The influence of preoperative weight loss on the postoperative course after esophageal cancer resection

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Objective: Preoperative weight loss might increase the risk of postoperative morbidity and mortality after esophagectomy for cancer. We hypothesized that patients with esophageal cancer with >10% weight loss during the 3 months before their diagnosis would be at an increased risk of postoperative complications, have a longer length of stay, and have worse overall survival.

Methods: In the present hospital-based cohort study, all patients who had undergone surgery for esophageal cancer in 1990 to 2010 at the Erasmus University Medical Center Rotterdam were included. Weight loss was defined as “no, or limited” ($\leq 10\%$) or “severe” ($> 10\%$). Logistic regression analysis was used to estimate the relative risk of complications, expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Hazard ratios were calculated to assess the length of hospital stay and survival. The risk estimates were adjusted for potential confounding factors.

Results: Of 922 included patients, 155 (17%) had experienced severe weight loss. These patients had no increased risk of early surgical, early nonsurgical, or late surgical complications (OR, 0.83 and 95% CI, 0.54-1.24; OR, 0.90 and 95% CI, 0.63-1.30; OR, 1.14 and 95% CI, 0.79-1.66, respectively) and had no increased length of stay (hazard ratio, 1.09; 95% CI, 0.89-1.35). Preoperative weight loss was followed by increased 5-year mortality (hazard ratio, 1.34; 95% CI, 1.02-1.74).

Conclusions: A >10% preoperative weight loss was followed by decreased 5-year survival after esophageal cancer surgery but no increased risk of postoperative complications. (J Thorac Cardiovasc Surg 2014;147:490-5)

Most patients with esophageal cancer will experience dysphagia, leading to reduced food intake.¹ Furthermore, increased energy consumption caused by systemic inflammation induced by the tumor enhances weight loss.² This systemic inflammation results from local effects of the tumor directly or a secondary host response to tumor tissue necrosis and hypoxia, which stimulates secretion of interleukins (interleukin-1 and -6), tumor necrosis factor- α , interferons (interferon- γ), hematopoietic growth factors, and acute phase proteins.^{3,4} Thus, unintentional and substantial (>10%-15%) weight loss will occur in approximately 80% of all patients with esophageal cancer before diagnosis.⁵

Malnutrition seems to be associated with increased early postoperative morbidity and mortality and reduced overall survival after major gastrointestinal surgery in general.^{4,6-8} Two studies of patients with esophageal cancer specifically did not detect any association between the body mass index (BMI), as a surrogate for nutritional status, and morbidity after esophagectomy.^{9,10} However, patients with esophageal cancer with a high BMI are often malnourished owing to substantial weight loss within a relatively short period.¹¹ We tested the hypotheses that patients with esophageal cancer with >10% unintentional weight loss during the 3 months before the diagnosis are at increased risk of postoperative complications, have a longer length of stay, and have a worse overall survival.

METHODS

Patients

The patients were identified from a cohort of patients with cancer of the esophagus or gastroesophageal junction treated at the Erasmus Medical Center, University Medical Center Rotterdam (Rotterdam, The Netherlands). Information on patient demographics, clinical and pathologic characteristics, details on treatment, surgical procedure, and postoperative course was prospectively collected by a specialized data manager. All patients diagnosed with invasive squamous cell carcinoma or adenocarcinoma of the esophagus who had undergone surgical tumor resection with or without preoperative chemotherapy or radiotherapy, from May 1, 1990 to October 29, 2010 were included.

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Abbreviations and Acronyms

BMI	= body mass index
CI	= confidence interval
HR	= hazard ratio
OR	= odds ratio

Surgery

The patients underwent an open transhiatal or transthoracic approach. With the transhiatal approach, the distal esophagus and all periesophageal tissue, including the lymph nodes and bilateral parietal pleura, was dissected under direct visualization through a widened hiatus of the diaphragm up to the level of the inferior pulmonary vein. All lymph nodes at the origin of the celiac axis were routinely dissected and included in the specimen. A gastric tube was typically created to replace the resected specimen. After mobilization of the cervical esophagus trough, a left-sided neck incision, the intrathoracic esophagus was bluntly resected from the neck to the abdomen using a vein stripper. An esophagogastronomy was created between the proximal esophageal remnant and the gastric conduit using either a circular stapler or a hand-sewn technique.

