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Original Article

Immunonutrition to improve the quality of life of upper gastrointestinal cancer patients undergoing neoadjuvant treatment prior to surgery (NEOIMMUNE): double-blind randomized controlled multicenter clinical trial

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SUMMARY. **Background: Malnutrition is common with esophagogastric cancers and is associated with negative outcomes. We aimed to evaluate if immunonutrition during neoadjuvant treatment improves patient's health-related quality of life (HRQOL) and reduces postoperative morbidity and toxicities during neoadjuvant treatment. Methods: A multicenter double-blind randomized controlled trial (RCT) was undertaken. Included patients had untreated nonmetastatic esophagogastric tumor, aged 18 ≥ years with a life expectancy of >3 months. The study**

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was powered for 80% power to detect a clinically relevant difference in EORTC-QLQC30 with standard deviation of 15 between groups. Primary end point was the quality of life as measured by the global health status at 30 days after surgery. An intention-to-treat analysis was employed. Results: The study was terminated at the interim analysis stage. About 300 patients were randomized: 149 to the IMPACT group and 151 to the control-formula group. Patient groups were well-balanced in terms of age, sex, body mass index, WHO performance status, and clinical tumor stage. Analysis of the primary end point for the study of global health status at 30-day postoperatively failed to show any significant differences between the groups (55.4 ± 18.6 [IMPACT] vs. 55.9 ± 19.8 [control]; $P = 0.345$). No significant differences between the groups were detected in the majority of domains from EORTC QLQC30 and OG25 tools after neoadjuvant therapy and 30 days postoperatively. Finally, no significant differences were seen between groups in neoadjuvant therapy or postoperative complications, or tumor response. Conclusion: The results of this multicenter double-blind RCT fail to demonstrate any HRQOL benefits to the utilization of immunonutrition during neoadjuvant therapy in patients with esophagogastric cancer.

KEY WORDS: **esophageal cancer, gastric cancer, immunonutrition.**

INTRODUCTION

Patients with esophageal and gastric cancer often present with symptoms such as abdominal pain and dysphagia or odynophagia with weight loss,[1,2] which can naturally cause malnutrition and cancer cachexia at diagnosis. Recently, the international Global Leadership Initiative has proposed a definition of malnutrition including phenotypical (nonvolitional weight loss, low body mass index [BMI], reduced muscle mass) and etiological criteria (reduced food intake or assimilation, inflammation, or disease burden).[3] This malnutrition can be compounded by an often very tough treatment regime including neoadjuvant chemotherapy and radiotherapy followed by radical surgery and adjuvant oncological treatment and prolonged recovery.[4–6] Additionally, cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.[7]

Malnutrition and cachexia are important prognostic factors that may mediate an increase in complications during neoadjuvant treatment and following radical surgery,[8,9] both of which have been suggested to adversely impact long-term survival in patients with esophageal and gastric cancer.[10–12] The mechanism through malnutrition lends itself to poorer outcome is most likely a combination of depletion in micro- and macronutrients leading to reduce immunity and susceptible to complications from treatment. Furthermore, malnutrition and complications during neoadjuvant and surgical treatment lead to poorer health-related quality of life (HRQOL). HRQOL is an increasingly important patient reported outcome measure in cancer therapy given its prognostic significance in affecting long-term survival following upper gastrointestinal surgery.[13,14]

Immunonutrition solutions are often enriched in nutrients with the aim of stimulating the host immune response, improving control of the inflammatory response and increasing nitrogen balance and protein synthesis during cancer treatment including radical surgery.[15] The evidence regarding the potential benefits of immunonutrition in the setting of upper gastrointestinal surgery is conflicting.[16–20] To date, there is a paucity of evidence concerning the effects of immunonutrition during neoadjuvant therapy in patients with upper gastrointestinal cancer, which this present randomized controlled trial (RCT) seeks to address. Potentially immunonutrition may improve the host immune response and reduce the toxicity of and response to neoadjuvant therapy, reducing the effect of complications during neoadjuvant therapy and postoperative complications upon global HRQOL.

The aim of this RCT was to evaluate if immunonutrition during neoadjuvant treatment prior to surgery will improve patients' HRQOL and reduce postoperative morbidity and toxicities during neoadjuvant treatment.

METHODS

Study design

Patients were randomized into two groups that received the test product or an isocaloric isonitrogenous control (Fig. 1, Supplementary Appendix 1). A daily dose of approximately an extra 1000 kcal of the study nutritional support was administered from at least 1 week prior to the beginning of the neoadjuvant treatment, by the oral route or via a tube. Patients received visit of dieticians every 15 days to evaluate the calorie uptake for a target to 25–30 kcal/kg as recommended. To increase tolerance and acceptance, oral or enteral administration was both allowed. Patient compliance to study product was assessed 5 days prior to radical surgery as the number of days during the neo adjuvant phase that the patient took 65% or more of the prescribed study treatment.

