of procedures required to achieve remission. Since so few patients with T1b EAC undergoing ET have had long term follow to assess HR-QOL, we designed our study to compare long-term HR-QOL associated with ET or esophagectomy among patients with HGD or T1a EAC. Such information could be useful for patients with T1b EAC considering esophagectomy versus attempt at ET.

Methods

Study Design

Survey instruments were mailed to patients who had undergone esophageal ET or esophagectomy for neoplastic BE with HGD or T1a EAC at the University of Michigan from 2000 to 2016. Patients were identified by using the University of Michigan Barrett's Esophagus Registry (UMBER) and the University of Michigan Esophagectomy Registry (UMER). Patients who had undergone both ET and esophagectomy for treatment were classified as having undergone esophagectomy. Study protocol was approved by the University of Michigan human research institutional review board.

Participants

Patients were excluded if they underwent neoadjuvant/adjuvant chemotherapy or radiation as part of their primary treatment, were lost to follow-up, did not have at least one endoscopy after ET demonstrating resolution of neoplasia, or who had died since their treatment. In addition, patients who had received esophagectomy or ET for more advanced disease (T1b

EAC or worse) were excluded. The rationale for excluding T1b EAC was that very few cases of ET were performed to treat patients with T1b making it impossible to evaluate this subset. Baseline demographics on patients were obtained from chart review at the time of the esophagectomy or initial endoscopic therapy, including age, gender, endoscopic, pathology findings, and Charlson Comorbidity Index (CCI). For ET patients, we abstracted the total number of endoscopic therapy sessions and stenoses requiring dilations which represented ET-related complications.

Quality of Life Questionnaires

Two validated survey questionnaires were mailed to the patient's home address: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 v3.0) which is a generic cancer quality of life instrument, along with the esophageal cancer disease-specific module Oesophageal-18 (OES-18) as previously reported and validated [20–25]. The QLQ-C30 uses a 4-point Likert scale and includes 5 functional scales (physical function, role function, emotional function, cognitive function, and social function), 1 global health scale, and 3 symptom scales (fatigue, nausea, and pain). There are 6 single-item questions regarding dyspnea, insomnia, appetite, constipation, diarrhea, and financial worries which are evaluated with a 4-point Likert scale. The OES-18 includes 18 items addressing areas such as dysphagia, swallowing, choking, eating, reflux, taste, abdominal pain, odynophagia, dry mouth, cough, and voice difficulties. In addition to the option of completing and returning paper questionnaires, subjects were given the option to complete the questionnaires online through REDCap (Research Electronic Data Capture, Nashville, TN), which offered access to the surveys via a secured website.

The raw scores of both questionnaires were linearly converted to a 0–100 scale for consistency of interpretation. For example, a scale with raw scores ranging from 1 to 4 (with 4 being perfect) would be converted to scaled scores of 0, 33, 66, and 100. A higher score in the functional and global health scales on the EORTC QLQ-C30 indicates a better QOL, whereas, a higher score in the symptom scales on EORTC QLQ-C30 and OES-18 indicates a worse QOL.

Statistical Analysis

Several different regression models were used. First, we used linear regression to estimate the effect of ET versus esophagectomy on functional and symptom domain scores (treated as continuous variables). Second, we performed logistic regression to estimate the same effects, categorizing the functional and symptom scores into abnormal or normal scores. In addition, among patients receiving ET, we performed linear and logistic regression for the effects of total number of therapy sessions (dichotomized at the median) or need for dilation on the outcomes for quality of life and symptom scores. For all models, we adjusted for age, CCI, and pathologic diagnosis (HGD or T1a EAC). Additionally, we adjusted for years since esophagectomy or first ET considering that the practice pattern has shifted toward favoring endoscopic therapy within the past 10 years. All analyses were performed using R 3.5.1 (Vienna, Austria) and the *tidyverse* package.

