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ORIGINAL ARTICLE

QOLEC2: a randomized controlled trial on nutritional and respiratory counseling after esophagectomy for cancer

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Abstract

Background Esophagectomy for cancer strongly impairs quality of life. The aim of this trial was to evaluate the effect of the nutritional and respiratory counseling on postoperative quality of life.

Methods At hospital discharge, patients were randomized into four groups receiving respectively: nutritional and respiratory counseling, nutritional counseling alone, respiratory counseling alone, or standard care. The main endpoint was the impairment in quality of life in the first month after surgery. Linear mixed effect models were estimated to assess mean score differences (MDs) in quality of life scores.

Results Patients receiving nutritional counseling reported less appetite loss (MD − 17.7, 95% CI − 32.2 to −3.3) than those not receiving nutritional counseling at 1 month after surgery. Dyspnea was similar between patients receiving vs. those not receiving respiratory counseling (MD − 3.1, 95% CI − 10.8 to 4.6). Global quality of life was clinically similar between patients receiving vs. those not receiving nutritional counseling over time (MD 0.9, 95% CI − 5.5 to 7.3), as well as in patients receiving vs. those not receiving respiratory counseling over time (MD 0.7, 95% CI − 5.9 to 7.2).

Conclusions Intensive postoperative care does not affect global quality of life even if nutritional counseling reduced appetite loss.

Keywords Esophageal cancer · Esophagectomy · Quality of life · Randomized controlled trial · Nutritional counseling

Introduction

Esophagectomy for cancer strongly impairs postoperative health-related quality of life (HRQL) [1, 2]. A systematic review showed that patients undergoing esophagectomy for cancer had scores of physical function, vitality, and performance of health in general significantly lower than those obtained from the reference population [3]. The analysis of the quality of life at 6-month follow-up showed that the total score and physical function were better before surgery and

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symptoms-based scales indicated that fatigue was worse 6 months after esophagectomy [4]. Difficulty to adapt to the new digestive tract conformation and to the effect of the thoracotomy might be responsible of this lower quality of life.

Nutritional status is compromised in the months/years following esophagectomy and may never return to baseline levels [5]. In fact, in our previous study, we observed that in the first 6 months after esophagectomy, all patients lose weight [6] and in a recent meta-analysis, 41 % of patients reported a greater than 10% weight loss at 6-month follow-up [7]. Eating difficulties are associated with deterioration in several aspects of HRQL up to 10 years after surgery for esophageal cancer [8]. However, long-term HRQL after esophagectomy is similar between EC survivors and European healthy subjects, despite persisting reflux and eating problems [9]. A recent review demonstrated the uncertainty on the optimal nutritional approach for patients with resectable esophageal cancer undergoing neoadjuvant treatment prior to esophagectomy [10].

Esophagectomy is associated with high rates of pulmonary complication and of acute respiratory distress syndrome [11]. In fact, pulmonary complications occurring in more than half of patients after open esophagectomy are a great concern [12]. Access to the esophagus is achieved through the deflation of one of the lungs and gas exchange maintained with one-lung ventilation [13]. During one-lung ventilation, the inflated lung is exposed to high-inspired oxygen concentrations and high inflation pressures, risking the development of ventilator-associated lung injury [14]. At the same time, the deflated lung sustains a period of ischemia followed by reperfusion. Together, these insults are likely to contribute to the high incidence of postoperative acute lung injury observed among this patient group [13]. In a retrospective study aimed to assess the clinical value of intensive long-term pulmonary rehabilitation program after esophagectomy, the pulmonary function values after rehabilitation were substantially similar when compared with pre-operative assessment, while an incomplete functional recovery with the pulmonary function strongly decreased was observed in standard care group [15].

We have therefore hypothesized that, similar to what was observed with the sleep impairment [16], the early postoperative HRQL could be improved by ameliorating the quality of nutrition and respiration after esophagectomy and designing a randomized control trial to assess if the adoption of nutritional and respiratory counseling may be effective in enhancing the quality of postoperative QoL after esophagectomy for cancer.

Methods

Study design

This randomized controlled trial aimed to assess the effectiveness of nutritional counseling and/or respirology counseling on postoperative quality of life after esophagectomy for cancer. This study was approved by the Ethics Committee of the Veneto Institute of Oncology (approval number: 8697-2012/46) and was registered at ClinicalTrials.gov (NCT01738633).

