Objective: To prospectively characterize changes in body weight, satiety, and postprandial gut hormone profiles following esophagectomy.

Background: With improved oncologic outcomes in esophageal cancer, there is an increasing focus on functional status and health-related quality of life in survivorship. Early satiety and weight loss are common after esophagectomy, but the pathophysiology of these phenomena remains poorly understood.

Methods: In this prospective study, consecutive patients undergoing esophagectomy with gastric conduit reconstruction were studied preoperatively and at 10 days, 6 weeks, and 3 months postoperatively. Glucagon-like peptide 1 (GLP-1) immunoreactivity of plasma collected immediately before and at 15, 30, 60, 90, 120, 150, and 180 minutes after a standardized 400-kcal mixed meal was determined. Gastrointestinal symptom scores were computed using European Organization for Research and Treatment of Cancer questionnaires.

Results: Body weight loss at 6 weeks and 3 months postoperatively among 13 patients undergoing esophagectomy was 11.1 ± 2.3% (P < 0.001) and 16.3 ± 2.2% (P < 0.0001), respectively. Early satiety (P = 0.043), gastrointestinal pain and discomfort (P = 0.001), altered taste (P = 0.008), and diarrhea (P = 0.038) scores increased at 3 months postoperatively. Area under the curve for the satiety gut hormone GLP-1 was significantly increased from 10 days postoperatively (2.4 ± 0.2-fold increase, P < 0.01), and GLP-1 peak increased 3.8 ± 0.6-, 4.7 ± 0.8-, and 4.4 ± 0.5-fold at 10 days, 6 weeks, and 3 months postoperatively (all P < 0.0001). Three months postoperatively, GLP-1 area under the curve was associated with early satiety (P = 0.0002, R^2 = 0.74), eating symptoms (P = 0.007, R^2 = 0.54), and trouble enjoying meals (P = 0.0004, R^2 = 0.73).

Conclusions: After esophagectomy, patients demonstrate an exaggerated postprandial satiety gut hormone response, which may mediate postoperative changes in satiety, body weight, and gastrointestinal quality of life.

Keywords: appetite, body weight, dumping syndrome, enteroneocline, esophageal cancer, esophagectomy, gastrointestinal symptoms, GLP-1, glucagon-like peptide 1, glucose, gut hormones, gut peptides, health-related quality of life, hunger, insulin, L-cell, malnutrition, nutrition, postprandial symptoms, satiety, survivorship, weight loss

Advances in neoadjuvant strategies, perioperative care, and increased early diagnosis have produced significant improvements in oncologic outcome for patients with esophageal cancer treated with curative intent. Even for patients presenting with locally advanced disease, approximately 1 in 2 patients will survive 5 years, with a 47% 5-year survival in patients treated with multimodal therapy in the most recent published randomized clinical trial.

With such welcome advances with respect to oncologic outcome and cure, there is an emerging focus on functional status and health-related quality of life (HR-QL) in survivorship, as the attritional impact of esophageal cancer treatment, in particular surgery, is widely appreciated. Functional recovery after surgery for esophageal cancer is commonly confounded by anorexia and early satiety, which may reduce oral nutrient intake with consequent malnutrition and sarcopenia. Approximately one-third of recurrence-free patients have more than 15 percent body weight loss (BWL) at 3 years after esophagectomy. Reduced food intake and postigestive symptoms may also impair the patient’s ability to participate in eating as a social activity, and reinforce a persistent illness identity impacting long-term HR-QL. An altered desire to eat and eating difficulties are major predictors of long-term BWL after esophagectomy. However, little is known of the mechanisms underpinning these phenomena, and hence therapeutic options to support patients in this context are extremely limited.

Bariatric surgery, a management paradigm where, in contrast to esophagectomy, reduced weight and appetite are clearly desired outcomes, has provided some novel insights from clinical and experimental models into the physiologic regulation of hunger, satiety, and nutrient intake. Meal initiation and termination, and long-term regulation of body weight (BW), are controlled to a significant extent by the central actions of circulating factors arising from the gut and adipose tissue. As a long-term signal of systemic energy balance, leptin circulates at levels proportionate to total fat mass, modifying nutrient intake via the hypothalamic arcuate nucleus. Conversely, glucagon-like peptide 1 (GLP-1) is released from the enteroneocline L-cells of the small and large intestine in response to postprandial luminal signals and serves 2 key functions, enhancing postprandial glucose disposal and terminating food intake via downregulation of orexigenic neuropeptide Y and agouti-related peptide neurones in the hypothalamus (Fig. 1). The exaggerated endogenous...