Results

Subject Description

Two hundred thirty-nine patients who had undergone ET and 153 who had undergone esophagectomy met screening criteria for study recruitment. Of these, the study team was informed of the deaths of 25 ET patients (10.5%) and 15 esophagectomy patients (9.8%) that were not previously recorded in the electronic medical record, and 17 ET (7.1%) and 15 esophagectomy (9.8%) patients had undeliverable addresses (Fig. 1). After excluding deceased patients and undeliverable addresses, 91 of 197 ET patients (46.2%) and 62 of 123 esophagectomy patients (50.4%) returned the study questionnaires which constituted the cohort used for analysis purposes (Fig. 1). Baseline demographic and clinical characteristics of patients who returned the questionnaires are listed in Table 1, with an overall median follow-up of 6.8 years after initial intervention (date of first EMR in the ET group or date of surgery in the esophagectomy group). The ET group was significantly older at time of diagnosis, had a shorter duration since therapy, and a lower prevalence of EAC compared to the esophagectomy group. There was no significant difference in comorbidity score amongst the two groups. The adjusted odds of a few functional scores were associated with advancing age (physical functioning, cognitive functioning) and higher CCI (role functioning, social functioning). HGD compared to T1a EAC was associated with some symptom scores being abnormal (fatigue, nausea/vomiting, insomnia, reflux, trouble with taste). None of the scores were associated with time since procedure. Gender was not significantly associated on univariate logistic regression with any of the scores (p values all > 0.10), so it was not included in multivariable models considering that the overall gender distribution between the ET and esophagectomy groups was also similar.

Functional and Global Health Outcomes in ET Versus Esophagectomy

Physical, role (assesses limitations in work or other activities), emotional (assesses worry, anxiety, and other mood changes), cognitive (assesses difficulty concentrating and forgetfulness), and social (assesses for interferences with family life or other social activities) functioning were assessed through the QLQ-C30. A score of 100 indicates perfect functioning, with any score less than 100 defined as abnormal. For the functional outcomes, the greatest proportion of ET patients with reported abnormal scores was in the physical sub-category at 69% (median score = 86.7; interquartile range [IQR] = 63.3, 100.0) and cognitive sub-category at 69% (median = 83.3; IQR = 66.7, 100.0). For the esophagectomy group, the greatest proportion of abnormal scores was in the emotional sub-category at 64% (median = 91.7; IQR = 66.7, 100.0). In the ET group, the lowest proportion of patients with abnormal scores was in the social sub-category at 48% (median = 100.0; IQR = 66.7, 100.0). In the esophagectomy group, the lowest was in the role functioning sub-category at 34% (median = 100.0; IQR = 70.8, 100.0). Global health score was abnormal in 91% (median = 75.0; IQR = 58.3, 83.3) of ET patients and 79% (median = 75.0; IQR = 66.7, 89.6) of esophagectomy patients. The ET group was associated with worse (lower) physical and role functioning scores compared to the esophagectomy group, including after adjusting for age, comorbidity, pathologic diagnosis, and time since initial therapy (Table 2). There was no difference in other domains of functional status, and no difference in the global health status scores.

Symptom Outcomes in ET Versus Esophagectomy

Several symptoms were assessed through the QLQ-C30 and OES-18. A score of 0 indicated complete lack of symptoms, with any score greater than 0 defined as abnormal. For both the ET and esophagectomy groups, the symptom with the greatest proportion of abnormal scores was in the fatigue sub-category at 78% (median = 22.2; IQR = 11.1, 44.4) and 76% (median = 22.2; IQR = 11.1, 33.3), respectively. For both the ET and esophagectomy groups, the symptom with the lowest proportion of reported abnormal scores was in the speech difficulty sub-category at 16% (median = 0.0, IQR = 0.0, 0.0) and 20% (median = 0.0; IQR = 0.0, 0.0), respectively. After adjusting for the same covariates as the functional outcomes, the ET group was associated with better (lower) scores compared to the esophagectomy group in regards to diarrhea, eating difficulty, choking, coughing, and speech difficulty (Tables 3 and 4). No differences between the two groups were found in the other symptom sub-scores.

Effects of Endoscopy on Functional and Symptom Outcomes

Within the ET group, we evaluated the effect on HR-QOL of the number of therapy sessions (stratified at the median number of sessions, 3) and need for endoscopic dilation (24.1% of ET patients), adjusted for age, comorbidity, pathologic diagnosis, and time since initial therapy. The odds of having an imperfect social functioning score in patients who had 3 or more therapy sessions was greater than 3 times the odds in those with 1 or 2 sessions (odds ratio [OR] = 3.71; 95% confidence interval [CI] = 1.33, 10.4, $p = 0.01$, Supplementary Table 1). Patients who underwent more ET sessions had less trouble with taste, but there were no other associations with the number of ET sessions (Supplementary Tables 2 and 3). ET patients who required dilation had greater odds of having an imperfect cognitive functioning score (OR = 4.40; 95% CI = 1.09, 17.9, $p = 0.04$, Supplementary Table 4), or dry mouth score (OR = 3.58; 95% CI = 1.15, 11.1, $p = 0.03$, Supplementary Tables 5 and 6) than ET patients who did not require dilation. We did not specifically evaluate QOL in patients who had significant bleeding requiring additional care (such as blood transfusion) or perforation since the event rate was very low (1% for each).