At discharge after esophagectomy, patients were randomized into one of four groups and received nutritional counseling (NC group), respiratory counseling (RC group), nutritional and respiratory counseling (NRC group), or standard care (SC group). Inclusion criteria were age above 18 years old and to be being scheduled for esophagectomy for cancer. Exclusion criteria were age below 18 years old, incapability to autonomously fill in questionnaires, and primary language not Italian.

Randomization

Participants were randomized according to a computer-generated sequence (simple randomization, allocation ratio 1: 1: 1: 1), and all allocations were included in sealed opaque envelopes (1 for each patient). Randomization was performed by the study coordinator at discharge. Blinding of patients and healthcare providers was not possible after assignment to interventions. Patients' allocations are described in Fig. 1.

Participants and setting

All patients undergoing esophagectomy for cancer at the Esophageal and Digestive Tract Surgical Unit of the Veneto Institute of Oncology in Padua, Italy, from January 2013 were contacted for enrolment. Inclusion criteria were age above 18 years and being scheduled for esophagectomy for cancer. Exclusion criteria were age below 18 years, inability to fill in a questionnaire, and primary language not Italian. Indication for surgery was evaluated by an experienced multidisciplinary team composed of a dedicated upper gastrointestinal surgeon, a medical oncologist, and a radiation oncologist. Fitness for surgery was evaluated by an experienced multidisciplinary team composed by an anesthesiologist, a cardiologist, a pneumologist, and a clinical nutritionist.

Tumor staging was performed according to the criteria of the International Union Against Cancer [17]. Patients with tumor staged above T3N0 or anyTN1 were offered neoadjuvant therapy as described elsewhere [18]. Patients were considered resectable when staged below T3N0 or after the termination of neoadjuvant treatment and when there was no evidence of distant metastases or locally advanced tumor with gross periesophageal involvement at restaging was present. Details concerning surgical techniques have been published elsewhere [18]. Briefly, esophagectomy was performed using an Ivor-Lewis procedure, via a laparotomy and right thoracotomy, for tumors of the mid-lower esophagus and gastric cardia. A hybrid minimally invasive esophagectomy approach that included a laparoscopic gastric tubulization and right