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Disclosure: The study was supported by a fellowship award from the Health Research Board, Ireland, to Dr Jessie Elliott (HRP 2015–1013). The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Web site (www.annalsurgery.com).
postprandial satiety gut hormone response observed after Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) for morbid obesity seems to contribute to increased satiety, and reduced food intake and BW in the long term after bariatric surgery.\textsuperscript{17–21} After RYGB, an exaggerated postprandial GLP-1 response is seen as early as 2 days postoperatively—an observation which is attenuated by remnant gastrostomy nutrient instillation, implicating increased early small intestinal nutrient exposure in increased postprandial GLP-1 release in this cohort.\textsuperscript{18,22} However, several studies report progressively increasing postprandial gut hormone responses after RYGB, associated small intestinal adaptations, and increased L-cell volume in rodents and humans.\textsuperscript{23–27}

We have recently identified elevated postprandial GLP-1 concentrations among patients at 2 years after esophagectomy, indicating that satiety gut hormones may mediate changes in BW in the long term after esophageal cancer surgery.\textsuperscript{28} However, the evolution of the postprandial gut hormone response after esophagectomy has never been prospectively studied, and the role of gut hormones as mediators of early appetite disturbance in this cohort is unknown. The aim of this study was to characterize the postprandial gut hormone response and its association with satiety, gastrointestinal quality of life, and BW in the early postoperative period among patients undergoing esophagectomy with gastric conduit reconstruction.

**METHODS**

**Study Participants**

The Esophageal and Gastric Centre at St James’s Hospital, Dublin, is a high volume National Centre, and detailed clinical, demographic, staging, treatment, pathologic, and follow-up data are prospectively maintained for all patients with a diagnosis of esophageal cancer. Consecutive patients with resectable esophageal or junctional cancer scheduled to undergo radical esophagectomy with gastric conduit reconstruction were identified at the weekly tumor board and preoperatively invited to participate in the study. Patients with significant dysphagia, any major comorbidity which might influence gut hormone physiology, neuropsychiatric illness, substance misuse, or previous gastrointestinal surgery were considered ineligible for the study.

**Treatment**

**Neoadjuvant Therapy**

During this period, patients with locally advanced adenocarcinoma were treated with either pre- and postoperative chemotherapy, as per the MAGIC regimen [Etoposide, Cisplatin, Fluorouracil or Capecitabine]\textsuperscript{30} or neoadjuvant chemoradiation as per the CROSS protocol [Carboplatin and Paclitaxel with concurrent radiotherapy,
Patients with locally advanced squamous cell carcinoma received neoadjuvant chemoradiation as per the CROSS trial. Patients with locally advanced squamous cell carcinoma received neoadjuvant chemoradiation as per the CROSS trial. Surgery was scheduled approximately 6 weeks after completion of neoadjuvant therapy.

**Surgery**

All patients with adequate respiratory function underwent radical abdominal-thoracic esophagectomy with thoracic or cervical anastomosis, whereas those with significant respiratory disease underwent transhiatal resection with cervical anastomosis, as previously described. Reconstruction using a posterior mediastinal gastric conduit approximately 5 cm in width with hand-sewn anastomosis, and pyloroplasty, was performed as routine.

**Nutritional Assessment and Support**

As per institutional protocol, all patients were reviewed in the multidisciplinary clinic and received detailed dietetic consultation and assessment before surgery. A 10-Fr needle catheter jejunoscopy (NCJ) was routinely placed at surgery, and NCJ feeding was commenced on the first postoperative day. Patients began oral intake on postoperative day 4 or 5 and progressed under the care of a dedicated team of clinical nutritionists to half portions of high-energy, high-protein normal diet with a frequent meal pattern on discharge, with oral nutritional supplementation as required. Overnight NCJ feeding was continued upon discharge for approximately 6 weeks postoperatively when ongoing requirements for supplemental enteral feeding were assessed. Postoperatively, NCJ feeding was withheld the evening before study assessments.