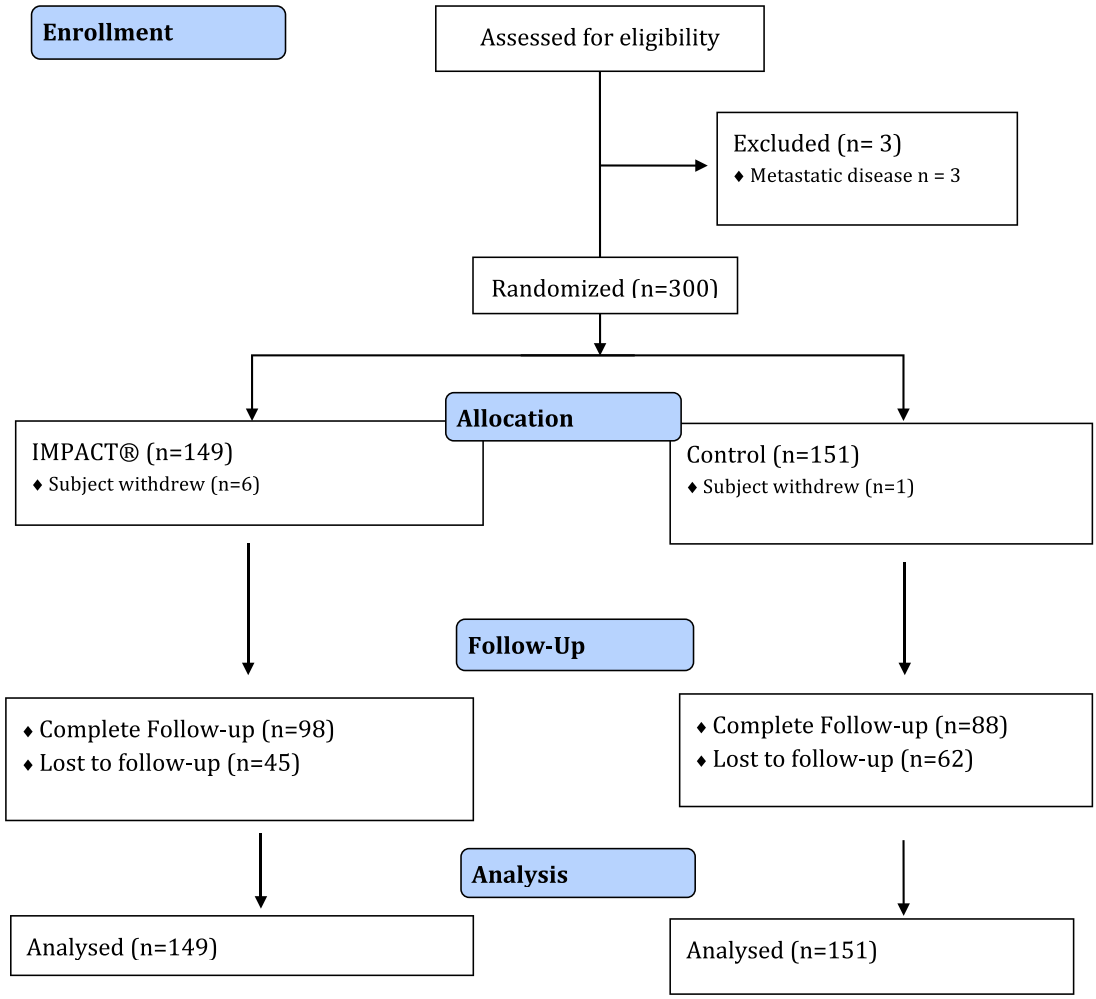

Fig. 1 Consort diagram of the flow of patients through the trial.

For ethical reasons, due to current international guidelines recommending immunonutrition in the perioperative setting with a grade B level of evidence, patients have to be nourished with immunonutrition systematically 5 days prior to surgery irrespective of nutritional status and 7 days postoperatively only in malnourished patients. Consequently, 5 days prior to surgery, patients discontinued nutritional support with the blinded treatment and for the 5 days preceding surgery. All patients received the same immunonutrition diet consisting of open-label IMPACT®. Patients post-surgery were fed according to current guidelines and medical practice. All malnourished patients were administered open-label IMPACT for 7 days. Nonmalnourished patients were fed according to standard medical practice for 7 days including the use of open-label IMPACT for 7 days only if provided as normal standard care practice. In all cases, open-label commercial IMPACT was not administered to patients for more than 13 days (Fig. 2). This may have had only a marginal impact on the study results when compared with the longitudinal administration during the average 60–90 days period of the neoadjuvant phase. Thereafter, all patients resumed the experimental diets according to the groups to which they were randomized at the beginning of the study.

Intervention and control formulae

IMPACT is a complete nutritional formula rich in fish oil and supplemented with arginine and nucleotides.

A specially designed comparative control for IMPACT was given to patients not assigned to receive IMPACT. The control patients' formula will be similar to IMPACT, isocaloric, without the bioactive ingredient characteristics of IMPACT (arginine, omega-3 fatty acids, and nucleotides). There was no difference in the taste or smell of the IMPACT or control formula thus maintaining the integrity of blinding within the trial.

Therapeutic strategy

Clinical tumor staging was based on the data obtained from CT scan, endoscopic ultrasound, and positron emission tomography results. Utilization of neoadju-