Discussion

Esophageal cancer is known to originate from Barrett’s esophagus with greater rates of malignant transformation in the setting of high-grade dysplasia [1]. Historically the only form of effective treatment for early esophageal cancer was esophagectomy. However, over the past 20 years endoscopic therapies for HGD and early EAC have become standard of care [1, 26, 27].

Though the efficacy of ET and esophagectomy for treatment of HGD and early EAC has been well described, there are scant data with head to head comparison of these modalities in relation to HR-QOL. To our knowledge, the only prior direct comparison was by Rosmolen, et al. They found a decreased negative impact of mental and physical QOL and symptomatology in patients treated with ET compared to esophagectomy, though the worry for cancer recurrence was significantly greater in patients treated with ET [28]. However, the greatest duration of follow-up length in Rasmolen’s study was only 6 months after therapy,

and the early surgical group consisted of patients with T2 cancer which are more advanced than early esophageal cancer most amenable to endoscopic therapy. To our knowledge, we are reporting the first study comparing the long-term HR-QOL between ET and esophagectomy for BE with HGD or early cancer. Our study has a median follow-up of nearly 7 years.

BE patients who develop dysplasia experience decreases in QOL primarily due to psychological distress and worry, which seems to be mitigated by successful treatment as has been previously described [17]. Although we did not use tools to specifically measure worry of cancer, our findings suggest that in the long-term, sense of worry (best assessed in our study by emotional functioning sub-score) appears similar, regardless of the type of treatment modality that is used. However, we found patient reported physical and role functioning was worse in those treated with ET compared to esophagectomy. The role functioning finding could be explained by its association with worse comorbidity that may have led to selection of ET over esophagectomy. In terms of physical functioning, it is not clear if this is a causal effect of ET or if due to unmeasured frailty at baseline that may have led to selection of which sort of treatment patients underwent. We did not find any differences in the remainder of the functional (emotional, cognitive, or social) and global health outcomes.

In contrast to the functional and global health outcomes, we found ET to be favorable to esophagectomy in several symptom outcomes which included diarrhea, eating difficulties, choking, coughing, and speech difficulties. Given the number of complications, previous studies have examined HR-QOL in esophagectomy patients and found that there are long-term impacts on QOL with recovery taking upwards of three years [14, 29–34]. Our findings suggest that in comparison to ET, symptom abnormalities identified in our study following esophagectomy for treatment of HGD or early EAC may be long-lasting.

Among ET patients, we found that patients with greater number of therapy sessions and need for dilation had a greater chance of reporting a few worse outcomes. Amongst the findings in the ET sub-group, we found that those requiring greater number of therapy sessions experienced worse social functioning. Previous studies found that BE patients perceived endoscopy burdensome due to increased costs to the patients and increased health care use; this might contribute to our findings, but here the social functioning was assessed years after completion of endoscopic therapy, so the burden of endoscopy may not be the only or most important cause [17]. In addition, among those undergoing ET, patients requiring dilation were more likely to have dry mouth or worse cognitive functioning; we hypothesize that those are more likely to be cofactors for esophageal stenoses being perceived as clinically significant rather than the sequelae of the stenoses or the ET.

Our study does have some limitations. Most importantly, subjects were recruited years after completing therapy, and the response rates were only approximately 50%, so there is potential for selection and recall biases. However, we found similar response rates in both groups, suggesting no systematic bias differentially affecting likelihood of responding from one group. Additionally, a large and similar proportion of the non-responders in each group had died. Additionally, there may have been unmeasured confounders, particularly in

comorbid diseases. Comorbidity was measured by the Charlson Comorbidity Index at the time of the initial diagnosis of dysplasia or EAC. But this may incompletely capture baseline functional status, and patients with worse functional status at baseline may have been more likely to undergo ET than esophagectomy, and could have therefore biased our observation that long-term physical functioning status was worse in patients undergoing ET. Although there is biologic plausibility to having worse symptoms after esophagectomy, there is also a possibility that some of the differences we found in our study were due to chance related to testing of multiple quality of life domains.

