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Original Article

The impact of Nutrition and Gastrointestinal Symptoms on Health-related Quality of Life in Survivorship after Oesophageal Cancer Surgery

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SUMMARY

Background and Aims: Oesophagectomy is the primary curative treatment for oesophageal cancer but is associated with considerable postoperative morbidity and mortality. To better understand the aetiology of impaired health-related quality of life (HRQL) in oesophageal cancer survivors (OCS), this study sought to determine the longitudinal changes in nutritional status, nutrition-impact symptoms (NIS), and HRQL in this cohort, and to determine which variables have the greatest impact on postoperative HRQL decline.
Methods: Data, derived from St. James' Hospital, Dublin, included patients who underwent oesophagectomy from October 2017 to May 2019 and attended clinic preoperatively and 6 months postoperatively. A subset attended a further 12-month appointment. HRQL and symptom data were collected using validated questionnaires and anthropometric measures were completed by clinicians. Data were analysed using SPSS.
Results: A total of 66 patients were studied preoperatively and 6 months postoperatively, of whom 37 were studied at 12 months postoperatively. Malnutrition remained prevalent at each timepoint, although rates did not significantly change longitudinally. Conversely, the prevalence of malabsorption (7.6%–14.3%,

Abbreviations: HRQL, Health-related quality of life; NIS, Nutrition-impact symptoms; OC, Oesophageal Cancer.

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P<0.001) and dumping syndrome (67.7%–74.3%, P=0.003) significantly increased with increasing time postoperatively. NIS were significantly associated with impaired HRQL function scores and were independent predictors of global quality of life (gQOL) score postoperatively (P=0.004). A diagnostic threshold of gastrointestinal symptom severity (11.5) that identifies patients at risk of impaired gQOL was therefore reported.

Conclusion: Malnutrition and NIS are prevalent post-oesophagectomy, the latter significantly associated with reduced HRQL. Targeted intervention in those with severe NIS could be highly beneficial, highlighting the need for dietetic input in OCS.

Introduction

An oesophageal cancer (OC) diagnosis is commonly associated with a poor prognosis, often a reflection of presentation with advanced or metastatic disease. Even where patients can be treated with curative intent, the pathway may be arduous with extensive treatment requirements, including preoperative (neoadjuvant) therapy and major cancer surgery [1]. The operation of oesophagectomy is the primary curative treatment for OC and is an exemplar of complex surgery [2,3], associated with considerable risk of major postoperative morbidity [4] and health-related quality of life (HRQL) impairment [5–8]. Advances in the modern era [1] have enabled improved 5-year survival rates in patients that undergo oesophagectomy [9] to approximately 50 per cent. Accordingly, with increased numbers of survivors, survivorship and HRQL have become important outcome measures [10–14]; and in this context, nutritional health is a key metric [13].

The importance of nutrition in survivorship of this cohort is highlighted in the Lasting Symptoms after Esophageal Resection (LASER) study, which found that two-thirds of oesophageal cancer survivors (OCS) have long-term, functional symptoms attributable to surgery, with many closely linked to nutritional issues [15]. The global health status and HRQL of these patients have thus been reported to be significantly lower than that of healthy populations, various cancer cohorts, and pre-treatment OC patients [16], and it is rare that they return to baseline. There is a spectrum of recovery; for instance, Sun *et al.* reported a HRQL recovery period of 6–12 months [17], while Derogar and Lagergren reported 6–36 months with a subgroup of patients whose HRQL deteriorates over time due to more symptoms and worse functioning [18]. Symptoms mainly comprise those which impede oral intake, known as nutrition-impact symptoms (NIS) [19]. These are long-lasting [17,20] and associated with poor survival [21]; highlighting the prognostic value of their identification [22].

Weight loss, dumping syndrome (DS) and malabsorption are key factors underpinning NIS. Body weight loss (BWL) is almost universal in this cohort, despite dietetic support and supplementation [23]. The inability to swallow (dysphagia), which characterises the presentation of OC in many patients, is a key factor, as well as tumour-mediated cachexia and the consequences of neoadjuvant therapies [24,25]. Postoperatively, changes in anatomy and physiology, particularly gastrointestinal and hormonal physiology, underpin the pathophysiological BWL observed [23,26]. Significant reductions in weight, including fat mass, skeletal muscle mass (SMM), and bone mineral density, at postoperative time-points compared to preoperatively are consistently reported [11,13,23,27–31]. Weight loss is most pronounced in the immediate 6 months post-oesophagectomy [11,32] with a reported 40–62% of patients losing greater than 10% of body weight and BMI during this time [11,12,23,33]. Loss of SMM is a key component, reported in 75% of patients at 6 months postoperatively [34]. Following this time-period, however, BWL [27] and SMM loss [31] can continue with a negative impact on prognosis and survival [23,34,35].

A NIS-related consequence of the mechanics of oesophagectomy, including a vagotomy and pyloroplasty, is DS [11,36]. The symptoms manifest as early or late DS with distinct pathophysiology [36]. In early DS, reduced stomach reservoir capacity results in rapid transit of voluminous and hyperosmotic chyme into the intestinal luminal space after food ingestion. This triggers duodenal distension, intravascular fluid shifts, activation of the sympathetic nervous system and gastrointestinal hormone hypersecretion; jointly resulting in gastrointestinal, vasomotor, and haemodynamic symptoms which occur within 10–60 minutes post-prandially [36–38]. Late DS, also called reactive hypoglycaemia, occurs after 60–120 minutes of ingestion. Insulin hypersecretion, caused by early and excessive concentrations of glucose in the small intestine followed by a rapid rise in blood glucose levels, results in delayed hypoglycaemia and the precipitation of adrenergic and/or neuroglycopenic symptoms. This is augmented by the incretin-mediated increase in insulin production and sensitivity [36,38–42].

In this National Centre, a Nutrition and Survivorship Clinic was established to monitor outcomes after OC surgery. It included detailed recording of nutritional symptoms, HRQL, and relevant laboratory measurements of nutritional well-being at a number of time-points. The aim of this report is to investigate the associations between nutritional status, NIS and HRQL in a cohort of OCS from the clinic. The objectives were threefold: first, to describe the prevalence of and longitudinal changes in malnutrition and NIS in survivorship after curative intent OC surgery; second, to investigate whether anthropometric/nutritional measures or NIS are associated with HRQL; and third, to identify predictors of impaired HRQL in OCS.