**Study Design and Protocol**

The institutional Research Ethics Committee approved the study (REC 2014/12/11), which was conducted in accordance with the principles of the Declaration of Helsinki with all patients providing written informed consent. The study was registered with ClinicalTrials.gov before recruitment of the first participant (NCT02381249) (Fig. 2).

Participants were studied preoperatively and at 10 days, 6 weeks, and 3 months postoperatively. At each outpatient assessment, participants were admitted to the St James’s Hospital Wellcome Trust-Health Research Board Clinical Research Facility at 09:00 after a 12-hour fast. Participants were allowed to drink water during this time and medications were not routinely withheld. On the 10th postoperative day, participants were assessed on the surgical ward, before discharge. Venous blood was collected from a peripheral intravenous cannula 5 minutes before and at 15, 30, 60, 90, 120, 150, and 180 minutes after a standardized 400-kcal mixed meal [160 g (184 mL): 27.2 g fat, 32.3 g carbohydrate, 6.7 g protein]. Meal standardization controlled the macronutrient stimulus delivered to the enteroendocrine L-cells, and meals were consumed at a comfortable rate, within a 15-minute interval, to control for the rate of eating. Visual analog scales were used to measure hunger, fullness, nausea, and desire to eat immediately before the standard meal and at each postprandial timepoint.

At each outpatient assessment, participants also completed a Sigstad dumping questionnaire and HR-QL questionnaires [European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and disease-specific modules QLQ-OES18 and QLQ-OG25]. The Sigstad score comprises a 16 symptom questionnaire where each symptom is differentially weighted. A score of greater than 7 may be considered indicative of dumping syndrome, whereas a score of less than 4 suggests an alternate diagnosis. Each HR-QL symptom item comprised 4 categories on a Likert scale: 1, not at all; 2, a little; 3, quite a bit; 4, very much. Linear transformation of Likert scores for answers in each conceptual area was performed as per EORTC recommendations and was also applied to the scores for “early satiety” (QLQ-OG25 item 5) and “trouble enjoying eating” (QLQ-OG25 item 4). Symptom scores hence comprise a numeric value from 0 to 100, with higher scores indicating more pervasive symptoms. Height, body anthropometry, and serial BW measurements were obtained in the fasting state with participants wearing light indoor clothing having voided urine, as previously described.

**Plasma Analysis**

All blood samples were immediately immersed in ice, centrifuged at 2500 rpm for 10 minutes at 4°C and plasma stored at −80°C to minimize gut hormone degradation. Plasma total GLP-1 levels were measured by enzyme-linked immunosorbent assay (ELISA; Multi Species GLP-1 Total ELISA, Merck Millipore, Darmstadt, Germany), validated to detect in the picomolar range with intra-assay and interassay variability of less than 2% and less than 12%, respectively. Plasma glucose, insulin, and C-reactive protein were determined using an automated analyzer (Cobas8000, Roche Diagnostics, Hoffmann-La Roche, Basel, Switzerland).

**Statistical Analysis**

Data were analyzed using GraphPad Prism (version 6.0) for Windows, GraphPad software (San Diego, CA). Data are presented...
as mean ± standard error unless otherwise specified. Area under the curve (AUC) was calculated using the trapezoidal rule. Univariate within-group comparisons were analyzed using paired Student t or Wilcoxon signed rank test, as appropriate. Univariate between-group comparisons were performed using the Student t or Mann-Whitney U tests for continuous variables or χ² or Fischer exact test for categorical variables. Relationships between continuous variables were interrogated using linear regression. One-way repeated measures analysis of variance (ANOVA) with post hoc Dunnett test was used to analyze differences in single data point measures over time from baseline (eg, BW, gut hormone AUC) while two-way repeated measures ANOVA with post hoc Holm-Sidak test was applied to assess for differences in multiple-response data over time from baseline (eg, visual analogue scores). All statistical analyses were two-tailed with the threshold of significance set at P < 0.05.

RESULTS

Participant Characteristics

Fourteen participants were recruited into the study from March to June of 2015. One participant chose to withdraw from the study immediately postoperatively. Clinicopathologic characteristics of the final study population are shown in Table 1. Assessments were carried out at 7 ± 2 days preoperatively, and at 10 ± 0.38 ± 2, and 106 ± 5 days postoperatively. All patients underwent R0 esophagectomy with gastric conduit reconstruction and pyloroplasty. There were no anastomotic leaks or significant gastrointestinal complications. No patient experienced delayed gastric emptying.