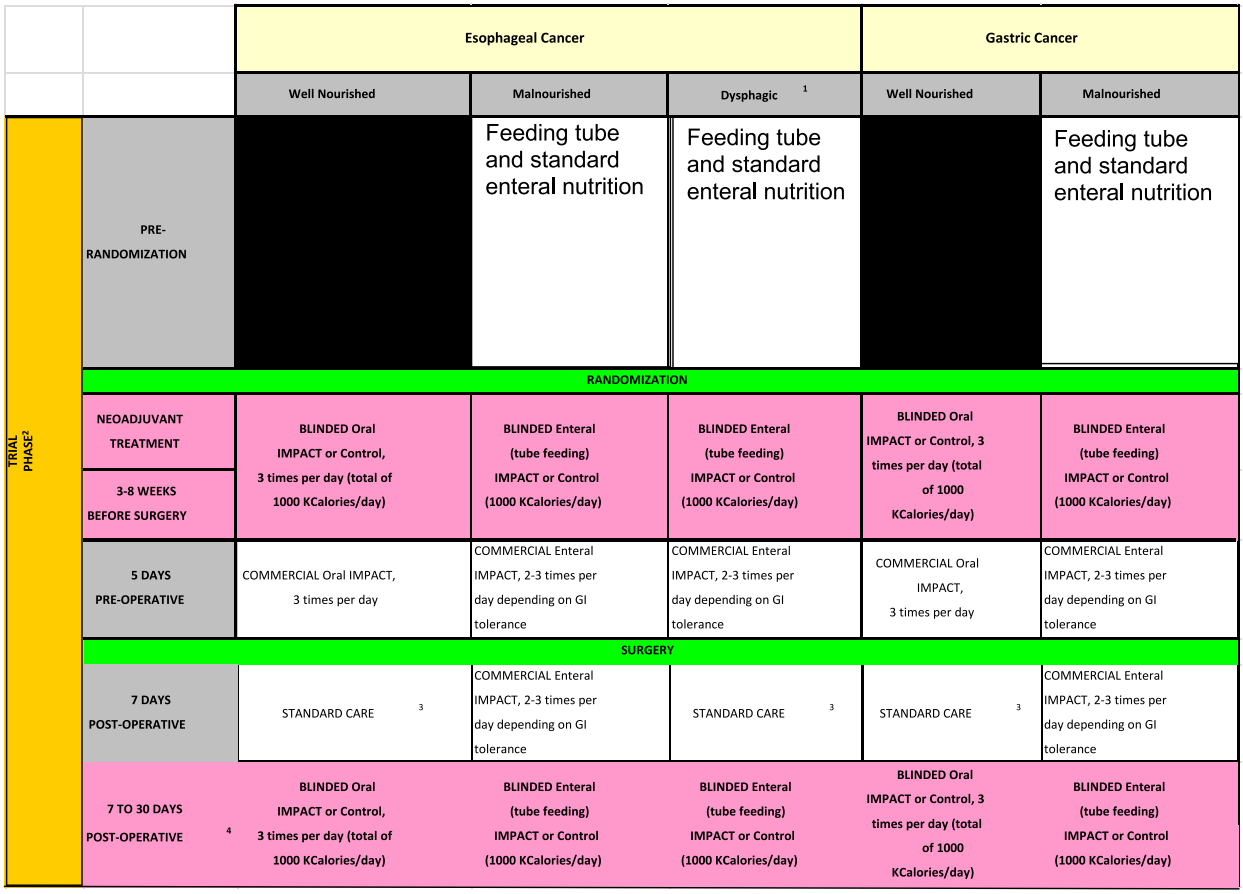

Fig. 2 Expected feeding regime for patients participating in the trial.

vant therapy was determined locally by multidisciplinary cancer boards. Neoadjuvant treatment regimen consisted in either neoadjuvant chemoradiation (41Gy + carbotaxol according to CROSS protocol[21] or 45 Gy + 4 cycles of 5FU-oxaliplatin) or in perioperative chemotherapy with 3 cycles of epirubicin, cisplatin, and infused fluorouracil or 2 cycles of 5-FU cisplatin in accordance with recommendations at that time.

Inclusion criteria

Locally advanced upper gastrointestinal squamous cell or adenocarcinomas, aged 18 years or older, life expectancy of 3 months or more, female patients of child bearing age must have had a negative serum beta-HCG test prior to enrolment and must have been willing employ effective contraception during the study period.

Exclusion criteria

Severe concomitant medical comorbidity (WHO performance status 3 or greater) that would jeopardize the expected follow-up protocol, pregnant or lactating women, other malignancies in the preceding 5 years, and more than 20% weight loss over a 6-month period.

Sample size

Considering EORTC QLQ-C-30 (Supplementary Appendix 2) Global Score based on the Global Health Status (items 29 and 30) and under the assumptions of 5% significance (two-sided alpha type one error of 5%), 80% power, clinically relevant difference of at least 5 points difference between the two arms with a standard deviation (SD) of 15, 1:1 treatment group allocation, it will be required to include 292 patients (146 patients/arm). Assuming a 20% drop-out rate 179 patients are required to be randomized to each treatment group (total = 358 patients).

Randomization

A minimization technique was used with stratified randomization according to:

- Stages Ib versus II versus III
- WHO performance status 0 versus 1 versus 2
- Centre for treatment
- Tumor location (esophagus vs. gastric)

- Weight loss in the last 6 months defined by the internationally accepted criteria of weight loss and SGA score[22]:
  - For malnourished patients, either loss of ≥10% of body weight or a physician's overall Subjective Global Assessment (SGA) score of severely malnourished (Score C).
  - For well-nourished patients, either weight loss of less than 10% or an SGA Score A or B.

Blinding

Double blinding to the allocated treatment group was performed so both the patient and the assessor from the research team were blinded to the allocated treatment.

End points

Primary end point was the quality of life as measured by the global health status (items 29 and 30) from the EORTC-QLQC30 at 30 days after surgery.

Secondary end points included longitudinal changes in EORTC QLQC30 and OG25 (Supplementary Appendix 3), time to global health score deterioration, complications during neoadjuvant therapy, nutritional status as measured by subjective global assessment of nutritional status, histopathological tumor response, 30-day postoperative morbidity, and length of hospital stay.

HRQOL scoring tools

EORTC QLQ-OG-25 and QLQ C30 questionnaire data were used to evaluate HRQOL. The different scores are included in the supplementary material.

Management of data

Patient data (with the exception of QOL questionnaires) were collected on clinical reporting forms and were substantiated by patient diaries and source documents at the clinical site. Data were collected using, a web-based electronic data capture system. The study monitor reviewed all clinical reporting form data to 100% source data verification to ensure adequate quality control and complete patient data.

HRQOL questionnaires were printed on three-part no carbon required paper and completed by the patients or by another person other than the patient (e.g. caregiver) if it was not possible for the patient to complete the questionnaires. A database was constructed from the questionnaires, and the data were entered, verified, and validated both manually and electronically.

Regarding missing data

Appropriate assumptions were made to account for missing data in the analysis (i.e. missing response to questions, missing questionnaire forms). The extent of missing data was assessed to investigate the impact of certain (imputation) assumptions being made on the primary analysis. As supportive analysis, all analyses were repeated after multiple imputation.

Statistical analysis

An intention-to-treat analysis was performed comprising all randomized patients, and univariate analysis was performed to compare scores, with an analysis of covariance using ANCOVA also performed. Cox regression analysis was also performed for the deterioration in global health score with covariates included in the model being treatment group (IMPACT or control), tumor stage (I, II, III), WHO performance status (0, 1, or 2), SGA score (A or B), and treating hospital.

The study complies with the Declaration of Helsinki rules and the principles of the Good Clinical Practices guidelines and was approved by the Institutional Review Board, the Nord-Ouest II ethic committee and the AFSSAPS (Agence Francaise de Securite Sanitaire des Produits de Santé). The trial was registered on ClinicalTrial.gov website NCT01423799.

RESULTS

The study was terminated prior to completion of recruitment at the interim analysis stage, as reviewers felt the sample size was underestimated given the true effect of IMPACT formula. Between 3 August 2012 and 24 April 2015, 300 patients were randomized in 16 centers (Supplementary Additional Table 1): 149 to the IMPACT group and 151 to the control-formula group. Patient groups were well balanced in terms of age, sex, ethnicity, BMI, WHO performance status, and clinical tumor stage (Table 1). Overall 190 (63.3%) discontinued their randomized therapy, 90 (60.4%) in the IMPACT group, and 100 (66.2%) in the control-formula group. Most commonly, this was due to an adverse event, 23 patients (15.4%) in the IMPACT group and 32 patients (21.2%) in the control-formula group; however in 12 patients (8.1%) in the IMPACT group and 14 patients (9.3%), this was due to disease progression during neoadjuvant therapy. Compliance was similar in both treatment groups, i.e. 50 days (52 days in IMPACT vs. 49 days in Control).