Materials and methods

Data source and data collection

The data was derived from the Nutrition and Survivorship Clinic at the National Oesophageal and Gastric Cancer Centre at St. James' Hospital, Dublin. This study includes patients who underwent oesophagectomy for OC between October 2017 and May 2019 and attended clinic preoperatively and 6 months postoperatively. A subset of patients attended a further 12-month clinic appointment. The preoperative and perioperative care of patients at this centre has been previously described [13]. Standard nutritional therapy involved exclusive jejunostomy feeding for 5 days postoperatively, commencing on the first postoperative day, which progressed slowly to half portions of easy to chew texture diet [43]. Patients were discharged on consuming half portions, overnight jejunostomy feeding, and oral nutritional supplements as required. Participant exclusion criteria included non-carcinoma related oesophagectomy, and disease recurrence or death prior to the 6-month postoperative appointment.

All patient data was collected prospectively at clinic visits. Ethical approval was obtained from the Hospital ethics committee. Reference population HRQL data was obtained from the European Centre for Research and Treatment of Cancer (EORTC) and other publications considered most appropriate [44,45]. Prior to clinic visits, patients had HRQL and symptom questionnaires posted to them to be completed before arrival. These included the general EORTC Quality of Life Questionnaire C30 (QLQ-C30), the OC specific EORTC QLQ-OG25, a modified Gastrointestinal Symptom Rating Scale (mGSRS), and the Sigstad dumping questionnaire [46]. At the survivorship clinic, anthropometric measurements and micronutrient screening were completed, and treatment and follow-up arranged as appropriate.

Nutritional and quality of life outcomes

BWL was classified according to the Blackburn criteria [47] and BMI was categorized according to the World Health Organisation [48]. Malnutrition was defined by nutritional risk index (NRI); (1.489*serum albumin [g/L])+(41.7*current weight/usual weight) [49], which has previously defined malnutrition in gastrointestinal cohorts [50–52]. Thresholds for classification of nutritional status are as follows; $\geq$100, well-nourished; 97.5–100, mild malnutrition; 83.5–97.5, moderate malnutrition; <83.5, severe malnutrition [53]. Malabsorption was indicated by a steatorrhoea-specific score >7, as assessed by specific questions in the mGSRS [27]. Finally, hand grip strength was measured on each hand three times, and the highest value was used as a functional surrogate for ‘probable sarcopenia’ using previously described sex-specific and BMI-dependant thresholds [54].

Assessment of NIS was limited to those assessed in the mGSRS (cramps, bloating, wind, belching, borborygmi, reflux, anorexia, nausea, vomiting, urgency to open bowels, incomplete passing of stool, oily stools, floating stools, and foul-smelling stools). Symptoms were assessed using a 4-point Likert scale and an estimate of symptom frequency and severity was found by totalling the scores. Dumping syndrome (DS) was assessed using Sigstad's scoring system where points are allocated to specific symptoms whose presence or absence were indicated by patients. Those with a total score greater than 7 were defined as having DS whereas those with a score less than or equal to 7 were defined as not having DS [55].

Quality of life outcomes included HRQL, which is an indication of one's function and level of symptomology [56], and global quality of life (gQOL), a measure of self-perceived health status. These were both recorded using the disease-specific and validated EORTC QLQ-C30 and QLQ-25 scales [57].

Statistical analysis

Data were analysed using SPSS software (IBM 27.0 for Windows, SPSS Inc, Chicago, IL). Continuous variables were assessed for normality using the Shapiro-Wilk test, and data are reported as mean, standard deviation (SD) or median, range as appropriate. Frequency data are presented as number (n), valid percent (%); where missing values are excluded from the prevalence analysis. Comparison of prevalence between groups was performed using the Chi-squared test. All EORTC questionnaire responses were previously linearly transformed as per the scoring manual [58]. Average differences in HRQL scores were classed as clinically relevant as per the evidence-based interpretation guidelines, available for inter- [59] and intra-group [60] comparison. These guidelines were developed using robust methodology to improve clinical interpretation of score differences, and, in the present study, differences were classed as clinically relevant if within the medium or large range [59].

Spearman's rank correlation was used in correlation analyses, as, consistently, at least one variable was non-normally distributed. Univariable comparisons within groups over two time-points were performed using paired *t*-tests or Wilcoxon signed-rank tests for continuous variables, and McNemar's test for dichotomous variables. For between group comparisons, the Mann-Whitney U test was used. For comparing data over three time-points, Cochran's Q test, one-way repeated measure ANOVA, or Friedman's test were performed, as appropriate. Receiver operating characteristic (ROC) curves were used to determine thresholds of continuous variables that may predict dichotomous outcomes. Standard single or multiple linear regression was used to investigate predictors of continuous outcomes, with independent variables inputted into the model based on their perceived clinical relevance. A significance level of 0.05 was used for all analyses and reported *P* values are two-tailed.

Results

Characteristics of the study cohort

The characteristics of the 6-month and 12-month cohort are shown in Table 1. Sixty-six patients were studied at the 6-month time-point, of whom 37 attended at 12 months postoperatively. Preoperative data was originally collected on 75 patients [13], resulting in an inclusion rate of 88% at 6 months and 49% at 12 months. The primary documented reasons for drop-out were disease recurrence and participants not reaching the 12-month postoperative time-point at the time of analysis. Their mean age was 63.3, the majority were male, and approximately half were ex-smokers. For more than 80% of patients in each cohort, OC was their first malignancy diagnosis with adenocarcinoma being the primary histological subtype. Neoadjuvant therapy and surgery was the main treatment approach, with preoperative chemotherapy and radiation therapy (CROSS protocol) and radical 2-stage en bloc oesophagectomy the most common combination. Over half the patients experienced a postoperative complication, and 22.7% and 18.9% of the 6 and 12-month cohort, respectively, experienced a complication classified as $\geq$3 according to the Clavien-Dindo Classification (CDC) system [61]. Tumour recurrence after last clinic appointment was documented in 15.2% at 6 months and 8.1% at 12 months postoperatively.