In summary, to our knowledge, our study included the largest number of patients to date comparing HR-QOL in ET to esophagectomy for the treatment of BE complicated by HGD or early EAC, and the first to provide long-term follow-up data. Our findings show multiple symptom status measures are associated with better symptom burden following ET compared to esophagectomy, supporting the recommendations of published guidelines [1, 26, 27]. We observed worse long-term physical and role functioning in ET patients, but this could be due to unmeasured baseline functional status rather than a causal effect of ET. Our findings could be useful in shared decision making with patients considering treatment options for Barrett's esophagus with high grade dysplasia or early adenocarcinoma. In particular, patients with T1b submucosal involvement could consider applying this information to aid in their decision between esophagectomy versus attempt at ET.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BE	Barrett's esophagus
CCI	Charlson comorbidity index
EMR	Endoscopic mucosal resection
ET	Endoscopic therapy
EORTC QLQ-C30	European organisation for research and treatment of cancer quality of life questionnaire
EAC	Esophageal adenocarcinoma
HR-QOL	Health-related quality of life
HGD	High-grade dysplasia
IQR	Interquartile range

LGD	Low-grade dysplasia
OR	Odds ratio
OES-18	Oesophageal-18
RFA	Radiofrequency ablation
UMBER	University of Michigan Barrett's Esophagus Registry
UMER	University of Michigan Esophagectomy Registry

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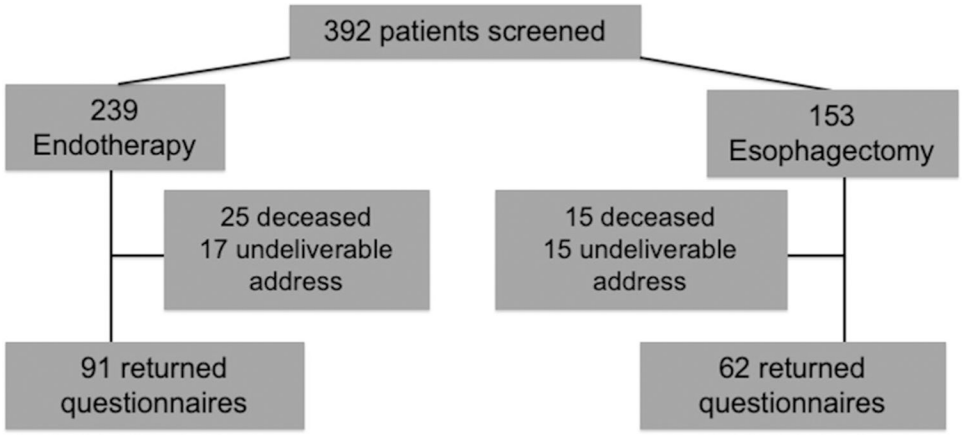

Fig. 1.
Diagram of patient inclusion

Table 1

Baseline and clinical characteristics of patients with returned questionnaires

	ET = 91	**ES = 62**	***p* value**
Age (years)	68.0 ± 8.6	62.6 ± 9.4	< 0.01
Gender (%M)	79 (86.8%)	54 (87.1%)	1.0
Years since initial therapy	5.0 (3.0, 6.0)	9.0 (6.3, 12.0)	< 0.01
EAC (%)	46 (50.5%)	55 (88.7%)	< 0.01
CCI	0.0 (0.0, 1.0)	0.5 (0, 1.0)	0.2

ET Endoscopic therapy, *ES* esophagectomy, *EAC* esophageal adenocarcinoma, *CCI* Charlson comorbidity index

Table 2

Functional and global health outcomes of endoscopic therapy versus esophagectomy from QLQ-C30