Analysis of health-related quality of life (EORTC-QLQC30)

Global health started to get impaired from the 132th and 140th days (median time) with Impact

Table 1 Comparison of patient demographics between IMPACT and Control Formula groups

	Total study population ($n = 300$) (%)	IMPACT formula ($n = 149$) (%)	Control formula ($n = 151$) (%)
Age (years)	63 (34–86)	62 (34–78)	64 (38–86)
Sex			
Male	253 (84.3)	125 (83.9)	128 (84.8)
Female	47 (15.7)	24 (16.1)	23 (15.2)
BMI (kg/m^2)	25.3 (14.7–50.3)	25.4 (17.3–50.3)	25.2 (14.7–50.3)
Weight (kg)	75 (44–135.3)	76 (44.5–135.3)	74 (44–135)
Weight loss in the last 6 months			
Missing	10 (3.3)	4 (2.7)	6 (4.0)
<10%	155 (51.7)	77 (51.7)	78 (51.7)
10–15%	118 (39.3)	59 (39.6)	59 (39.1)
>15%	17 (5.7)	9 (6.0)	8 (5.3)
Smoking status			
Nonsmoker	61 (20.3)	27 (18.1)	34 (22.5)
Ex smoker	186 (62.0)	91 (61.1)	95 (62.9)
Current smoker	53 (17.7)	31 (20.8)	22 (14.6)
WHO Performance status			
0	174 (58.0)	89 (59.7)	85 (56.3)
1	114 (38.0)	55 (36.9)	59 (39.1)
2	12 (4.0)	5 (3.4)	7 (4.6)
Clinical tumor stage			
I	8 (2.7)	6 (4)	2 (1.3)
II	78 (26)	38 (25.5)	40 (26.5)
III	214 (71.3)	105 (70.5)	109 (72.2)
IV	0 (0)	0 (0)	0 (0)
Tumor location			
Esophagus (including Siewert I and II)	264 (88.0)	134 (89.9)	130 (86.1)
Gastric (including Siewert III)	36 (12.0)	15 (10.1)	21 (13.9)
Tumor histology			
Squamous cell carcinoma	88 (29.3)	46 (30.9)	42 (27.8)
Adenocarcinoma	212 (70.7)	103 (69.1)	109 (72.2)
Total treatment duration (days)	130 (2–316)	132 (2–206)	129 (3–316)
Treatment duration during neoadjuvant therapy (days)	27 (6–62)	26 (14–56)	28 (6–62)
Chemotherapy	134 (44.7)	60 (40.3)	74 (49.0)
Chemoradiotherapy	141 (47.0)	76 (51.0)	65 (43.0)

BMI, body mass index.

and Control formula, respectively. Figure 3 shows that this deterioration followed the same pace across time in both groups, without any statistical difference between. Analysis of the primary end point for the study of global health status at 30 days postoperatively failed to show any significant differences between the groups (55.4 ± 18.6 [IMPACT] vs. 55.9 ± 19.8 [control]; $P = 0.345$). Furthermore, no significant difference between the groups was seen upon the completion of neoadjuvant therapy in global health status (59.1 ± 20.3 (IMPACT) vs. 59.2 ± 17.5 (control); $P = 0.531$). Multivariate Cox regression also confirmed the utilization of IMPACT during neoadjuvant therapy did not affect time to deterioration of global health score (hazard ratio = 1.25; 95% CI 0.89–1.76; $P = 0.197$).

Furthermore, no significant differences were seen between the groups after neoadjuvant therapy or 30 days postoperatively in global health status, physical, role, emotional, cognitive, social function, fatigue scale, nausea and vomiting, pain scale, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties when assessed with the EORTC-QLQC30 tool (Table 2). Similarly, IMPACT treatment during neoadjuvant therapy did not affect time to deterioration in physical function ($P = 0.478$), role function ($P = 0.701$), emotional function ($P = 0.088$), cognitive function ($P = 0.555$), social function ($P = 0.751$), fatigue ($P = 0.410$), nausea and vomiting ($P = 0.232$), pain ($P = 0.907$), dyspnea ($P = 0.968$), insomnia ($P = 0.933$), appetite loss ($P = 0.937$), constipation ($P = 0.362$), diarrhea ($P = 0.313$), and financial difficulties ($P = 0.857$).

Analysis of disease-specific health-related quality of life (EORTC-OG25)

The only significant difference between the groups was seen for dysphagia at 30 days postoperatively, which was lower in the control-formula group (23.0 ± 23.7 [IMPACT] vs. 17.8 ± 19.6 [control]; $P = 0.022$). No significant differences between the groups were seen after neoadjuvant therapy or 30 days postoperatively in eating restrictions, reflux scale, odynophagia, pain and discomfort, anxiety, eating with others, dry mouth, trouble with taste, body image, swallowing saliva, choking, coughing, talking, weight loss, and hair loss (Table 3). Furthermore, no significant differences between the groups were seen over the study period in time to deterioration of