Body Weight Loss

Significant BWL occurred over the first 3 months after surgery, with 16.3 ± 2.2 percentage BWL from premorbid weight observed at 3 months postoperatively (P < 0.0001; Fig. 3, Supplementary Table 1, http://links.lww.com/SLA/B63). Greater premorbid BW was associated with more marked BWL at 6 weeks and 3 months postoperatively (P = 0.03, R² = 0.39 and P = 0.03, R² = 0.37, respectively).

<table>
<thead>
<tr>
<th>TABLE 1. Clinicopathologic Characteristics of Study Population (n = 13)</th>
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<td>Patient Details</td>
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<td>3-stage esophagectomy</td>
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<td>Transhiatal esophagectomy</td>
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<td>R0 resection</td>
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T, N indicates tumor and nodal stage; MAGIC, Etoposide, Cisplatin, Fluorouracil/Capetabine pre and postoperatively; CROSS, preoperative Carboplatin, Paclitaxel, 41.4 Gy/23 Fr; R0, complete resection.

Satiety, Gastrointestinal Symptoms, and Quality of Life

Selected hunger, satiety, and gastrointestinal quality of life item scores are shown in Figure 4. On HR-QL analysis, an increase in early satiety (P = 0.043) and time taken to compete meals (P = 0.01, data not shown) contributed to a trend toward an increased composite eating symptoms score (P = 0.079). Composite gastrointestinal pain and discomfort, taste change, and diarrhea scores were greater at 3 months postoperatively versus presurgery (P = 0.01, 0.006, 0.038 respectively).

Postingestive symptoms as measured by the Sigstad score increased significantly following surgery from 0.0 ± 2.2 preoperatively to 6.0 ± 1.7 and 8.4 ± 1.6 at 6 weeks and 3 months postoperatively (P = 0.0002; Supplementary Figure 1, http://links.lww.com/SLA/B63). Eight patients (62%) had a Sigstad score more than 7 suggestive of “dumping syndrome” at 3 months, whereas 3 patients (23%) did not experience such symptoms with a score of less than 4.

Glucose and Insulin

Fasting glucose was elevated versus baseline at 10 days postoperatively (5.5 ± 0.8 vs 6.2 ± 1.2, P = 0.002), in association with increased C-reactive protein (2.5 ± 2.4 vs 91.2 ± 62.7 mg/L, P = 0.004), consistent with postoperative insulin resistance; however, fasting plasma glucose was not different from baseline at 6 weeks or 3 months postoperatively (P = 0.27). A rapid and transient postprandial increase in plasma glucose was observed postoperatively, with a peak value 20% to 30% greater after surgery compared with preoperatively, occurring 15 to 30 minutes postprandially (preoperatively: 6.1 ± 0.3 mmol/L, 10 d: 8.2 ± 0.5, 6 wks: 8.1 ± 0.4, 3 mo: 7.6 ± 0.4, P = 0.001). The early postprandial glucose AUC (0–30 mins) was significantly increased at all postoperative timepoints (P = 0.007). The postprandial insulin AUC was greater at 3 months postoperatively versus baseline (P = 0.019); however, no patient developed symptomatic or biochemical postprandial hypoglycemia during the protocol (Fig. 5).
Glucagon-like Peptide 1

There was no difference in fasting total GLP-1 levels at any postoperative timepoint versus preoperatively ($P = 0.52$); however, the AUC for GLP-1 more than doubled by 10 days postoperatively ($P < 0.01$), and the GLP-1 peak increased approximately 4-fold at all postoperative timepoints ($P < 0.0001$; Fig. 6). GLP-1 AUC and peak were similar from 10 days to 3 months postoperatively, and there was no relationship between GLP-1 AUC or peak and time elapsed postoperatively ($P = 0.41, R^2 = 0.02$ and $P = 0.64, R^2 = 0.01$). There was no difference in postprandial GLP-1 response by anastomotic location (cervical vs thoracic); however, the postprandial GLP-1 response was significantly greater among patients treated with surgery only as compared with multimodal therapy at 10 days ($P < 0.001$), but not at 6 weeks ($P = 0.09$) or 3 months postoperatively ($P = 0.16$).