Domain of functioning	ET median (IQR)	ES median (IQR)	Unadjusted difference in mean score (CI)	Adjusted* difference in mean score (CI)	Proportion with abnormal score (ET/ES)	Unadjusted OR** for abnormal score (CI)	Adjusted* OR** for abnormal score (CI)
Physical functioning	86.7 (63.3, 100.0)	96.7 80.0, 100.0)	− 8.8 (− 14.7, − 2.9)	**− 10.1 (− 17.8, − 2.4)**	69.2%/50.0%	2.25 (1.15, 4.39)	2.21 (0.875, 5.60)
Role functioning	100.0 (66.7, 100.0)	100.0 (70.8, 100.0)	− 7.2 (− 14.4, − 0.1)	**− 10.4 (− 19.8, − 1.0)**	49.5%/33.9%	1.91 (0.980, 3.72)	2.43 (0.970, 6.07)
Emotional functioning	83.3 (66.7, 100.0)	91.7 (66.7, 100.0)	0.2 (− 5.9, 6.3)	2.8 (− 5.2, 10.8)	65.9%/63.9%	1.09 (0.554, 2.15)	0.670 (0.263, 1.71)
Cognitive functioning	83.3 (66.7, 100.0)	83.3 (83.3, 100.0)	− 4.6 (− 10.0, 0.8)	− 3.8 (− 10.8, 3.2)	69.2%/55.7%	1.79 (0.911, 3.50)	1.51 (0.598, 3.82)
Social functioning	100.0 (66.7, 100.0)	100.0 (66.7, 100.0)	− 3.1 (− 10.5, 4.4)	− 4.8 (− 14.6, 5.0)	48.4%/38.7%	1.48 (0.769, 2.86)	1.74 (0.711, 4.26)
Global health status	75.0 (58.3, 83.3)	75.0 (66.7, 89.6)	− 5.7 (− 11.6, 0.2)	− 5.8 (− 13.7, 2.0)	91.2%/79.0%	2.75 (1.07, 7.11)	1.85 (0.523, 6.52)

ET Endoscopic therapy, *ES* esophagectomy, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval, *QLQ-C30* quality of life questionnaire core 30

* Adjusted for age, pathologic diagnosis, Charlson comorbidity index (CCI), and time since procedure; bold values are $p < 0.05$

** Odds ratio (< 1 favors ET, > 1 favors ES) for having an abnormal score of < 100

Table 3

Symptom outcomes of endoscopic therapy versus esophagectomy from QLQ-C30

Symptom	ET median (IQR)	ES median (IQR)	Unadjusted difference in mean score (CI)	Adjusted* difference in mean score (CI)	Proportion with abnormal score (ET/ES)	Unadjusted OR** for abnormal score (CI)	Adjusted* OR** for abnormal score (CI)
Fatigue	22.2 (11.1, 44.4)	22.2 (11.1, 33.3)	2.3 (− 5.0, 9.6)	− 0.3 (− 9.9, 9.2)	78.0%/75.8%	1.13 (0.528, 2.43)	0.748 (0.257, 2.18)
Nausea/ vomiting	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	− 3.1 (− 7.4, 1.2)	− 4.9 (− 10.5, 0.7)	17.6%/27.4%	0.565 (0.260, 1.23)	0.543 (0.185, 1.59)
Pain	16.7 (0.0, 33.3)	16.7 (0.0, 33.3)	7.3 (− 0.9, 15.4)	7.4 (− 3.5, 18.3)	60.4%/51.6%	1.43 (0.746, 2.75)	1.17 (0.478, 2.85)
Dyspnea	33.3 (0.0, 33.3)	0.0 (0.0, 33.3)	1.5 (− 7.1, 10.0)	5.9 (− 5.6, 17.4)	51.1%/45.9%	1.23 (0.642, 2.36)	1.49 (0.612, 3.62)
Insomnia	33.3 (0.0, 33.3)	0.0 (0.0, 33.3)	5.4 (− 3.8, 14.6)	4.1 (− 7.8, 15.9)	56.7%/46.7%	1.49 (0.775, 2.88)	1.25 (0.517, 3.03)
Appetite	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	− 3.7 (− 10.9, 3.4)	− 7.8 (− 17.4, 1.8)	22.0%/30.6%	0.638 (0.306, 1.33)	0.426 (0.158, 1.15)
Constipation	0.0 (0.0, 16.7)	0.0 (0.0, 0.0)	1.5 (− 5.7, 8.7)	− 2.0 (− 11.5, 7.6)	25.3%/24.2%	1.06 (0.501, 2.24)	1.06 (0.383, 2.91)
Diarrhea	0.0 (0.0, 33.3)	33.3 (0.0, 33.3)	− 11.2 (− 20.4, − 2.1)	**− 16.1 (− 28.1, − 4.1)**	32.2%/52.5%	0.431 (0.221, 0.841)	**0.287 (0.114, 0.724)**
Financial difficulty	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	2.6 (− 3.9, 9.1)	2.7 (− 6.0, 11.4)	31.9%/24.6%	1.43 (0.691, 2.98)	1.29 (0.494, 3.35)