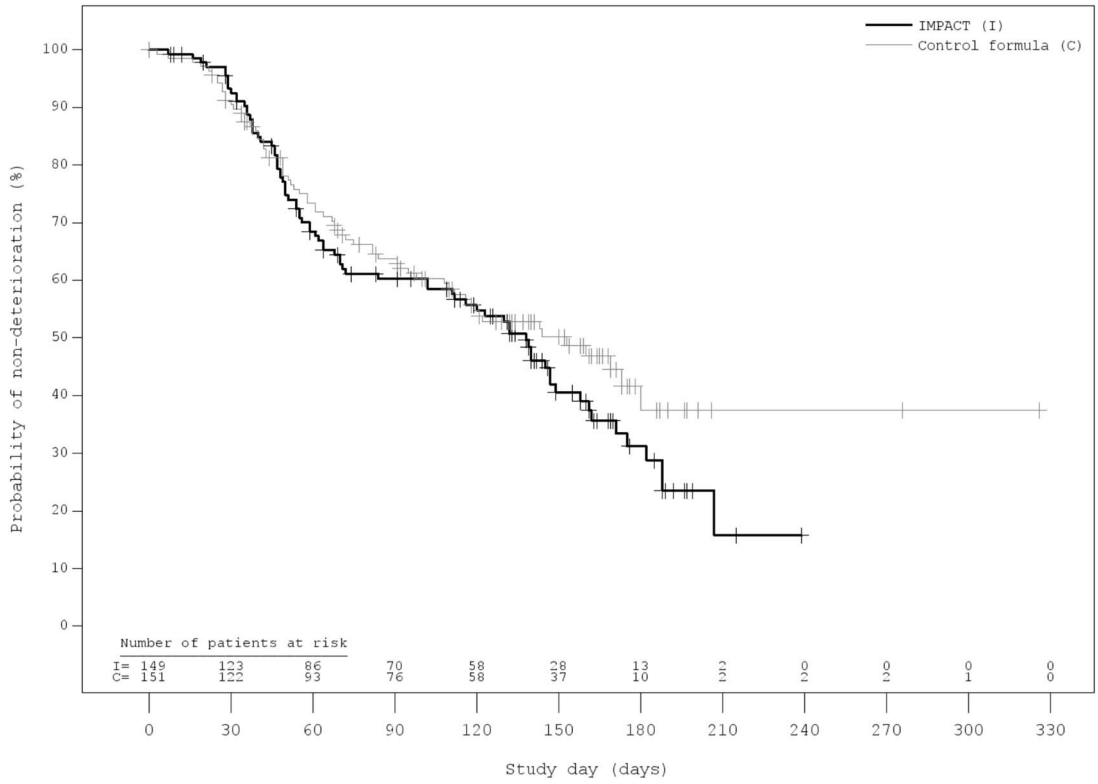

Fig. 3 Kaplan–Meier plot showing no significant difference between the groups in the time to global health score deterioration.

Table 2 Main study end points from EORTC-QLQC30

	Baseline			Completion of neoadjuvant therapy			30-days postoperatively		
	IMPACT formula ($n = 136$) (%)	Control formula ($n = 146$) (%)	*P* value	IMPACT formula ($n = 104$) (%)	Control formula ($n = 106$) (%)	*P* value	IMPACT formula ($n = 92$) (%)	Control formula ($n = 79$) (%)	*P* value
EORTC-QLQC30									
Global health	65.4 ± 20.7	59.9 ± 23.7	—	59.1 ± 20.3	59.2 ± 17.5	0.531	55.4 ± 18.6	55.9 ± 19.8	0.345
Physical function	90.6 ± 13.3	89.3 ± 14.8	—	80.9 ± 19.1	80.0 ± 20.9	0.882	67.9 ± 22.6	66.7 ± 23.2	0.971
Role function	84.9 ± 24.3	80.8 ± 28.2	—	69.7 ± 30.0	67.1 ± 32.2	0.953	51.8 ± 32.8	49.2 ± 32.7	0.900
Emotional function	72.6 ± 22.3	74.0 ± 23.4	—	77.4 ± 19.9	75.0 ± 22.0	0.165	77.1 ± 20.9	72.2 ± 23.4	0.229
Cognitive function	87.3 ± 20.2	87.0 ± 19.4	—	87.8 ± 16.6	85.7 ± 18.9	0.398	86.6 ± 16.2	81.6 ± 23.2	0.408
Social function	85.0 ± 23.1	82.4 ± 25.1	—	75.1 ± 25.3	77.1 ± 26.5	0.210	64.7 ± 26.5	69.4 ± 27.3	0.071
Fatigue scale	23.9 ± 21.5	27.2 ± 24.3	—	42.8 ± 26.6	42.6 ± 26.0	0.686	47.9 ± 22.3	49.6 ± 25.9	0.817
Nausea and vomiting	9.6 ± 17.5	11.8 ± 21.4	—	22.9 ± 27.9	19.3 ± 24.0	0.266	11.2 ± 19.7	10.9 ± 18.9	0.754
Pain scale	21.1 ± 22.7	23.3 ± 25.2	—	22.6 ± 28.1	26.7 ± 29.4	0.498	33.2 ± 27.3	34.4 ± 28.8	0.772
Dyspnea	11.5 ± 20.0	15.3 ± 24.5	—	22.1 ± 30.0	20.3 ± 27.5	0.404	34.1 ± 29.6	40.1 ± 28.4	0.653
Insomnia	24.6 ± 30.8	25.6 ± 30.3	—	23.4 ± 25.4	26.4 ± 30.4	0.358	34.4 ± 33.9	40.9 ± 33.3	0.303
Appetite loss	24.9 ± 32.5	25.2 ± 30.9	—	42.8 ± 34.9	37.7 ± 37.4	0.384	46.0 ± 33.8	41.0 ± 31.8	0.223
Constipation	23.5 ± 30.7	23.5 ± 30.6	—	26.0 ± 30.9	29.2 ± 31.1	0.332	19.6 ± 25.8	19.7 ± 26.6	0.697
Diarrhea	6.2 ± 15.9	5.3 ± 16.0	—	11.6 ± 21.8	15.2 ± 23.7	0.184	23.1 ± 26.6	26.9 ± 30.4	0.658
Financial difficulties	9.9 ± 22.7	10.2 ± 23.2	—	10.9 ± 24.1	11.7 ± 23.2	0.799	14.1 ± 25.3	13.5 ± 26.4	0.232

dysphagia ($P = 0.666$), eating restrictions ($P = 0.413$), reflux ($P = 0.103$), odynophagia ($P = 0.482$), pain and discomfort ($P = 0.361$), anxiety ($P = 0.727$), eating with others ($P = 0.069$), dry mouth ($P = 0.681$), trouble with taste ($P = 0.713$), body image ($P = 0.377$), swallowing saliva ($P = 0.145$), choking ($P = 0.430$), coughing ($P = 0.459$), talking ($P = 0.495$), weight loss ($P = 0.294$), and hair loss ($P = 0.656$).