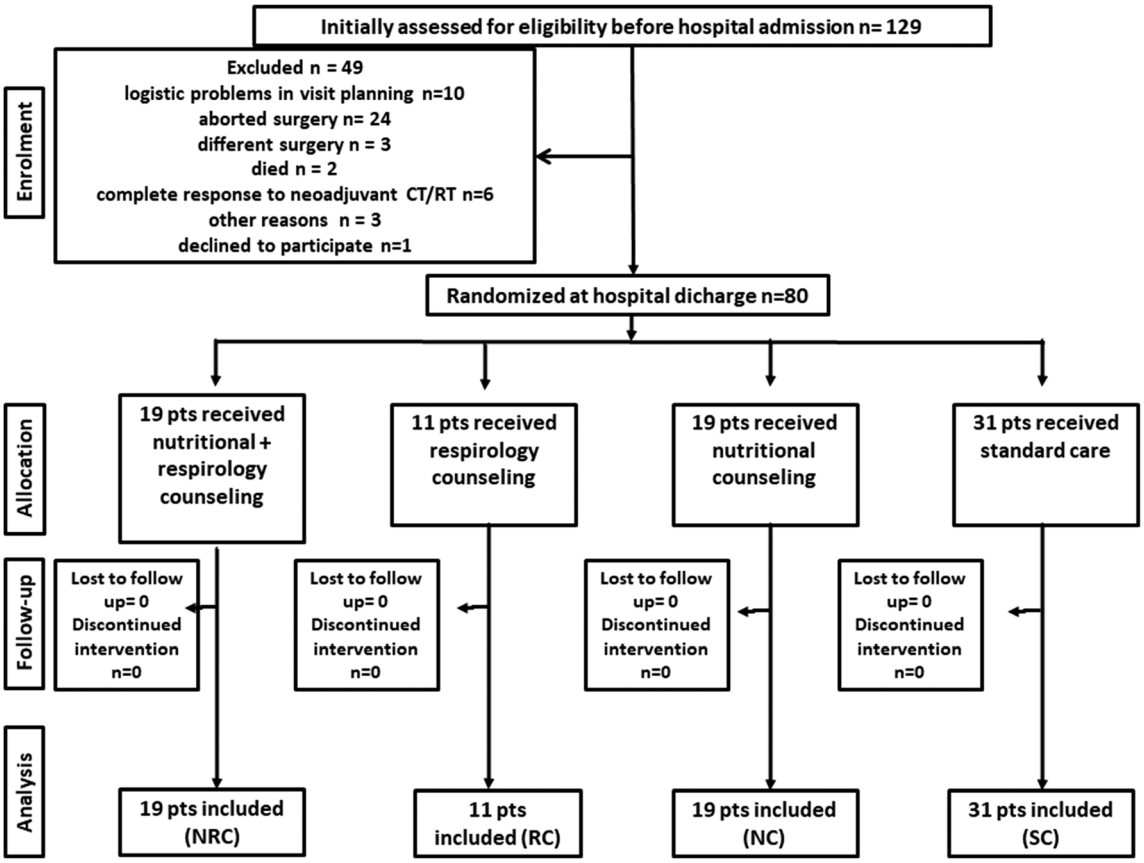

Fig. 1 Patients' allocations

thoracotomy was in recent time adopted [19]. A three-stage McKeown's procedure, with an additional left cervical incision, was reserved for tumors in the upper third of the esophagus. At least 6–8 cm of healthy esophagus was resected above the proximal edge of the tumor to avoid neoplastic involvement of the resection margins. In this group of patients, en bloc lymph node dissection was performed, including the paraesophageal, sub carinal, posterior mediastinal, and paracardial lymph nodes, as well as those located along the lesser gastric curvature, the origin of the left gastric artery, the celiac trunk, the common hepatic artery, and the splenic artery. The alimentary tract was reconstructed using the gastric pull-up technique; if the stomach was unavailable, either a jejunal loop or the left colon was used [18].

Interventions

The scheme and timing of the interventions are summarized in Fig. 2. Patients were divided into intervention groups (NC, RC, NRC groups) and a control group (SC group). The intervention groups received nutritional (NC group) and (NRC group)/or respirology counseling (RC group) after surgery, while the standard care group (SC group) treated according to standard care received nutritional and/or respirology support by surgeon at follow-up visits and at the surgeon's discretion. Patients receiving standard care had the standard surgical visit in the outpatients' clinic at 1 and 3 months after surgery. Patients were left free to ask for nutritional supplementation and respirology physiotherapy according to their needs. Nurses were left free to provide their routine assistance at their routine timetable.

An assessment of the nutritional status will be performed by the nutritionist at baseline (at the first surgical consultation before hospital admission for intervention), at months 1 and 3 after hospital discharge, in both the intervention group and the control group. Nutritional assessment consisted in anthropometric measurements, body composition analysis, physical function by hand grip strength (HGS), and evaluation of food intake. Anthropometry included the measuring of weight, height, waist circumference, and body mass index (BMI). Weight and height were measured by a professional medical scale and a stadiometer (Seca model 709, Germany), with a sensitivity of 0.1 kg and 0.1 cm, respectively. Body composition was assessed by a bioelectrical impedance analysis (BIA) (NutriLAB, Akern). Measurements included resistance (*R*), reactance (Xc), and phase angle (PhA). These values, included in specific prediction equations of the device, allowed the estimate of the following body compartments: fat-free mass