ET Endoscopic therapy, *ES* esophagectomy, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval, *QLQ-C30* quality of life questionnaire core 30

* Adjusted for age, pathologic diagnosis, Charlson comorbidity index (CCI), and time since procedure; bold values are $p < 0.05$

** Odds ratio (< 1 favors ET, > 1 favors ES) for having an abnormal score of > 0

Table 4

Symptom Outcomes of Endoscopic Therapy versus esophagectomy from OES-18

Symptom	ET median (IQR)	ES median (IQR)	Unadjusted difference in mean score (CI)	Adjusted* difference in mean score (CI)	Proportion with abnormal score (ET/ES)	Unadjusted OR** for abnormal score (CI)	Adjusted* OR** for abnormal score (CI)
Eating difficulty	8.3 (0.0, 16.7)	16.7 (0.0, 33.3)	− 9.4 (− 16.2, − 2.6)	**− 15.9 (− 24.9, − 6.8)**	50.5%/72.6%	0.386 (0.193, 0.772)	**0.207 (0.0766, 0.562)**
Dysphagia	0.0 (0.0, 11.1)	0.0 (0.0, 0.0)	1.5 (− 5.1, 8.0)	3.5 (− 5.1, 12.2)	26.4%/21.3%	1.32 (0.612, 2.86)	1.63 (0.582, 4.59)
Reflux	0.0 (0.0, 0.0)	0.0 (0.0, 16.7)	− 3.1 (− 7.4, 1.2)	− 4.9 (− 10.5, 0.7)	17.6%/27.4%	0.565 (0.260, 1.23)	0.543 (0.185, 1.59)
Pain	16.7 (0.0, 33.3)	16.7 (0.0, 33.3)	1.2 (− 4.8, 7.3)	− 2.2 (− 10.1, 5.6)	73.6%/72.6%	1.05 (0.510, 2.18)	0.789 (0.292, 2.14)
Trouble swallowing saliva	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	2.2 (− 5.5, 9.8)	− 4.5 (− 14.5, 5.6)	23.6%/24.6%	0.947 (0.442, 2.03)	0.504 (0.179, 1.41)
Choking with swallow	0.0 (0.0, 0.0)	0.0 (0.0, 33.3)	− 4.2 (− 12.6, 4.2)	**− 11.3 (− 22.5, − 0.2)**	21.1%/31.1%	0.592 (0.282, 1.24)	**0.325 (0.119, 0.888)**
Dry mouth	33.3 (0.0, 50.0)	0.0 (0.0, 33.3)	3.3 (− 7.3, 13.8)	6.6 (− 7.3, 20.4)	51.6%/49.2%	1.10 (0.577, 2.11)	1.35 (0.560, 3.26)
Trouble with taste	0.0 (0.0, 33.3)	0.0 (0.0, 0.0)	3.3 (− 4.5, 11.2)	1.2 (− 9.2, 11.6)	31.1%/23.3%	1.48 (0.703, 3.13)	1.11 (0.406, 3.04)
Cough	0.0 (0.0, 33.3)	33.3 (0.0, 33.3)	− 3.3 (− 12.4, 5.7)	**− 14.0 (− 25.7, − 2.3)**	42.9%/54.1%	0.636 (0.331, 1.22)	**0.291 (0.114, 0.746)**
Speech difficulty	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	− 3.0 (− 9.2, 3.2)	**− 8.8 (− 16.9, − 0.7)**	15.6%/19.7%	0.752 (0.321, 1.76)	**0.306 (0.0959, 0.978)**

ET Endoscopic therapy, *ES* esophagectomy, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval, Oesophageal cancer module 18

* Adjusted for age, pathologic diagnosis, Charlson comorbidity index (CCI), and time since procedure; bold values are $p < 0.05$

** Odds ratio (< 1 favors ET, > 1 favors ES) for having an abnormal score of > 0