Analysis of clinical and pathological outcomes

The proportion of patients receiving surgery (71.8% [IMPACT] vs. 66.9% [control]) and well-nourished

Table 3 Main study end points from EORTC-OG25

	Baseline			Completion of neoadjuvant therapy			30 days postoperatively		
	IMPACT formula ($n = 149$) (%)	Control formula ($n = 151$) (%)	*P* value	IMPACT formula ($n = 101$) (%)	Control formula ($n = 103$) (%)	*P* value	IMPACT formula ($n = 91$) (%)	Control formula ($n = 77$) (%)	*P* value
EORTC-OG25									
Dysphagia	28.7 ± 24.0	30.1 ± 26.6	—	26.9 ± 32.1	28.5 ± 31.5	0.735	23.0 ± 23.7	17.8 ± 19.6	0.022
Eating restrictions	36.7 ± 30.5	32.8 ± 29.4	—	40.1 ± 31.6	39.6 ± 32.4	0.659	42.1 ± 24.9	36.0 ± 24.4	0.150
Reflux scale	20.2 ± 26.6	17.7 ± 23.8	—	18.7 ± 27.8	21.2 ± 28.3	0.352	20.6 ± 23.0	18.9 ± 25.0	0.425
Odynophagia	31.0 ± 31.1	33.5 ± 29.5	—	27.2 ± 30.2	29.8 ± 30.9	0.412	15.9 ± 23.1	11.8 ± 17.5	0.064
Pain and discomfort	25.1 ± 27.6	27.3 ± 26.3	—	21.3 ± 26.7	24.4 ± 30.1	0.210	13.2 ± 19.4	16.2 ± 21.9	0.468
Anxiety	57.4 ± 28.3	58.1 ± 30.8	—	48.0 ± 27.4	53.8 ± 29.0	0.566	40.9 ± 29.3	45.9 ± 29.6	0.968
Eating with others	17.9 ± 29.2	18.2 ± 30.5	—	17.8 ± 29.1	17.0 ± 29.9	0.909	14.9 ± 27.0	12.8 ± 24.0	0.214
Dry mouth	17.6 ± 27.5	18.2 ± 26.3	—	31.0 ± 29.8	32.7 ± 30.6	0.759	37.0 ± 31.2	35.5 ± 32.4	0.526
Trouble with taste	11.8 ± 22.5	10.6 ± 23.6	—	35.0 ± 29.8	33.0 ± 34.0	0.661	29.4 ± 31.7	24.9 ± 32.9	0.185
Body image	10.8 ± 21.9	12.8 ± 25.9	—	14.8 ± 24.3	15.4 ± 23.6	0.907	21.1 ± 31.0	17.8 ± 26.1	0.262
Swallowing saliva	8.2 ± 18.4	6.9 ± 18.4	—	9.2 ± 21.1	12.7 ± 24.2	0.208	5.1 ± 13.1	6.1 ± 19.4	0.815
Choking	9.6 ± 20.7	10.3 ± 21.8	—	7.9 ± 19.5	10.3 ± 19.2	0.415	6.6 ± 15.9	6.6 ± 15.4	0.653
Coughing	21.9 ± 23.5	21.0 ± 25.8	—	22.2 ± 27.4	28.2 ± 28.2	0.082	44.6 ± 33.6	36.8 ± 30.9	0.143
Talking	3.7 ± 12.7	4.6 ± 13.4	—	6.3 ± 19.3	5.5 ± 13.3	0.817	20.1 ± 30.2	19.7 ± 27.8	0.990
Weight loss	22.0 ± 28.3	26.1 ± 32.8	—	24.8 ± 28.4	23.3 ± 27.9	0.463	27.1 ± 28.9	25.1 ± 27.1	0.427
Hair loss	8.0 ± 22.1	5.9 ± 20.9	—	16.7 ± 29.7	20.9 ± 28.3	0.929	22.2 ± 37.0	23.5 ± 31.8	0.906

after neoadjuvant therapy (58.2% [IMPACT] vs. 50.9% [control]) was similar between groups (Table 4). The utilization of IMPACT during neoadjuvant therapy also did not significantly affect the incidence of complications during neoadjuvant therapy, postoperative complications at 30 days, length of hospital stay, or readmission (Table 4). Furthermore, there were no significant differences between the groups in the tumor regression as measured by Mandard grade (Table 4).

DISCUSSION

The NEOIMMUNE double-blind multicenter RCT was terminated prior to completion of recruitment at the interim analysis stage. The results of 300 patients recruited are presented in this manuscript. No significant differences between groups in changes, at diagnosis and 30 days postoperatively, were identified in global health score and time to global health deterioration, physical, role, emotional, cognitive, and social functioning along with fatigue score. No significant differences in changes, at diagnosis, after neoadjuvant therapy and 30 days postoperatively were seen in pain, nausea and vomiting, dyspnea, insomnia, appetite loss, and change in bowel habit. Analysis of EORTC-OG25 in changes 30 days postoperatively showed with IMPACT improvements in time to pain and discomfort. Within the IMPACT group toxicity during neoadjuvant treatment, tumor regression, postoperative complications, length of hospital stay and survival were unaffected.

The main limitation of this study was that it was unfortunately terminated early at the interim analysis stage for two main reasons. Firstly, the power calculation was believed to be modest based upon the SD seen in the primary outcome measure at the interim analysis. Secondly, the drop-out rate was considered to be high with only 99 patients in the intervention group have complete data for the analysis of the primary outcome. Both of these limitations are a reflection of the ambitious primary end point chosen for this study of quality of life, which does naturally have a high SD but tends to minimize with a larger sample size. Approximately 30% of patients failed to receive surgery either due to disease progression or physical deterioration during neoadjuvant therapy causing the patients to be unfit for surgery, which further reduced the power of the study for the primary endpoint. This proportion of patients may reflect the wide tumor inclusion criteria used for the study and therefore in the future may suggest a much larger sample size is required for a study such as this. Further compliance within longitudinal studies measuring patient-reported outcome measures in surgery remains an ongoing challenge to surgical trials both now and in the future. Additionally, as international guidelines recommended immunonutrition in the perioperative setting with a grade B level of evidence during the study period,[23,24] all patients received immunonutrition for 5 days immediately preceding surgery regardless of nutritional status. This may have led to partial homogenization of the groups and thus reduced any effects of the intervention (IMPACT during neoadjuvant therapy) upon postoperative outcomes. Furthermore, data pertaining the route of administration (orally or via feeding tube) of the immunutrition were not analyzed in this study. Finally, other nutritional parameters including sarcopenia, vitamin levels, and