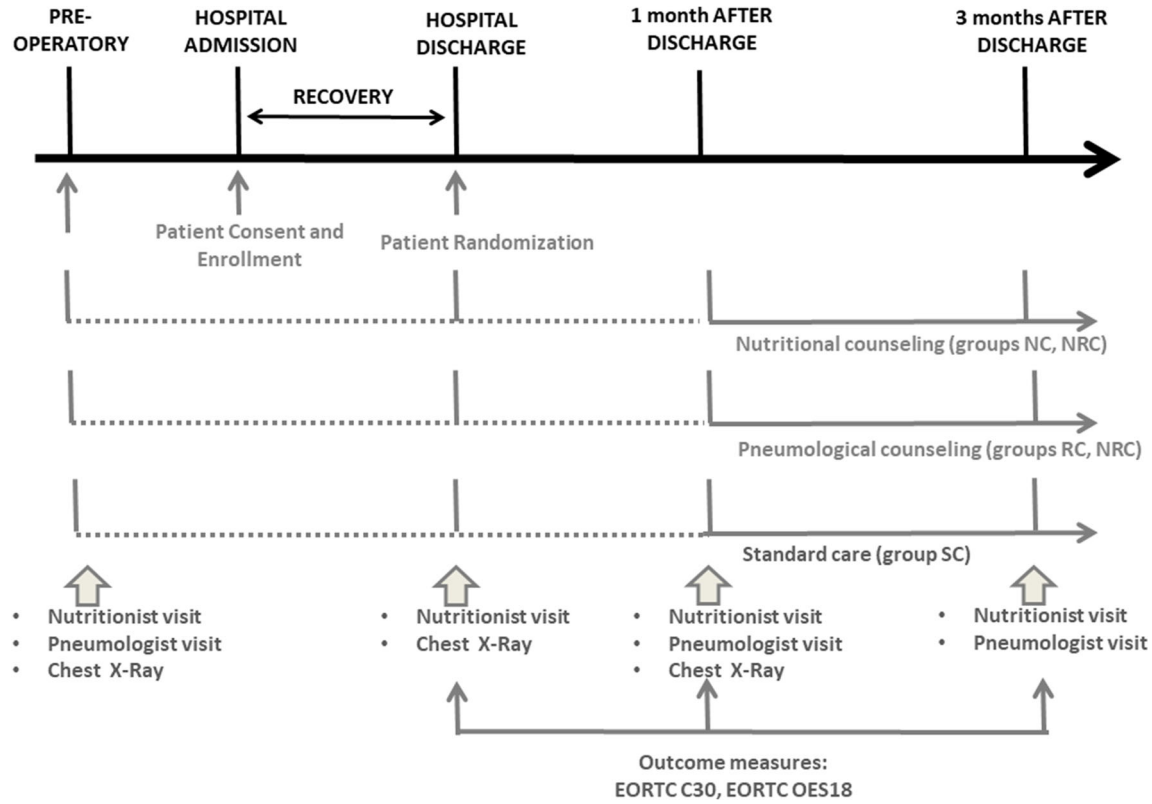

Fig. 2 Scheme and timing of the interventions

(FFM), fat mass (FM), body cell mass (BCM), total body water (TBW), and intra (ICW) and extracellular water (ECW) [20–22].

At the first visit, dietary intake was evaluated by 24-h recall, and food intake data were analyzed by a professional software with Italian food composition tables (MètaDieta, Meteda srl, Italy). Energy, macronutrients, and main micronutrients were assessed. All patients received preoperative supplementation with oral nutritional supplements enriched with immunonutrients (arginine, omega-3-fatty acids, ribonucleotides) for 5 days before surgery, at a dose of 3 brick/day, according to ESPEN Guidelines in oncology [23].

Patients were subsequently randomized into 4 groups, the interventional and the control ones. The first two received nutritional counseling for 3 months after surgery, and the others were treated according to standard care, receiving only dietary suggestion before hospital discharge by dietitian, who delivered an information leaflet about post-esophagectomy diet. The goal of the nutritional counseling in the intervention group was to meet individual nutrient requirements and to minimize nutritional symptoms that are surgery related (early postprandial satiety with consequent low food intake, dumping syndrome, reflux, dyspepsia, etc.) in order to maintain postoperative nutritional status [24]. Energy requirements will be estimated with 25–30 kcal/kg/day and protein requirements with 1.5 g/kg ideal body weight/day [23, 25]. The nutritional care plan was individualized for each patient. As a rule, nutritional counseling (dietetic advice on eating and feeding difficulties, skills for modifying food texture where necessary) was the first-line option in patients capable of consuming at least 75% of their nutritional requirements; patients consuming 50–75% received counseling associated to oral nutritional supplements; patients consuming < 50% will be evaluated for artificial nutrition [23, 26].

An assessment of the respiratory status was performed by the pneumologist at baseline (at the first surgical consultation before hospital admission for intervention), at hospital discharge (chest X-ray), at months 1 (chest X-ray and visit) and 3 after hospital discharge (visit). In the intervention groups (RC and NRC groups), each patient underwent two respirology visits: at 1 month and at 3 months after hospital discharge for esophagectomy. The respirology counseling lasted about 30 min for session.