GLP-1, Early Satiety, and Gastrointestinal Symptoms

The AUC for GLP-1 at 3 months postoperatively correlated with a number of HR-QL gastrointestinal symptom scores including early satiety ($P = 0.0002, R^2 = 0.74$), eating symptoms ($P = 0.007, R^2 = 0.54$), lack of appetite ($P = 0.004, R^2 = 0.57$), and trouble enjoying meals ($P = 0.0004, R^2 = 0.73$; Fig. 6). In addition, the reported severity of postigestive symptoms as measured by Sigstad score correlated with the magnitude of the GLP-1 peak at 3 months postoperatively ($P < 0.001, R^2 = 0.73$) (Supplementary Figure 1, http://links.lww.com/SLA/B63).

DISCUSSION

Weight loss after esophagectomy occurred in tandem with early satiety and increased gastrointestinal symptoms, associated with an early exaggerated postprandial GLP-1 response. We have previously shown that pharmacologic blockade of this exaggerated satiety gut hormone response results in increased food intake among patients after esophagectomy and after RYGB for obesity. Understanding the role of satiety gut hormones as mediators of food intake and weight loss among patients undergoing RYGB for obesity has facilitated the development of practical, targeted therapeutic interventions for morbid obesity, such as GLP-1 analogues, which produce significant BWL as confirmed in 2 recent RCTs. However, the significance of such insights in upper gastrointestinal cancer surgery, where postoperative changes in satiety represent a critical challenge impacting recovery of nutritional well-being and quality of life, as yet remains largely unexplored.

Satiety gut hormones, such as GLP-1, are secreted from the enteroendocrine L-cells of the small intestine in response to luminal nutrients and bile and provide a meal termination signal, enhancing satiety through activation of neurons in the hypothalamic arcuate nucleus and other centers involved in the regulation of food intake. We have previously demonstrated significantly elevated postprandial GLP-1 levels among postesophagectomy patients studied cross-sectionally at approximately 2 years postoperatively, compared with unoperated matched control subjects. From the present study, where for the first time the postprandial gut hormone profile of patients undergoing esophagectomy is prospectively characterized, a number of observations can be made. First, the finding of an exaggerated postprandial satiety gut hormone response as early as 10 days after esophagectomy may be partly explained by altered nutrient and bile transit leading to early postprandial small intestinal L-cell hyperstimulation. This is supported by the finding of rapid and transiently increasing plasma glucose, and increased early postprandial glucose AUC, at all postoperative timepoints. Notably, gastric emptying and small intestinal transit times inversely correlate with postprandial GLP-1 levels in patients after RYGB and VSG. Moreover, rapid gastric emptying has been associated with increased gut hormone responses after esophagectomy. This exaggerated postprandial satiety gut hormone response likely occurs as a result of increased exposure of open-type, nutrient and bile acid sensing enteroendocrine L-cells to luminal contents, in the early postprandial phase.
A significant relationship between the peak GLP-1 response and self-reported visceral symptoms as determined by the Sigstad score was also observed. This emphasizes the likely role of rapid nutrient transit in producing the early negative visceral symptoms, and stimulating an exaggerated postprandial gut hormones response, as exemplified by GLP-1, which may further perpetuate postprandial hypoglycemia through GLP-1-mediated increased glucose disposal (Fig. 1). Notwithstanding the small number of patients in the “surgery only” group who did not receive neoadjuvant treatment, the early postoperative difference in postprandial GLP-1 AUC between those treated with surgery only versus multimodal therapy, may suggest that cytotoxic agents exert a prolonged effect on the enteroendocrine secretory capacity of the small intestinal mucosa, with potential implications for postoperative gut healing via the co-secreted mucosal growth factor GLP-2.

The effect of cytotoxic chemotherapy on the enteroendocrine L-cell has not been well studied to date; however, the low baseline gastrointestinal HR-QL symptom scores are consistent with the absence of significant ongoing mucositis among patients post neoadjuvant therapy at this timepoint.