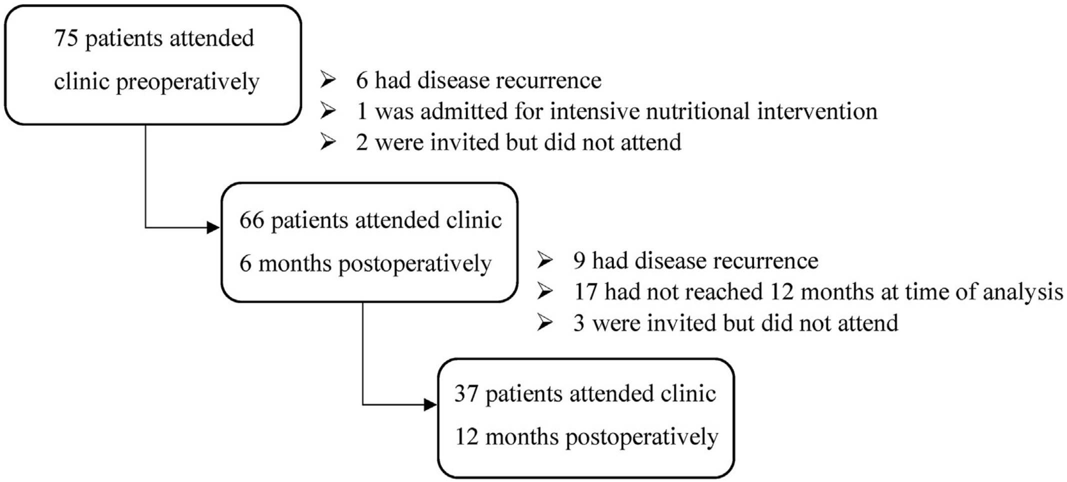


Figure 1. A clinic visit flow diagram outlining patient attendance at the Survivorship clinic.

Table 1
Demographic, clinicopathologic and treatment characteristics of the cohort of patients who attended their preoperative, 6-month postoperative, and 12-month postoperative appointment at the Nutrition and Survivorship Clinic

Variable	Preoperative cohort (n=75)	6-month cohort (n=66)	12-month cohort (n=37)
Demographic Characteristics			
Sex			
Male (n, %)	63, 84.0%	55, 83.3%	32, 86.5%
Female (n, %)	12, 16.0%	11, 16.7%	5, 13.5%
Age at surgery (mean, SD)	62.7, 10.3%	63.3, 9.9	63.3, 9.9
Smoking status			
Current smoker (n, %)	13, 17.3%	10, 15.2%	5, 13.5%
Ex-smoker >1year (n, %)	35, 46.7%	31, 47.0%	19, 51.4%
Never smoked (n, %)	24, 32.0%	22, 33.3%	13, 35.1%
Unknown/not specified (n, %)	3, 4.0%	3, 4.5%	0, 0.0%
Alcohol intake			
Non-drinker (n, %)	12, 16.0%	8, 12.1%	4, 10.8%
Ex-drinker (n, %)	9, 12.0%	9, 13.6%	5, 13.5%
Heavy drinker (>14/21UPW) (n, %)	17, 22.7%	15, 22.7%	7, 18.9%
Social drinker (<14/21UPW) (n, %)	35, 46.7%	32, 48.5%	21, 56.8%
Unknown/not specified (n, %)	2, 2.7%	2, 3.0%	0, 0.0%
Clinicopathologic and Treatment Characteristics			
ASA grade at diagnosis			
1 (n, %)	8, 10.7%	8, 12.1%	4, 10.8%
2 (n, %)	51, 68.0%	44, 66.7%	24, 64.9%
3 (n, %)	16, 21.3%	14, 21.2%	9, 24.3%
Previous malignancy			
Yes (n, %)	10, 13.3%	10, 15.2%	6, 16.2%
No (n, %)	62, 82.7%	53, 80.3%	31, 83.8%
Unknown/not specified (n, %)	3, 4.0%	3, 4.5%	0, 0.0%
Barrett's oesophagus (n, %)	29, 38.7%	26, 39.4%	17, 45.9%
Tumour histology			
Adenocarcinoma (n, %)	64, 85.3%	56, 84.8%	31, 83.8%
Squamous cell carcinoma (n, %)	11, 14.7%	10, 15.2%	6, 16.2%
Main curative treatment			
Surgery (n, %)	13, 17.3%	13, 19.7%	8, 21.6%
Neoadjuvant therapy and surgery (n, %)	57, 76.0%	48, 72.7%	26, 70.3%
Surgery and endoscopic treatments (n, %)	3, 4.0%	3, 4.5%	2, 5.4%
Surgery and adjuvant therapy (n, %)	1, 1.3%	1, 1.5%	1, 2.7%
Surgery and radical CT/RT (n, %)	1, 1.3%	1, 1.5%	0, 0.0%
Neoadjuvant therapy type			
CROSS (n, %)	25, 33.3%	22, 33.3%	8, 21.6%
MAGIC (n, %)	8, 10.7%	6, 9.1%	6, 16.2%
FLOT (n, %)	20, 26.7%	15, 22.7 %	7, 18.9%
Not specified/Did not receive (n, %)	22, 29.3%	23, 34.8%	16, 43.2%
Surgery type			
Transhiatal oesophagectomy (n, %)	20, 26.7%	19, 28.8%	12, 32.4%
2-Stage oesophagectomy (n, %)	42, 56.0%	36, 54.5%	20, 54.1%
3-Stage oesophagectomy (n, %)	13, 17.3%	11, 16.7%	5, 13.5%
Postoperative complication			
Yes (n, %)	44, 58.7%	38, 57.6%	20, 54.1%
No (n, %)	31, 41.3%	28, 42.4%	17, 45.9%
CDC ≥3 (n, %)	18, 24.3%	15, 22.7%	7, 18.9%
Postoperative readmission			
Yes (n, %)	11, 14.7%	10, 15.2%	7, 18.9%
No (n, %)	64, 85.3%	56, 84.8%	30, 81.1%
Recurrence			
Yes (n, %)	12, 16.0%	10, 15.2%	3, 8.1%
No (n, %)	63, 84.0%	56, 84.8%	34, 91.9%

ASA indicates American Society of Anaesthesiologists; CDC, Clavien-Dindo Classification; CT/RT, chemotherapy/radiotherapy; SD, standard deviation; UPW, units per week.
CROSS protocol: weekly carboplatin and paclitaxel administration with concurrent Gy radiotherapy for 5 weeks. MAGIC protocol: perioperative triplet regimen of epirubicin, cisplatin, and fluorouracil. FLOT protocol: perioperative triplet regimen of docetaxel, oxaliplatin, leucovorin, and fluorouracil.