In the first visit, initially, there was the anamnesis and the pneumologist collected information about the postoperative course after esophagectomy and about patient's general lifestyle (focused on familial respiratory problems, diet, smoking habit, alcohol consumption, level of physical activity and sedentary lifestyle, type of work). In both visits, after the physical examination, patients underwent the pulmonary function test (PFT) during which several parameters were collected (see "Outcomes" section) and used to diagnose and manage ongoing respiratory problems. PFT takes approximately 15 min for

patient. According to clinical and instrumental data, the specialist could establish a diagnosis and prescribe the relevant therapy and a rehabilitative program, or, depending on the diagnosis suspected, pneumologist could request other tests (e.g., chest X-rays or blood gas analysis) for further investigations.

Outcomes

Primary outcomes were items DY (dyspnoea), AP (appetite loss), and QL2 (global quality of life) of the QLQ C30 at 1 month after surgical operation. Secondary outcomes were item EA (eating) of OES18 at 1 month after surgical operation; items DY, AP, and QL2 of the QLQ C30 at 3 months after surgical operation; and item EA of OES18 at 3 months after surgical operation. All C30 and OES18 scales were recorded at admission for surgery and at discharge, 1 month and 3 months after surgery.

Questionnaires

The EORTC QLQ-C30 is a 30-item questionnaire for assessing the generic quality of life of cancer patients [27]. The QLQ-OES18 is the specific module for esophageal cancer, and it is designed for patients with local, locally advanced, or metastatic disease treated with single or combination treatment including surgery, chemotherapy, radiotherapy, or endoscopic palliation [28]. These questionnaires have been validated in the Italian language, and we used them in these versions [4].

Sample size

The enrollment started in January 2013 and was terminated in June 2017. The aim was to enroll 32 patients in each group. The sample size was calculated to identify a clinically significant difference of 10 points (2-sided test with type I error of 0.05 and a power of 0.80) in C30 scales according to the developers of the EORTC questionnaires [29].

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR) and categorical data as number and percentage. Specific aspects of QoL were selected a priori for evaluation in order to reduce the risk of multiple testing. Linear mixed effect models were used to assess mean score differences (MDs) with 95% confidence intervals (95% CI) for the selected QoL aspects, accounting for the longitudinal structure of the data. According to the developers of the EORTC questionnaires, a difference of 10 or more points identified a clinically significant impairment in C30 and OES18 scales. Therefore, any MD ≥ 10 or ≤ -10 was considered clinically significant (with any confidence interval above 10 or below − 10 indicating statistical significance). Linear mixed effect models were used to assess mean score differences (MDs) with 95% confidence intervals (95% CI) for additional nutritional measures (PA, FFm, Kcal, prot, BMI), accounting for the longitudinal structure of the data. Any confidence interval not including 0 indicated statistical significance. The variation in additional respiratory measures from admission to 1st month was classified as "resolved," "not changed," or "occurred" and evaluated between patient who received respiratory counseling and those who did not receive respiratory counseling using Fisher's exact test. All tests were 2-sided, and a p value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) [30].

Results

Early termination

In June 2017, the activity of the Esophageal and Digestive Tract Surgical Unit was suspended awaiting a new chief, and this led to the decision to terminate the study early. The local ethics committee approved the early termination (session date 14 March 2017; memorandum 41). Among 129 eligible patients at hospital admission, 43 were excluded because of complete response to neoadjuvant CT/RT (6 patients), logistic problems in visit planning (10 patients), aborted surgery (24 patients), or different surgery (3 patients). In addition, two patients died for postoperative complications, one declined to participate, and other three patients were excluded for other reasons. Finally, 80 patients completed the trial (Fig. 1).

Complete information was available for all participants with no missing data. Demographic and clinical characteristics were similar in the four treatment groups (Table 1). The final sample included 80 patients (71 males and 9 females; median age 63 years).

Nutritional counseling

Thirty-eight patients received nutritional counseling, while 42 did not. Demographic and clinical characteristics are shown in Table 1. Receiving nutritional counseling reduced appetite loss at 1 month (MD − 23, 95% CI − 36 to −8) and tended to reduce eating issues (MD − 9, 95% CI − 19 to 0) but not global quality of life (Table 2). Nutritional counseling did not influence appetite loss, global quality of life, or eating issues at 3 months after surgery (Table 2). Receiving nutritional counseling did not result in any significant changes in additional nutritional measures (PA, FFm, Kcal, prot, BMI; Supplementary Table 2). These results did not change after