Patients who underwent the transthoracic approach (3-stage McKeown) received a right-sided posterolateral thoracotomy in which the esophagus, periesophageal tissue in the posterior mediastinum, the thoracic duct, and azygos vein were dissected. Subcarinal lymph nodes were routinely included in the specimen. Right-sided paratracheal and aorta-pulmonary window lymph nodes were dissected in all cases of squamous cell carcinoma and cases of adenocarcinoma in which macroscopically suspicious tumor involvement was found. The subsequent abdominal and cervical phase was similar to that of the transhiatal approach.¹² All patients received a feeding jejunostomy or nasojejunal catheter for perioperative enteral feeding.

Study Exposure

The exposure was defined as unintentional weight loss during the 3 months before diagnosis and categorized as “no or limited ($\leq 10\%$)” or “severe ($>10\%$)” weight loss. At the first visit to the outpatient clinic, the patients estimated their weight for the 3 months before their first visit. This weight was considered their baseline weight. All reported weight loss was considered unintentional. The patients were weighed at the same visit to the outpatient clinic (actual weight), and the percentage of weight loss in the 3 months before the diagnosis was calculated by subtracting the baseline weight from the actual weight, dividing this difference by the baseline weight, and multiplying by 100. No uniform consensus has been reached on the definition of malnutrition in relation to weight loss, but it has often been referred to as $>10\%$ to 15% weight loss within 6 months,¹³ $>5\%$ in 3 months,¹⁴ or $>10\%$ within 6 months¹⁵ before surgery. The choice of 10% weight loss as a cutoff was predefined and chosen on the basis of earlier studies, in which such weight loss was found to be associated with an increased risk of postoperative complications after major abdominal surgery.¹⁵

Study Outcomes

We included 3 study outcomes: (1) postoperative complications, (2) length of hospital stay, and (3) overall survival. Postoperative complications were categorized into early surgical complications, early nonsurgical complications, and late surgical complications. Early complications were those that occurred within 30 days after primary esophagectomy. Late complications were defined as those occurring >30 days after the primary surgery. Early surgical complications included anastomotic leak, recurrent laryngeal nerve paresis or paralysis, bleeding, ileus, severe chyle leakage, leakage of the feeding jejunostomy, gastroparesis for >10 days

after surgery, wound infection, and necrosis of the substitute. Early non-surgical complications were categorized as infectious complications (including pneumonia, sepsis, and urinary tract infection) and noninfectious complications (including acute respiratory distress syndrome, myocardial infarction, and thromboembolic events). Late surgical complications were those occurring >30 days after surgery and included anastomotic stenosis requiring dilatation, pyloric stenosis requiring intervention, intercostal neuralgia, ileus, excessive weight loss, and cachexia. The length of hospital stay was defined as the number of days in the hospital since the date of the primary operation.

Overall survival was calculated from the date of esophagectomy until death or the end of the follow-up period, which was up to 5 years postoperatively. The patients were seen in the outpatient clinic every 3 months during the first postoperative year, every 6 months the second year, and yearly thereafter until 5 years after surgery. Imaging was not routinely performed during the follow-up visits but only for those patients presenting with clinical signs of recurrence.

Statistical Analysis

The relative risks of weight loss in relation to complications were calculated using logistic regression analysis and are expressed as odds ratios (ORs), with the 95% confidence intervals (CIs). In a multivariate model, the OR of complications in relation to weight loss was adjusted for potential confounding by age (continuous variable), gender, tumor stage (histopathologic stage, classified according to the 6th version of the Union for International Cancer Control-pTNM classification and categorized into 4 groups: 0-I, II, III, and IV), comorbidity (including cardiovascular, respiratory, and neurologic disease, diabetes mellitus, and psychiatric disorders and categorized as 0 or ≥ 1), and neoadjuvant chemotherapy and/or radiotherapy (yes or no).

The chi-square test and *t* test were used to examine the association between the baseline clinical characteristics and weight loss.

To assess whether the BMI was associated with weight loss and could potentially influence the results, a Wald test was used to test the interactions between the BMI and weight loss. The BMI was defined as the weight before surgery divided by the patient's height in meters squared (kg/m^2) and categorized into 3 groups: <25 , 25 – 29 , ≥ 30 kg/m^2 .

The Kaplan-Meier method was used to illustrate the hospital admission time and overall survival in the comparison groups, and the log-rank test was used to analyze the statistically significant differences between the curves.

Cox regression analysis was used to calculate the hazard ratios (HRs), with the 95% CIs, regarding hospital admission time and overall survival. In a multivariate model, the HRs of differences in admission time and overall survival were adjusted for potential confounding by age, gender, tumor stage, comorbidity, and use of neoadjuvant treatment. $P < .05$ was considered statistically significant.