Table 2
Longitudinal anthropometric changes in the 12-month cohort

Variable	Preop (n=37)	6 months (n=37)	12 months (n=37)	*P*	*P* (preop vs 6m)	*P* (preop vs 12m)	*P* (6m vs 12m)
Weight, kg (mean, SD)	80.3, 14.6	73.2, 12.0	72.9, 12.7	**<0.001**[b]	**<0.001**[b]	**<0.001**[b]	1.000[b]
BMI, kg/m^2 (mean, SD)	27.4, 4.6	24.9, 3.4	24.8, 3.8	**<0.001**[b]	**<0.001**[b]	**<0.001**[b]	1.000[b]
BMI >25 kg/m^2 (n, %)	26, 70.3%	19, 51.4%	17, 45.9%	**0.001**[c]	**0.007**[c]	**<0.001**[c]	0.439[c]
NRI (mean, SD)	105.5, 7.1	102.5, 5.0	103.1, 4.9	**0.039**[b]	**0.040**[b]	0.164[b]	0.737[b]
Mild Malnutrition (n, %)	4, 10.8%	9, 24.3%	7, 18.9%	0.257[c]			
Moderate Malnutrition (n, %)	2, 5.4%	4, 10.8%	4, 10.8%	0.641[c]			
Severe Malnutrition (n, %)	1, 2.7%	0, 0%	0, 0%	0.368[c]			
Grip Strength (r), kg (mean, SD)	33.0, 7.8	31.2, 7.3	32.6, 8.1	0.217[b]			
Grip Strength (l), kg (mean, SD)	30.7, 8.3	31.2, 6.9	30.6, 8.4	0.897[b]			
MUAC, cm (mean, SD)		26.9, 2.2	26.9, 2.5				0.852[d]
Waist Circumference, cm		94.0, 64–106$^+$	90.9, 11.9$^\#$				0.704[e]
Hip Circumference, cm		96.7, 65–108$^+$	97.5, 6.6$^\#$				0.992[e]
Waist: Hip ratio, (median, range)		0.9, 0.8–1.0	0.9, 0.8–1.2				0.629[e]
% BWL (mean, SD)		8.4, 5.8	8.8, 7.1				0.487[d]
>10% BWL (n, %)		14, 37.8%	16, 43.2%				0.727[f]
Probable Sarcopenia (n, %)	7, 35%[a]	12, 32.4%	11, 29.7%	0.472[c]			

BMI indicates body mass index; BWL, body weight loss; l, left; MUAC, mid-upper arm circumference; NRI, nutritional risk index; Preop, preoperatively; r, right; SD, standard deviation; vs, versus. Bold indicates where longitudinal changes are significant (*P*<0.05).
$^\#$mean, SD, $^+$median, range.
[a] Probable sarcopenia measures available in n=20 preoperatively.
[b] One-way repeated measures ANOVA and post-hoc test significance result.
[c] Cochran's Q and post-hoc test significance result.
[d] Paired sample *t*-test significance result.
[e] Wilcoxon signed-rank test significance result.
[f] McNemar's test significance result.

The prevalence of malnutrition, as per NRI, was 24.2% preoperatively and 37.9% 6 months postoperatively in the 6-month cohort, and was 29.7% at 12 months postoperatively. Longitudinal changes in anthropometric and nutritional measurements in the 12-month cohort are shown in Table 2. Mean weight and BMI significantly decreased over time, reflected by a significant decrease in the prevalence

Table 3
Gastrointestinal Symptoms as measured by the mGSRS at 6 and 12 months postoperatively

Symptom	n, % of patients who scored 2 or 3		Sig of the difference in scores from 6-12 months in 12-month cohort
	6 months (n=66)	12 months (n=36[a])	*P*
Cramps	9, 13.6%	(n=35) 4, 11.4%	0.513
Bloating	9, 13.6%	(n=35) 3, 8.6%	0.090
Wind	17, 25.7%	8, 22.2%	0.467
Belching	12, 18.2%	8, 22.3%	0.132
Borborygmus	10, 15.5%	3, 8.4%	0.808
Reflux	(n=65) 9, 13.8%	2, 5.6%	0.739
Anorexia	(n=65) 12, 18.4%	(n=35) 4, 11.5%	0.109
Nausea	11, 13.6%	3, 8.4%	0.475
Vomiting	0, 0%	0, 0%	0.655
Urgency to open bowels	5, 7.6%	4, 11.1%	0.467
Incomplete passing of stool	5, 7.5%	(n=35) 4, 11.5%	0.660
Oily stool	(n=65) 6, 9.2%	(n=35) 4, 11.4%	0.564
Floating stool	7, 10.6%	2, 5.6%	0.480
Foul-smelling stool	9, 13.7%	6, 16.6%	0.218
Sleep disturbance due to bowels	0, 0%	(n=35) 1, 2.9%	0.739

P, significance result of Wilcoxon signed-rank test; Sig, significance.
[a] n=1 missing data at 12 months postoperatively.

Table 4
The clinical relevance of statistically significant differences in HRQL scores between patients with and without dumping syndrome

HRQL item	6 months (n=65)					12 months (n=35)				
	Dumping syndrome (median)	Non-dumping syndrome (median)	*P*	Median score difference	Clinically relevant (EBIG)	Dumping syndrome (median)	Non-dumping syndrome (median)	*P*	Median score difference	Clinically relevant (EBIG)
Physical function	83.33	100	0.005	16.67	Yes	83.33	100	0.046	16.67	No
Social function	66.67	100	0.001	33.33	Yes	83.33	100	0.011	16.67	Yes
Fatigue	33.33	11.11	<0.001	22.22	Yes	33.33	11.11	0.004	22.22	Yes
Dyspnoea	33.33	0	0.001	33.33	Yes	33.33	0	0.016	33.33	Yes
Eating restrictions	25.00	8.33	0.011	16.67	Yes	25	8.33	0.038	16.67	Yes
Trouble enjoying meals	33.33	0	0.007	33.33	Yes	33.33	0	0.028	33.33	Yes
Pain and discomfort	33.33	16.67	0.001	16.66	Yes	33.33	16.67	0.038	16.66	Yes

P, significance result of Mann-Whitney U test.
EBIG, Evidence-based Interpretation Guidelines (Fig. 1).

of overweight/obesity. Mean NRI score also significantly decreased from preoperatively to 6 months, yet the majority of malnourished patients remained in the 'mild malnutrition' category. Severe BWL was identified in 37.8% at 6 months and 43.2% at 12 months, and probable sarcopenia was diagnosed in 35%, 32.4% and 29.7% at the respective time-points.