Table 4 Comparison of clinical and pathological outcomes between IMPACT and control formula groups

	Total study population ($n = 300$) (%)	IMPACT formula ($n = 149$) (%)	Control formula ($n = 151$) (%)
Patients receiving surgery	208 (69.3)	107 (71.8)	101 (66.9)
Patients well-nourished after neoadjuvant therapy ($n = 216$ assessed)	118 (54.6)	64 (58.2)	54 (50.9)
Neoadjuvant therapy type and complications			
Chemotherapy	134 (44.7)	60 (40.3)	74 (49.0)
Chemoradiotherapy	141 (47.0)	76 (51.0)	65 (43.0)
Blood and lymphatic	91 (31.1)	51 (35.7)	40 (26.7)
Anemia	50 (17.1)	29 (20.3)	21 (14.0)
Neutropenia	13 (4.4)	8 (5.6)	5 (3.3)
Thrombocytopenia	21 (7.2)	10 (7.0)	11 (7.3)
Gastrointestinal	203 (69.3)	100 (69.9)	103 (68.7)
Stomatitis	5 (1.7)	3 (2.1)	2 (1.3)
Diarrhea	63 (21.5)	29 (20.3)	34 (22.7)
Nausea	120 (41.0)	61 (42.7)	59 (39.3)
Vomiting	62 (21.2)	30 (21.0)	32 (21.3)
Response to neoadjuvant therapy			
Mandard*	42 (14.0)	24 (16.1)	18 (11.9)
1	31 (10.3)	17 (11.4)	14 (9.3)
2	24 (8.0)	13 (8.7)	11 (7.3)
3	32 (10.7)	15 (10.1)	17 (11.3)
4	11 (3.7)	4 (2.7)	7 (4.6)
5	160 (53.3)	76 (51.0)	84 (55.6)
Missing			
Postoperative complications			
In-hospital mortality	4 (1.3)	1 (0.7)	3 (2.0)
90-day mortality	10 (3.3)	4 (2.7)	6 (4.0)
Postoperative complications	137 (45.7)	72 (48.3)	65 (43.0)
Infectious complications	73 (24.3)	38 (25.5)	35 (23.2)
Noninfectious complications	118 (39.3)	61 (40.9)	57 (37.7)
Anastomotic leak	8 (2.7)	3 (2.1)	5 (3.3)
Pneumonia	34 (11.6)	16 (11.2)	18 (12.0)
Wound infection	1 (0.3)	0 (0)	1 (0.7)
Length of hospital stay	11.0 ± 8.1	11.6 ± 8.6	9.6 ± 7.2
Readmission	21 (7.0)	14 (9.4)	7 (4.6)
Number of patients eligible for adjuvant chemotherapy	71 (23.7)	36 (24.2)	35 (23.2)

Blood and lymphatic complications include anemia, bone marrow failure, leukocytosis, leukopenia, lymphopenia, neutropenia, and thrombocytopenia.
*Mandard grading; Grade 1 = no residual cancer, Grade 2 = rare residual cancer cells, Grade 3 = fibrosis outgrowing residual cancer, Grade 4 = residual cancer outgrowing fibrosis, and Grade 5 = absence of regressive changes.

serum arginine were not investigated in this RCT, however, have become of great interest in correlation with short- and long-term prognosis in more recent years, and therefore maybe an area for future investigation and may serve as a better end point for an RCT such as this in the future.

The esophageal and gastric cancers treatment pathways are extremely intensive and have substantial adverse impacts upon patient HRQOL.[25,26] The effects of neoadjuvant therapy, followed by radical surgery and potential complications from both, can be cumulative in nature lending itself to a very long recovery from surgery when measured by HRQOL. Immunonutrition during the perioperative period has previously been shown to improve patients' immune-related factors[16–19] and reduce the incidence and severity of postoperative infectious complications.[19,20] However, except a recently published RCT, most recent trials have failed to show a benefit to immunonutrition in the perioperative period during esophageal and gastric cancer treatment, and thus its inclusion in the standard perioperative pathway remains controversial.[27–30] In the recent ERAS recommendations, evidence in support of immunonutrition for patients undergoing surgery for esophageal and gastric cancer was judged conflicting and authors concluded that its routine use cannot be supported at this time.[31,32]

The hypothesis under investigation in this present double-blind multicenter RCT was immunonutrition during neoadjuvant therapy would improve patients HRQOL, reduce toxicity, increase compliance with neoadjuvant therapy, and therefore increase tumor regression, reduce postoperative complications and improve survival. However, this study failed to prove this hypothesis with equivalence shown between the groups for almost all primary and secondary end points. This may reflect the complexity of the effects of systemic neoadjuvant therapy, which can impact the whole body ecosystem as well as the intended target of the tumor microenvironment. An alternative explanation for the negative findings of this study is that HRQOL is a multifactorial end point and thus a single intervention such as immunonutrition

during neoadjuvant therapy may be unlikely to yield a statistically or clinically significant benefit. However, future studies should continue to consider using patient reported outcome measures as primary end points in their design, as consistently these are considered the most important outcomes by patients.[33]

Additionally, in this trial, we only performed a nutritional intervention whereas cachexia is a multifactorial syndrome that likely requires a multimodal intervention.[34] Combining resistance and aerobic training, dietary advice, oral supplements, and suppression of the inflammatory process may have a more cumulative effect in preventing, mediating, or even reversing the effects of cancer cachexia and may be beneficial in patients esophageal and gastric cancer.[35]

In conclusion, this double-blind randomized controlled multicenter clinical trial failed to show a significant benefit in terms of HRQOL to the utilization of immunonutrition during neoadjuvant therapy in patients with esophageal or gastric cancer. Furthermore, no significant improvements were observed in secondary outcomes including 30-day postoperative complications. Thus, while according to the latest ESPEN recommendations peri- or at least postoperative administration of immunonutrition is only recommended in malnourished patients. At present, there is no evidence base to strongly recommend its use during neoadjuvant therapy.[36]

SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in DOTESO online.