All analyses were performed using Stata, version 11, for Mac (Stata-Corp, Inc, College Station, Tex).

RESULTS

Patient Characteristics

During the study period, 1271 patients with cancer of the esophagus or gastroesophageal junction were considered for surgical resection at the Erasmus Medical Center University Medical Center Rotterdam. Exclusions were made because the primary plan (surgical tumor resection) was not pursued (235 patients [18%]), different histologic type (17 patients [1.3%]), and missing information of explanatory variables (67 patients [5.2%]). Of the 922 remaining patients (73%), 155 (17%) had lost $>10\%$ of

TABLE 1. Patient characteristics (n = 922)

Variable	Total	Weight loss ≤ 10%	Weight loss > 10%	P value
Total	922 (100)	767 (83)	155 (17)	NS
Age (y)	63 ± 10	62 ± 10	60 ± 10	.0348
Gender				
Male	712 (77)	609 (79)	103 (66)	.0005
Female	210 (23)	158 (21)	52 (34)	NS
BMI* (kg/m ²)				
<25	419 (45)	324 (48)	95 (75)	.001
25-29	285 (31)	260 (39)	25 (20)	NS
≥30	95 (10)	88 (13)	7 (6)	NS
Missing	89 (13)	73 (13)	16 (15)	NS
Comorbidity†				
None	421 (46)	360 (47)	61 (40)	NS
≥1	501 (54)	407 (53)	94 (61)	NS
Neoadjuvant treatment				
No	721 (79)	601 (78)	120 (77)	NS
Yes	201 (22)	166 (22)	35 (23)	NS
Histologic type				
Squamous cell	263 (25)	223 (29)	60 (37)	NS
Adenocarcinoma	622 (69)	527 (69)	95 (61)	NS
Adenocarcinoma in Barrett's epithelium	17 (2)	17 (2)	0 (0)	NS
Tumor stage‡				
0-I	173 (19)	162 (21)	11 (7)	NS
II	257 (28)	212 (28)	45 (29)	NS
III	432 (47)	342 (45)	90 (58)	.001
IV	10 (1)	6 (1)	4 (30)	NS
Unknown	49 (7)	45 (7.8)	4 (4)	NS
Surgical approach				
Transhiatal	722 (79)	610 (80)	112 (73)	NS
Transthoracic	169 (18)	135 (18)	34 (22)	NS
Other§	28 (3)	20 (3)	8 (5)	NS

Data presented as mean ± standard deviation or n (%). NS, Nonsignificant; BMI, body mass index. *BMI was determined from weight before surgery. †Comorbidities included cardiovascular, respiratory, and neurologic disease, diabetes mellitus, and psychiatric disorders. ‡Tumor stage after pathologic examination according to the 6th revision of the Union for International Cancer Control-TNM classification. §Defined as left-sided thoracotomy or transthoracic esophagectomy with cervical anastomosis.

their usual weight in the 3 months before diagnosis and were thus classified as exposed. The 336 patients (26.4%) who had undergone nonradical resection (ie, R1 and R2 resection) were excluded from the long-term survival analyses but were included in the short-term outcome analyses (eg, length of hospital stay, postoperative mortality, and early surgical, nonsurgical, and long-term complications). The association between the baseline characteristics and weight loss were assessed using chi-square analyses. Male gender, higher tumor stage, and a low BMI were associated with the >10% weight loss ($P < .05$ for all). Moreover, the patients with >10% weight loss were younger ($P < .05$, t test). The patient and tumor characteristics of the exposed and nonexposed patients are listed in Table 1.

TABLE 2. Postoperative course after esophagectomy for cancer (n = 922)

Variable	Total	Weight loss ≤ 10%	Weight loss > 10%
Length of hospital stay (d)*	22 ± 21	22 ± 21	20 ± 15
Postoperative mortality†	71 (8)	55 (7.1)	16 (10)
Early surgical complications‡			
None	674 (73.0)	556 (60.0)	118 (12.8)
≥1	249 (27.0)	212 (23.0)	37 (4.0)
Early nonsurgical complications§			
None	450 (48.8)	370 (40.1)	80 (8.7)
≥1	473 (51.3)	398 (43.0)	75 (8.1)
Late surgical complications			
None	570 (63)	468 (52.8)	92 (10.4)
≥1	327 (36.9)	267 (30.1)	60 (6.8)

Data presented as mean ± standard deviation or n (%). *Admission time was calculated from the day of surgery until discharge. †Defined as death within 90 days after surgery. ‡Defined as complications occurring within 30 days after the initial surgery, including anastomotic leak, recurrent laryngeal nerve paresis or paralysis, bleeding, small bowel obstruction, chyle leakage, leakage of the feeding tube, gastroparesis for >10 days after surgery, wound infection, or necrosis of the substitute for which a reoperation was required. §Defined as acute respiratory distress syndrome and thromboembolic events. ||Defined as complications occurring >30 days after the initial surgery, including anastomotic stenosis (requiring dilatation or therapy), pyloric stenosis, intercostal neuralgia, ileus, weight loss, and cachexia.