Nutrition-impact symptoms (NIS) and dumping syndrome (DS)

Nutrition-impact symptoms remained prevalent throughout the postoperative period, with 41% and 36% of patients reporting >2 bothersome symptoms (scored a 2 or 3 on a 0–3 Likert scale) at 6 and 12 months, respectively. In the 12-month cohort, scores for individual symptoms did not significantly change from 6 to 12 months (Table 3), nor did average total mGSRS score (11.1 versus 10, $P=0.523$). The prevalence of malabsorption increased from 7.6% at 6 months to 14.3% at 12 months ($P<0.001$).

Mean Sigstad score (SS) was 9.45 at 6 months and 8.91 at 12 months. The prevalence of DS, defined by SS>7, significantly increased from 67.7% (44/65) to 74.3% (26/35) from 6 to 12 months ($P=0.003$). There were no significant differences in the prevalence of DS between sexes.

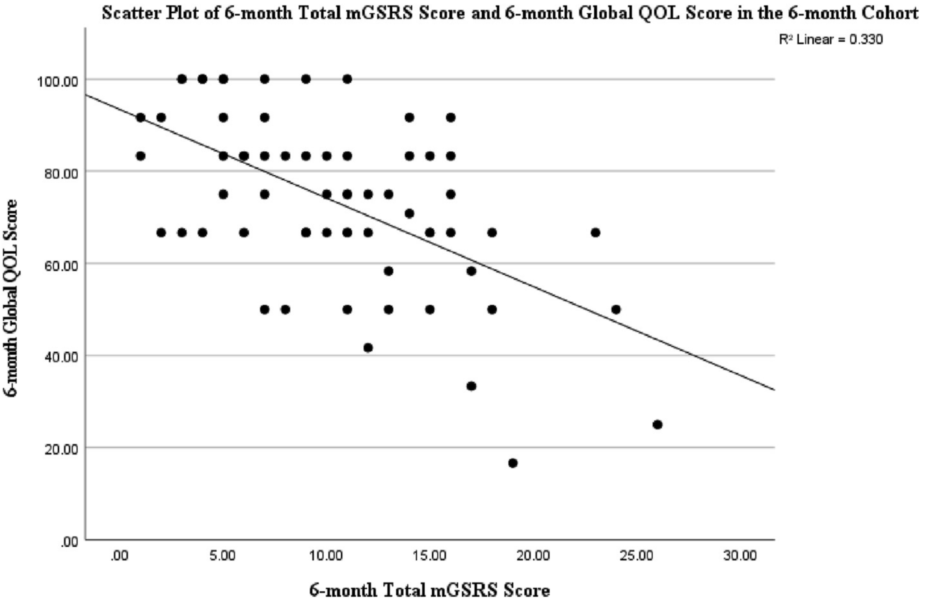
Health-related quality of life

Mean HRQL scores of various populations are shown in supporting information Table 1, and clinically relevant differences between groups [59] are marked. Clinically relevant improvements [60] in dyspnoea and appetite loss were found from 6 to 12 months in the 12-month cohort, whereas statistically significant improvements were found for emotional function, nausea and vomiting, dyspnoea, appetite loss, dysphagia, and taste changes.

A gQOL score of <66.1, the general population reference score [45], was set as the threshold for impaired gQOL. This was found in 20% and 14.3% of the population at 6 and 12 months, respectively. The demographic and clinicopathologic characteristics of those with and without impaired gQOL were compared (data not shown). At both time-points, patients with impaired gQOL had higher Sigstad, steatorrhoea-specific, and total mGSRS scores. All other variables assessed, including sex, age, smoking/alcohol status, and anthropometric measurements, did not differ significantly between those with and without impaired gQOL.

Nutritional status and HRQL

HRQL did not differ between those with and without a BMI $\geq$25kg/m^2, apart from 'worry about weight loss' at 6 months, which was significantly higher in the under/normal weight cohort compared to the overweight/obese cohort ($P=0.022$). Sarcopenic patients had several higher symptom scores



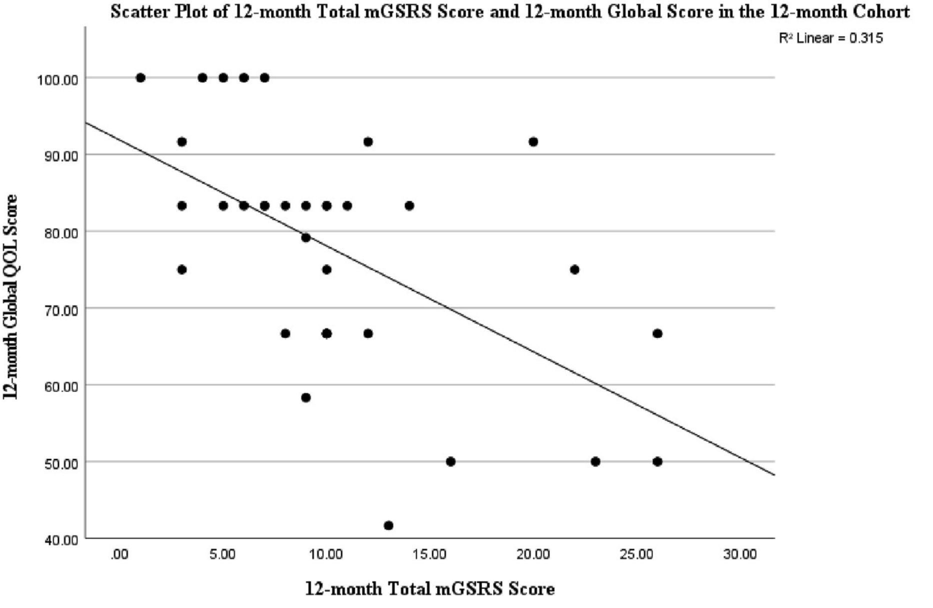


Figure 2. Simple scatter plots of the correlations between total mGSRS score and global QOL score at 6 and 12 months postoperatively.

postoperatively, and an increased gQOL at 6 months (P=0.029), compared to non-sarcopenic patients (supporting information Table 2). Several weak correlations (<0.4) were found between NRI score and HRQL scores, suggesting worsening of HRQL with decreasing NRI score (supporting information Table 3).