The study in addition highlights the prevalence of early satiety among patients after esophagectomy. Although “hunger” per se was reduced at early postoperative timepoints (Supplementary Figure 2, http://links.lww.com/SLA/B63), this had recovered by 3 months postoperatively, which may reflect the previously documented recovery of ghrelin production over time after upper gastrointestinal surgery.48 We previously reported similar fasting ghrelin concentrations among patients 2 years post esophagectomy and healthy control subjects.28 Early satiety, however, was persistent at all postoperative timepoints, and was strongly correlated with the postprandial GLP-1 response. In our cross-sectional study, the postprandial GLP-1 response correlated with postprandial BWL at 2 years;28 however, no such relationship with BWL was observed at the early timepoints of 10, 42, or 90 days after surgery in the current study. It, therefore, seems that early BWL after esophagectomy is likely multifactorial, with perioperative oral diet restriction, ghrelin deficiency, and surgical stress potentially compounding pre-existing dysphagia- and chemotherapy-associated preoperative BWL. However, the persistence of the exaggerated postprandial satiety gut hormone response and associated early satiety suggests that upregulation of this gut-brain axis may be an important factor in the development and perpetuation of weight reduction and nutritional impairment in the long term after surgery.

A number of limitations are acknowledged. Follow-up was until 3 months postoperatively to capture the period of steepest postoperative BWL; however, factors contributing to weight loss may differ from those contributing to weight loss maintenance in the long term. Repeated profiling at 1 and 2 years postoperatively may clarify whether similar postprandial satiety gut hormone responses exist in the long term after esophagectomy, as we have previously shown after RYGB.49 Although only the postprandial GLP-1 response is characterized in this study, it is probable that other postprandial gut hormones such as peptide YY and oxyntomodulin exhibit similar patterns. In this regard, we have previously demonstrated 2-fold increased postprandial peptide YY concentrations among postesophagectomy subjects compared with controls.17,28 Future studies may delineate the individual contribution of various gut hormones using specific gut hormone receptor blockers such as

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**FIGURE 5.** Insulin and glucose. A, Rapid and transient postprandial increases in blood glucose were observed after esophagectomy, without any difference in fasting blood glucose at 6 weeks or 3 months postoperatively. The early postprandial glucose AUC was significantly increased at all postoperative timepoints. The postprandial glucose AUC was greater at 10 days postoperatively, consistent with postoperative insulin resistance (data not shown). No patient developed symptomatic or biochemical hypoglycemia during the study protocol. B, The postprandial insulin response increased, with significantly greater insulin AUC at 3 months postoperatively, compared with baseline, suggesting a possible trophic effect of chronic GLP-1 excess on pancreatic islet cell function over time. One-way repeated measures ANOVA with post hoc Dunnett test.
FIGURE 6. The exaggerated postprandial gut hormone response, early satiety, and gastrointestinal quality of life after esophagectomy. A, The postprandial GLP-1 AUC was significantly increased at 10 days, 6 weeks, and 3 months postoperatively versus baseline ($P < 0.05$), whereas the GLP-1 peak increased approximately 4-fold at all postoperative timepoints ($P < 0.0001$). One-way repeated measures ANOVA with post hoc Dunnett test. B, At 3 months postoperatively, the postprandial GLP-1 AUC in response to a standardized 400-kcal meal stimulus correlated with early satiety ($P = 0.0002$, $R^2 = 0.74$), eating symptoms ($P = 0.007$, $R^2 = 0.54$), lack of appetite ($P = 0.004$, $R^2 = 0.57$), and trouble enjoying meals ($P = 0.0004$, $R^2 = 0.73$).
exendin-(9–39). Furthermore, given the apparent physiologic similarities to the VSG, where altered bile acid metabolism seems to be essential for surgical BW reduction, the magnitude and pattern of changes in serum bile acids after upper gastrointestinal cancer surgery warrant further investigation.

In conclusion, an exaggerated postprandial satiety gut hormone response, early satiety and negative visceral symptoms may contribute to weight loss after esophagectomy. A potential therapeutic approach for the postesophagectomy patient with persistently impaired gastrointestinal function and quality of life after surgery may be to modulate early satiety by targeting the exaggerated satiety gut hormone response.

ACKNOWLEDGMENTS
The authors thank the assistance and support of the Wellcome Trust-HRB Clinical Research Facility at St James’s Hospital, Dublin, in providing a dedicated environment for the conduct of high-quality clinical research activities; the Health Research Board, Ireland, which funded this study through a fellowship award to Dr Jessie Elliott (HPF 2015–1013); and Science Foundation Ireland that provided funding to Professor Carel le Roux (12/Y1/B2480).

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