Table 1 Patient characteristics according to randomization arm

	Patient who did not receive nutritional counseling ($n = 42$)	Patient who received nutritional counseling ($n = 38$)
Age (years)[a]	61 (55–67)	66 (56–70)
Male/female	38:4	33:5
Histology:		
Adenocarcinoma	32 (76)	23 (61)
Squamous cell carcinoma	10 (34)	15 (39)
Neoadjuvant therapy	37 (88)	33 (89)
Pathological stage:		
0 (complete response)	6 (14)	11 (29)
I–II	22 (53)	15 (39)
III–IV	14 (33)	12 (32)
Jejunostomy	20 (48)	18 (47)
Duration of surgery (min)[a]	430 (385–500)	420 (353–509)
Complications	6 (14)	4 (11)
Duration of hospital stay (days)[a]	15 (14–20)	15 (14–17)

Data expressed an *n* (%) or [a] median (IQR)

adjusting for receiving jejunostomy during esophagectomy (Supplementary Table 1).

Respiratory counseling

Thirty patients received respiratory counseling, while 50 did not. Demographic and clinical characteristics are shown in Table 3. Receiving respiratory counseling did not influence dyspnea or global quality of life at 1 month and at 3 months after surgery (Table 4). Receiving respiratory counseling did not result in any significant changes in additional respiratory measures (parenchymal thickening, streaks/bands of cicatricial atelectasis in lung base pleural effusion, pneumothorax; Supplementary Table 3) from admission to first month after surgery as measured at the routine chest X-ray.

Discussion

Several systematic reviews showed that patients undergoing esophagectomy for cancer had scores of physical function, nutritional status, and performance of health significantly lower than those obtained from the reference population [3, 5, 31]. After esophagectomy for cancer, eating difficulties, pain, fatigue, nausea and vomiting, and appetite loss were clinically relevant and statistically significantly worse symptoms experienced among those with a weight loss of ≥ 15% [32]. Although interventions to support dietary adjustments, prevent malnutrition and excessive weight loss, and enhance HRQOL following surgery for upper GI cancers are needed, evidence-based interventions to support long-term dietary alterations and restrictions following upper GI surgery are still lacking [33]. Moreover, postoperative pulmonary function was observed to have a strong correlation with the long-term

Table 2 Primary and secondary outcome measures: estimates of main effects of interventions

		Outcome measure	Nutritional counseling (yes vs. no): MD (95% CI)
Primary outcomes	Change from discharge to 1st month	Appetite loss (C30-AP)	− 23 (− 36 to − 8)
		Quality of life (C30-QL2)	7 (− 2 to 16)
Secondary outcomes	Change from discharge to 1st month	Eating (OES18-EAT)	− 9 (− 19 to 0)
	Change from discharge to 3rd month	Appetite loss (C30-AP)	7 (− 25 to 11)
		Quality of life (C30-QL2)	7 (− 4 to 18)
		Eating (OES18-EAT)	− 3 (− 17 to 10)

MD mean difference, *CI* confidence interval. Any MD ≥ 10 or ≤ − 10 was considered clinically significant; any CI above 10 or below − 10 indicated statistical significance

Table 3 Patient characteristics according to randomization arm

	Patient who did not receive respiratory counseling ($n = 50$)	Patient who received respiratory counseling ($n = 30$)
Age (years)[a]	61 (54–67)	67 (61–73)
Male/female	45:5	26:4
Histology:		
Adenocarcinoma	35 (70)	20 (67)
Squamous cell carcinoma	15 (30)	10 (33)
Neoadjuvant therapy	43 (86)	27 (90)
Pathological stage:		
0 (complete response)	11 (22)	6 (20)
I–II	21 (42)	16 (53)
III–IV	18 (36)	8 (27)
Jejunostomy	24 (48)	14 (47)
Duration of surgery (min)[a]	420 (370–500)	434 (401–501)
Complications	6 (12)	4 (13)
Duration of hospital stay (days)[a]	15 (14–19)	15 (14–18)

Data expressed an *n* (%) or [a] median (IQR)

outcome and HRQL after esophagectomy, and its deterioration is associated to a significant deterioration in global quality of life [15]. Thus, the aim of this study was to evaluate the effect of the nutritional and respiratory counseling on quality of life after esophagectomy for cancer.