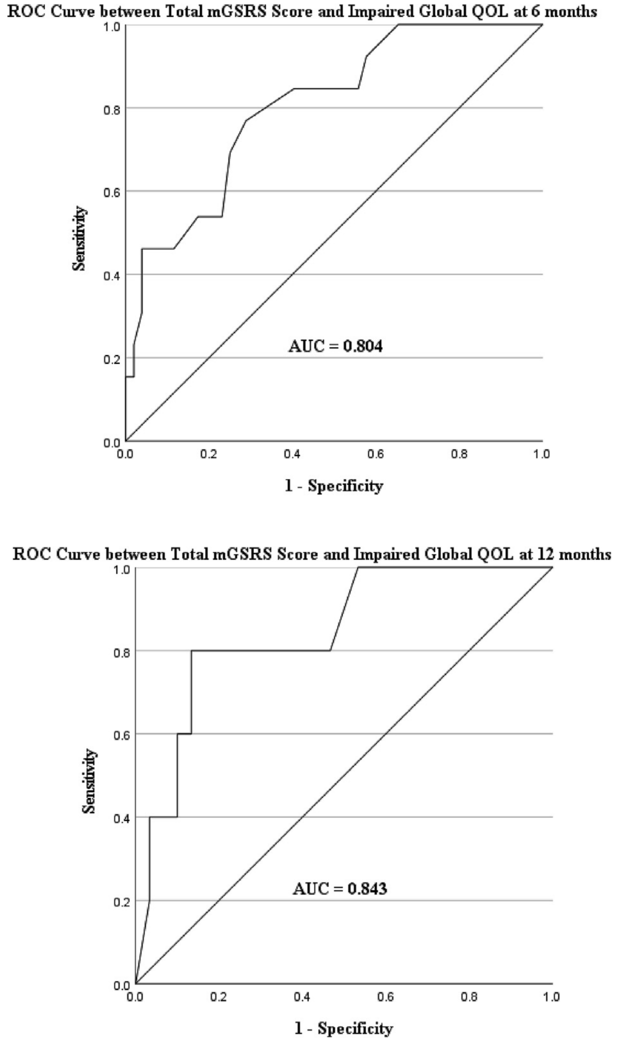


Figure 3. Receiver operating characteristic curves between total mGSRS score and impaired global QOL at 6 and 12 months postoperatively.

Dumping syndrome and HRQL

Numerous HRQL scores significantly differed at each postoperative time-point, both statistically as well as clinically, between those with and without DS, as shown in Table 4. Items that scored worse in patients with DS at both time-points were physical function (P=0.005/0.046), social function (P=0.001/0.011), fatigue (P<0.001/=0.004), dyspnoea (P=0.001/0.016), eating restrictions (P=0.011/0.038), trouble enjoying meals (P=0.007/0.028), and pain and discomfort (P=0.001/0.038). Similarly, several significant correlations were found between SS and HRQL scores which showed that increasing SS has a negative impact on HRQL (supporting information Table 4). Strong correlations (≥0.5) were found between SS and fatigue at 6 months (0.649, P<0.001), and social function (-0.518, P=0.001), fatigue (0.506, P=0.002), and dyspnoea (0.522, P=0.001) at 12 months.

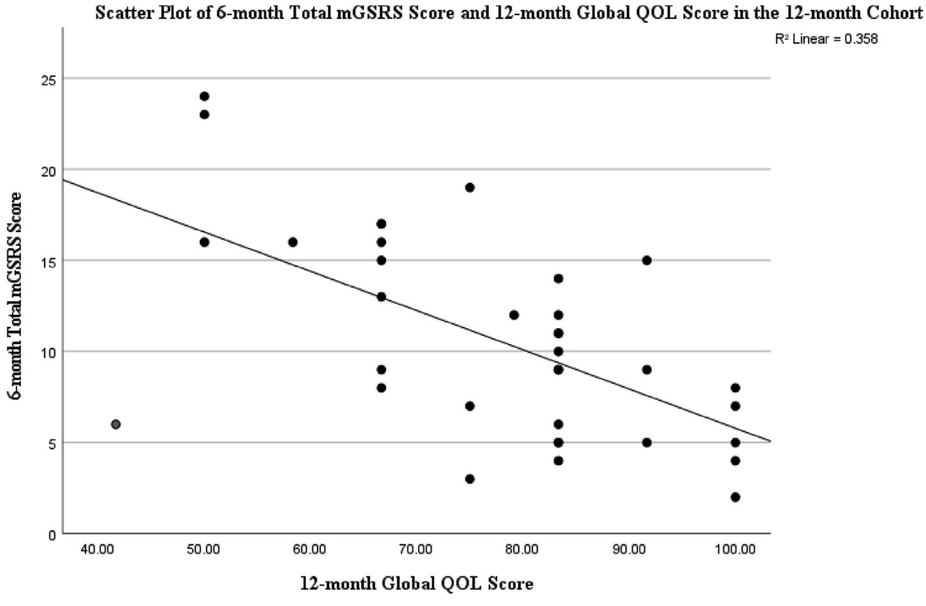


Figure 4. Simple scatter plot of 6-month total mGSRS score and 12-month global QOL score in the 12-month cohort.

Nutrition-impact symptoms and HRQL

Supporting information Table 4 displays the correlations between total mGSRS score and HRQL scores. At both postoperative time-points, strong correlations (≥0.5) were found between mGSRS score and gQOL score (-0.526, $P<0.001$; -0.582, $P<0.001$ [Figure 2]), cognitive function (-0.538, $P<0.001$; -0.636, $P<0.001$), insomnia (0.566, $P<0.001$; 0.506, $P=0.002$), eating restrictions (0.546, $P<0.001$; 0.672, $P<0.001$), and odynophagia (0.516, $P<0.001$; 0.599, $P<0.001$). These correlations suggested worsening of HRQL with increased NIS. Malabsorption also had a significant negative impact on several HRQL items (supporting information Table 5), including cognitive function ($P=0.031/0.014$).