REFERENCES

1. Bodger K, Eastwood P G, Manning S I *et al.* Dyspepsia workload in urban general practice and implications of the British Society of Gastroenterology Dyspepsia guidelines (1996). Aliment Pharmacol Ther 2000; 14: 413–20.
2. Shawihdi M, Thompson E, Kapoor N *et al.* Variation in gastroscopy rate in English general practice and outcome for oesophagogastric cancer: retrospective analysis of hospital episode statistics. Gut 2014; 63: 250–61.
3. Cederholm T, Jensen G L, Correia M *et al.* GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr 2019; 38: 1480–1.
4. Elliott J A, Casey S, Murphy C F *et al.* Risk factors for loss of bone mineral density after curative esophagectomy. Arch Osteoporos 2019; 14: 6.
5. Rietveld S C M, Witvliet-van Nierop J E, Ottens-Oussoren K *et al.* The prediction of deterioration of nutritional status during chemoradiation therapy in patients with esophageal cancer. Nutr Cancer 2018; 70: 229–35.
6. Jarvinen T, Ilonen I, Kauppi J *et al.* Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. World J Surg Oncol 2018; 16: 27.
7. Muscaritoli M, Anker S D, Argiles J *et al.* Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elabo- rated by special interest groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010; 29: 154–9.
8. Anandavadivelan P, Lagergren P. Cachexia in patients with esophageal cancer. Nat Rev Clin Oncol 2016; 13: 185–98.
9. Hynes O, Anandavadivelan P, Gossage J *et al.* The impact of pre- and post-operative weight loss and body mass index on prognosis in patients with esophageal cancer. Eur J Surg Oncol 2017; 43: 1559–65.
10. Fujiya K, Kawamura T, Omae K *et al.* Impact of malnutrition after gastrectomy for gastric cancer on long-term survival. Ann Surg Oncol 2018; 25: 974–83.
11. Markar S, Gronnier C, Duhamel A *et al.* The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg 2015; 262: 972–80.
12. Rutegard M, Lagergren P, Rouvelas I *et al.* Surgical complications and long-term survival after esophagectomy for cancer in a nationwide Swedish cohort study. Eur J Surg Oncol 2012; 38: 555–61.
13. Lagergren P, Schandl A, Aaronson N K *et al.* Cancer survivorship: an integral part of Europe's research agenda. Mol Oncol 2019; 13: 624–35.
14. Wikman A, Johar A, Lagergren P. Presence of symptom clusters in surgically treated patients with esophageal cancer: implications for survival. Cancer 2014; 120: 286–93.
15. Mariette C. Immunonutrition. J Visc Surg 2015; 152: S14–7.
16. Aiko S, Kumano I, Yamanaka N *et al.* Effects of an immune-enhanced diet containing antioxidants in esophageal cancer surgery following neoadjuvant therapy. Dis Esophagus 2012; 25: 137–45.
17. Cerantola Y, Hubner M, Grass F *et al.* Immunonutrition in gastrointestinal surgery. Br J Surg 2011; 98: 37–48.
18. Mazaki T, Ishii Y, Murai I. Immunoenhancing enteral and parenteral nutrition for gastrointestinal surgery. Ann Surg 2015; 261: 662–9.
19. Marano L, Porfidia R, Pezzella M *et al.* Clinical and immunological impact of early postoperative enteral immnunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol 2013; 20: 3912–8.
20. Braga M, Gianotti L, Radaelli G *et al.* Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double blind phase 3 trial. Arch Surg 1999; 134: 428–33.
21. Van Hagen P, Hulshof M C, van Lanschot J J *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366(22): 2074–84.
22. Detsky A S, McLaughlin J R, Baker J P *et al.* What is subjective global assessment of nutritional status? JEPN J Parenter Enteral Nutr 1987; 11: 8–13.
23. Arends J, Bachmann P, Baracos V *et al.* ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 2017; 36: 1187–96.
24. Weimann A, Braga M, Carli F *et al.* ESPEN guideline: clinical nutrition in surgery. Clin Nutr 2017; 36: 623–50.
25. Brenkman H J F, Tegels J J W, Ruurda J P *et al.* Factors influencing health-related quality of life after gastrectomy for cancer. Gastric Cancer 2018; 21: 524–32.
26. Kauppila J H, Ringborg C, Johar A, Lagergren J, Lagergren P. Health-related quality of life after gastrectomy, esophagectomy, and combined esophagogastrectomy for gastroesophageal junction adenocarcinoma. Gastric Cancer 2018; 21: 533–41.
27. Mudge L A, Watson D I, Smithers B M *et al.* Multicentre factorial randomized clinical trial of perioperative immunonutrition versus standard nutrition for patients undergoing surgical resection of oesophageal cancer. Br J Surg 2018; 105: 1262–72.
28. Sultan J, Griffin S M, Di Franco F *et al.* Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. Br J Surg 2012; 99: 346–55.
29. Hubner M, Cerantola Y, Grass F *et al.* Preoperative immunonutrition in patients at nutritional risk: results of a double-blinded randomized clinical trial. Eur J Clin Nutr 2012; 66: 850–5.
30. Kanekiyo S, Takeda S, Iida M *et al.* Efficacy of perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy. Nutrition 2019; 59: 96–102.

31. Low D E, Allum W, De Manzoni G *et al.* Guidelines for perioperative care in esophagectomy: enhanced recovery after surgery (ERAS®) society recommendations. World J Surg 2019; 43: 299–330.
32. Mortensen K, Nilsson M, Slim K *et al.* Enhanced recovery after surgery (ERAS®) group. Consensus guidelines for enhanced recovery after gastrectomy: enhanced recovery after surgery (ERAS®) society recommendations. Br J Surg 2014; 101: 1209–29.
33. Avery K N, Metcalfe C, Berrisford R *et al.* The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer – the ROMIO (randomized oesophagectomy: minimally invasive or open) study: protocol for a randomized controlled trial. Trials 2014; 15: 200.
34. Fearon K C H. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer 2008; 44(8): 1124–32.
35. Brown C, Laird B J A, Wigmore S J, Skipworth R J E. Understanding cancer cachexia and its implications in upper gastrointestinal cancers. Treat Options Oncol 2022; 23: 1732–47.
36. Weimann A, Braga M, Carli F *et al.* ESPEN practical guideline: clinical nutrition in surgery. Clin Nutr 2021; 40(7): 4745–61.