In our series, receiving nutritional counseling reduced appetite loss at 1 month and tended to reduce eating issues but not global quality of life. However, nutritional counseling did not influence appetite loss, global quality of life, or eating issues at 3 months after surgery, and receiving nutritional counseling did not result in any significant changes in additional nutritional measures (PA, FFm, Kcal, prot, BMI). The failure to obtain long-lasting HRQL effect and to decrease body weight loss might be due to several reasons. Firstly, in our institution, jejunostomy was created in all "frail" patients (i.e., patients with preoperative food intake impairment, patients who had upper esophageal cancer, and elderly patients) who would have been at risk of anastomotic leakage [34]. An extensive use of enteral nutrition might have mitigated the differences between the group who received nutritional counseling and those who did not. Secondly, the alteration of the digestive physiology after esophagectomy might make the simple counseling less effective than expected. In an interesting double-blind, placebo-controlled, randomized crossover study, esophagectomy patients and healthy controls received either 1 mL 0.9% saline or 1 mL (100 μg) octreotide acetate subcutaneously followed by a standardized ad libitum meal on each of two assessments [35]. Ghrelin levels were similar for both groups, but postprandial GLP-1 and PYY responses were significantly greater among esophagectomy group as compared with controls [35]. Thus, patients who had esophagectomy demonstrated an exaggerated postprandial satiety gut hormone response that was attenuated by octreotide and that can in part explain the persisting eating problems.

In our series, receiving respiratory counseling did not influence dyspnea or global quality of life at 1 month and at 3 months after surgery. Receiving respiratory counseling did not result in any significant changes in additional respiratory measures (parenchymal thickening, streaks/bands of cicatricial atelectasis in

Table 4 Primary and secondary outcome measures: estimates of main effects of interventions

		Outcome measure	Respiratory counseling (yes vs. no): MD (95% CI)
Primary outcomes	Change from discharge to 1st month	Dyspnea (C30-DY)	− 2 (− 16 to 11)
		Quality of life (C30-QL2)	0 (− 10 to 9)
Secondary outcomes	Change from discharge to 3rd month	Dyspnea (C30-DY)	7 (− 7 to 20)
		Quality of life (C30-QL2)	0 (− 12 to 10)

MD mean difference, *CI* confidence interval. Any MD ≥ 10 or ≤ − 10 was considered clinically significant; any CI above 10 or below − 10 indicated statistical significance

lung base pleural effusion, pneumothorax) from admission to first month after surgery as measured at the routine chest X-ray. Several studies on pharmacology intervention or anesthesiologic techniques aimed to improve pulmonary function after esophagectomy, but the results have been deluding. A promising large multicentric randomized trial tested the effect of perioperative treatment with inhaled salmeterol, but this treatment was found to not prevent acute lung injury after esophagectomy [13]. Moreover, a recent systematic review and meta-analysis showed no differences in postoperative pain scores or pulmonary complications after esophagectomy between systemic and epidural analgesia and between systemic and paravertebral analgesia [36]. On the other hand, a small retrospective study aimed to test an intensive long-term pulmonary rehabilitation program after esophagectomy showed some benefit in terms of pulmonary function [15]. However, this study was limited by the small sample size and the retrospective design. Finally, the only major improvement in terms of decreasing the pulmonary complication was obtained with a major change in the surgical technique. The minimally invasive esophagectomy and laparoscopic and thoracoscopic esophagectomy avoiding the thoracotomy operative time lead to a significant decrease in pulmonary infection rate compared with open esophagectomy [12]. Similar results, in terms of decreased pulmonary infection and consequent sequelae, were obtained with the transhiatal esophagectomy that completely avoid thoracotomy [37].

This study has some limitations. The main one is its early termination, which was decided to prevent setting bias. The limited sample size and the evaluation of HRQL involving several scales may have affected the results because of the problem of multiple testing. However, specific aspects of HRQL were selected a priori for evaluation to reduce this potential bias. In addition, BMI and chest X-ray were used as an objective measure of nutritional status and lung complication. Finally, patients in the groups who received postoperative counseling were left to use them freely; thus, the frequency of use might have influenced the lack of significant improvement. Further studies on postoperative counseling should take into account patients' adherence to the use of the provided advices.

In conclusion, intensive postoperative care does not affect global quality of life. Nutritional counseling reduced appetite loss and tended to reduce eating issues after esophagectomy for cancer, but respiratory counseling has limited impact on dyspnea. Effective implementation of postoperative care should be investigated.

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Compliance with ethical standards

This study was approved by the Ethics Committee of the Veneto Institute of Oncology (approval number: 8697-2012/46) and was registered at ClinicalTrials.gov (NCT01738633).

Conflict of interest The authors declare that they have no conflict of interest.

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