ROC curves were used to determine a threshold for total mGSRS score that indicates impaired gQOL (<66.1). As shown in Figure 3, the area under the curve (AUC) between total mGSRS score and impaired gQOL at 6 and 12 months was 0.804 (CI:0.677–0.931, $P=0.001$) and 0.843 (CI:0.666–1.00, $P=0.015$), supporting it as a good diagnostic test. A threshold of 11.5 was selected as the sum of sensitivity and specificity was as closest to, or above, 1.5 at each time-point, as recommended by Power *et al.* [62] (sensitivity/specificity: 76.9%/71.2% at 6 months, 80%/80% at 12 months).

A bivariate regression analysis was conducted to examine how well 6-month total mGSRS score could predict gQOL score at 12 months. The scatterplot between these two variables, shown in Figure 4, revealed one outlier which was removed from the analysis: resulting in a sample size of 34. The Spearman correlation between the two variables was -0.586 ($P<0.001$), the regression equation for predicting 12-month gQOL score was 98.589-1.861(6-month mGSRS score) ($P<0.001$), and the adjusted r^2 was 0.508.

Predictors of HRQL

Standard multiple linear regression was performed to assess the impact of a set of predictor variables on gQOL score (Table 5). Predictor variables were selected based on plausibility to impact HRQL and results of previous analyses, and included NRI, Sigstad score (SS), steatorrhoea-specific score, mGSRS score, whether the patient had a postoperative complication of CDC≥3 and whether the patient had a preoperative ASA grade of 3. At 6 months, the model explained 41.1% of variance in gQOL score

Table 5
Multiple linear regression analysis of predictor variables for global quality of life score at 6 and 12 months postoperatively

Predictor Variable	6 months				12 months			
	Beta	CI	*P*	$[Part]^2$ x100	Beta	CI	*P*	[Part] [2] x100
Nutritional risk index	0.033	-0.588–0.821	0.741	0.10	0.199	-0.336–1.592	0.192	3.31
Sigstad score	-0.127	-1.195–0.335	0.265	1.17	-0.401	-2.251–-0.301	**0.012**	13.40
Steatorrhoea-specific score	0.079	-1.573–2.557	0.635	0.21	-0.342	-4.515–0.990	0.200	3.20
mGSRS score	-0.572	-3.163–-0.628	**0.004**	8.24	-0.095	-1.697–1.225	0.743	0.20
CDC≥3	0.189	-0.889–17.785	0.075	3.03	-0.026	-11.117–13.196	0.862	0.06
ASA grade of 3	-0.285	-22.228–-3.898	**0.006**	7.51	-0.136	-15.482–5.731	0.354	1.66
Model Summary	Adjusted R square: 0.411 (*P*<0.001)				Adjusted R square: 0.387 (*P*=0.003)			

ASA, American Society of Anaestheologists; Beta, standardised beta coefficient; CDC, Clavien-Dindo Classification; CI, confidence interval; mGSRS, modified Gastrointestinal Symptom Rating Scale; *P*, significance value; Part, semipartial correlation coefficient. Bold indicates where longitudinal changes are significant (*P*<0.05).

(P<0.001). Total mGSRS score (β [CI]: -0.572 [-3.163 − -0.628], P=0.004) and ASA grade equalling 3 (β [CI]: -0.285 [-22.228 − -3.898], P=0.006) independently contributed to the model equation and, together, explained 15.75% of gQOL variance. At 12 months, the model explained 38.7% of variance in gQOL score (P=0.003), with SS independently contributing to the model equation (β [CI]: -0.401 [-2.251 − -0.301], P=0.012) and explaining 13.40% of gQOL variance.

Discussion

With improved survival rates in OC treated with curative intent, HRQL has become a major focus of research and an intervention target to enhance recovery and optimise survivorship [11,34]. Nutritional health is central to this goal in this cohort of patients. An understanding of nutrition in HRQL will also provide evidence-based information for clinical decision-making and for resourcing optimal care pathways [63]. This study has shown that malnutrition, NIS, and DS are prevalent in OCS, and that NIS and DS are significantly associated with reduced HRQL. This highlights numerous modifiable targets.

Collection of information on outcomes from a patient perspective is an accepted part of oncological research [64], particularly in OC [65], and is facilitated through HRQL questionnaires. Responses can inform preoperative patients on what to expect postoperatively, guide standard advice [5,63], and identify patients requiring further intervention [21]. Moreover, postoperative HRQL scores, including gQOL and physical function, are independent predictors of long-term survival in OCS [21,66]. The HRQL of this cohort was comparable to the reference general population, which is an unusual finding compared to previous publications [16,67], particularly regarding physical function [5,68–70]. The survivorship clinic may be a factor, which provided contact with dietetic professionals through the first year of survivorship. This is consistent with increases in gQOL and physical function reported in other cancer types when patients have this level of nutritional and dietetic support [71]. Emotional function was higher in the sample cohort compared to reference populations at 12 months postoperatively, and it significantly improved from 6-month scores. This effect of treatment completion on emotional function has been reported elsewhere [5,63,72], and is possibly related to the feeling of optimism from the recovery process after they have undergone curative intent surgery [63].

Notwithstanding encouraging gQOL and function scores observed, most patients have a considerable symptom burden. Some patients with a high level of symptomology report good HRQL scores, however a subset still reported impaired gQOL. Independent risk factors for this included increased Sigstad, steatorrhoea-specific, and mGSRS score, but neither demographic nor clinicopathologic factors. As these risk factors are all related to gastrointestinal function, the benefit of comprehensive and intensive nutritional management in this cohort is further highlighted.

Extensive gastrointestinal resection and reconstruction, an inherent consequence of oesophagectomy, increases the risk of malnutrition postoperatively [33,34], which is associated with reduced HRQL and survival [16,73–76]. At 1-year postoperatively, the prevalence of malnutrition in this cohort was 43.2% when defined by BWL >10%, and 29.7% as per NRI. This is lower than what is reported in similar studies [33,74,77], possibly achieved through postoperative jejunostomy feeding for typically one month post-discharge, dietetic interventions, and increased monitoring via the survivorship clinic. It is worth noting that evidence supporting the use of malnutrition assessment tools such as the Patient-Generated Subjective Global Assessment tool [78] and the Global Leadership Initiative on Malnutrition tool [79] is superior to the NRI [80,81]. However, the NRI was used to allow for comparisons with previous publications on oesophageal cancer cohorts from this [27] and other centres nationally [82,83]. Furthermore, the volume of subjective participant questionnaires employed in this study indicated use of a straightforward, objective malnutrition screening tool such as the NRI, which carries limited evidence suggesting its utility [84–86].

Probable sarcopenia prevalence did not significantly increase postoperatively despite postoperative BWL, suggesting loss of fat mass was greater than SMM in this cohort. As sarcopenia is negatively associated with overall survival [87,88] and major morbidity [31], this is a positive, clinically relevant finding. Notwithstanding, it is worth considering that using hand grip strength as a surrogate for sarcopenia does not follow European clinical consensus guidelines [89] and may have underestimated its prevalence. It was for this reason that the term ‘probable sarcopenia’ was used throughout the present study.

Vagal denervation and endogenous neuroendocrine signal loss can result in exocrine pancreas insufficiency post-oesophagectomy [76]. In this study, the prevalence of malabsorption significantly increased from 6 to 12 months postoperatively. Malabsorption and steatorrhoea contribute to malnutrition through nutrient loss, especially of fat soluble vitamins, so identifying patients and treatment with pancreatic enzymes is both essential and effective [27]. It has not been previously investigated whether the overall effect of steatorrhoea reduces HRQL [90], where present study found a reduction in several HRQL scores, including cognitive function. This association warrants further investigation and may be related to fat soluble vitamin [91] and/or other micronutrient deficiency [92,93].

Although many nutritional parameters were better than reported in previous studies, the prevalence of DS was high. There may be many contributing factors, including the routine use of pyloroplasty in patients at this centre, which may accelerate gastric emptying. A key element is likely the detailed prospective evaluation of relevant symptoms in each patient, something which we suspect is not standard practice outside of such structures and clinical research [13]. Moreover, it is clear that an inconsistency in assessment and diagnostic methods for DS limits reliable comparisons between studies [94]. Importantly, DS was strongly associated with HRQL, principally fatigue and social function. Social function recovery is essential as it allows OCS to separate themselves from the identity of a 'cancer patient' [95], but unpleasant social interactions and anxiety associated with DS may impede this [38]. Taken together, these findings confirm that dumping syndrome is a major, prevalent problem after oesophagectomy that requires objective, evidence-based diagnosis, management, and treatment guidelines. Management and treatment may be aided by novel interventions, such as continuous glucose monitoring, which could be a useful tool in the diagnosis and management of reactive hypoglycaemia [96]. It may also facilitate strategies to reduce the impact of dumping on HRQL, especially social and cognitive function [97].

Nutrition-impact symptoms are key contributors to malnutrition [11], and it is known that they reduce HRQL [98–101]. However, this has rarely been explicitly studied in OCS. This may be because the symptom pattern of OCS as they recover is unclear [102] and holds inter-individual variability. The present study found that symptoms do not improve from 6 to 12 months postoperatively, suggesting lack of adaption of the gastrointestinal tract to anatomical changes in the first year after surgery. Total mGSRS score was strongly correlated with numerous HRQL scores at both postoperative time-points, including gQOL, and it independently contributed to variance in gQOL at 6 months. Therefore, a total mGSRS score threshold for identifying those whose HRQL could benefit from specialised nutritional input was determined. This mGSRS test is patient-centred, timely, and efficient; thus fulfilling the requirements of a high-quality test as reported by Power *et al.* [62]. This study also revealed it to be a sensitive and specific screening tool for use in clinical practice, allowing those at highest risk of impaired gQOL to be referred for targeted symptom management intervention. It was also found that 12-month gQOL score could be predicted by the 6-month mGSRS score using the reported equation. This would allow an opportunity for early intervention in those identified as high risk of impaired HRQL with the aim of reducing their symptom burden by the 12-month postoperative time-point.

The strengths of this study include detailed, prospective data collection at a dedicated structured clinic [13] and the use of validated questionnaires [10,103], which minimise information bias. Additionally, assessment at two postoperative time-points allowed for more rigorous evaluations of postoperative contributors to HRQL. We acknowledge some limitations, including a relatively modest sample size from a single institution, and encourage result validation in a larger study group, including the regression analyses and mGSRS threshold. Sources of potential bias include participant drop-out, self-reporting of symptoms, and the sole inclusion of patients who remained recurrence-free throughout the study period, introducing a survivorship bias. Notably, correction for multiple comparisons was not employed in this analysis. Tools such as Bonferroni have been criticised for being overly restrictive and increasing the risk of Type 2 errors. In this analysis, we explored a wide spectrum of patient outcomes and the results have been interpreted in a holistic manner, rather than focusing on single results of significance.

Conclusion

This study has shown that malnutrition and DS are prevalent after OC surgery, and that NIS reduce HRQL. The clinic structure and the study data support such programmes for these cohorts of patients, in particular those with severe NIS. We have proposed a mGSRS threshold of >11.5, however validation of this in a larger sample is needed. The high prevalence of DS is noted, and its detailed assessment complimented by continuous glucose monitoring to diagnose and manage reactive hypoglycaemia represents an important area to study. These data show that nutritional health is inextricably linked to symptoms, HRQL, and recovery and survivorship after oesophageal cancer surgery, and strategies to optimise the patient pathway through the treatment cycle into survivorship should create clinics with a major focus on dietetics/nutritional health to accommodate these significant patient needs.

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Author contributions

Sarah Bennett: Formal analysis, Investigation, Methodology, Visualization; Roles/Writing - original draft **Conor F Murphy**: Data Curation, Investigation, Writing - review & editing, Resources. **Michelle Fanning**: Conceptualization, Writing - review & editing. **John V Reynolds**: Writing - review & editing. **Suzanne L Doyle**: Project administration, Visualization; Roles/Writing - original draft, Resources, Supervision **Claire L Donohoe**: Conceptualization, Writing - review & editing.

Not relevant

Software, Validation, Funding Acquisition.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nutos.2021.11.005.

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