Complications

A total of 249 patients (27%) developed a surgical complication within 30 days after surgery. In general, no increased risk of such early surgical complications was found between the patients with and without weight loss (adjusted OR, 0.83; 95% CI, 0.54-1.24). No statistically significant increased risk of anastomotic leak was found (adjusted OR, 0.87; 95% CI, 0.46-1.64), wound infections (adjusted OR, 1.1; 95% CI, 0.47-2.45), or necrosis of the substitute (adjusted OR, 1.1; 95% CI 0.34-13.20; Table 2).

A total of 472 patients (51%) developed an early nonsurgical complication. No increased risk of such complications was found between the exposed and nonexposed groups (adjusted OR, 0.90; 95% CI, 0.63-1.30; Table 2).

Late surgical complications were diagnosed in 327 patients (35%). No increased risk was identified in patients with weight loss (Table 2).

Length of Hospital Stay

The mean admission time was 22 ± 20.9 days and 20 ± 15.3 days for patients with and without weight loss, respectively (Table 1). The Kaplan-Meier curve comparing the admission time is shown in Figure 1. No difference was found in the admission time for patients with and without weight loss (log-rank, 0.6194). In the adjusted analysis, weight loss did not influence the length of stay (HR, 1.06; 95% CI, 0.85-1.33; Table 3).

Survival

The Kaplan-Meier curve comparing patients with and without weight loss regarding overall survival for up to

FIGURE 1. Length of hospital stay in days after esophagectomy in 922 patients with and without weight loss 3 months before the esophageal cancer diagnosis.

5 years after surgery showed a statistically significantly worse overall survival for patients with weight loss ($P < .0001$; Figure 2). After adjustment for potential confounders, the patients with weight loss had slightly increased mortality within 5 years after surgery (adjusted HR, 1.34; 95% CI, 1.02-1.74) (Table 4).

Interactions

No statistically significant interactions were found between the BMI and preoperative weight loss regarding

TABLE 3. Risk of complications after esophagectomy in association with weight loss 3 months before esophageal cancer diagnosis

Complications	n (%)	Weight loss ≤ 10%	Weight loss > 10%
Early surgical*			
All surgical	249 (27.0)	1.0 (Reference)	0.83 (0.54-1.24)
Anastomotic leak	89 (10)	1.0 (Reference)	0.87 (0.46-1.64)
Wound infection	41 (4)	1.0 (Reference)	1.1 (0.47-2.45)
Necrosis of the substitute	25 (3)	1.0 (Reference)	1.1 (0.34-3.20)
Other surgical†	108 (12)	1.0 (Reference)	0.9 (0.52-1.61)
Early nonsurgical			
All nonsurgical	472 (51)	1.0 (Reference)	0.90 (0.63-1.30)
Infectious‡	336 (36)	1.0 (Reference)	1.20 (0.77-1.91)
Noninfectious§	76 (8)	1.0 (Reference)	0.47 (0.17-1.23)
Late surgical			
All late surgical	327 (35)	1.0 (Reference)	1.14 (0.79-1.66)
Anastomotic stenosis	245 (27)	1.0 (Reference)	1.10 (0.68-1.81)

Data presented as number of complications (%) or odds ratio (95% confidence interval). *Defined as complications occurring within 30 days after the initial surgery. †Defined as anastomotic leak, recurrent laryngeal nerve paresis or paralysis, bleeding, small bowel obstruction, chyle leakage, leakage of the feeding tube, gastroparesis for >10 days after surgery, wound infection, and necrosis of the substitute for which a reoperation was required. ‡Defined as pneumonia, sepsis, and urinary tract infection requiring treatment. §Defined as acute respiratory distress syndrome and thromboembolic events occurring within 30 days after the initial surgery. ||Defined as complications occurring >30 days after the initial surgery, including anastomotic stenosis (requiring dilatation or therapy), pyloric stenosis, intercostal neuralgia, ileus, weight loss, and cachexia.

FIGURE 2. Overall 5-year survival of 681 patients with and without weight loss 3 months before the esophageal cancer diagnosis who underwent esophagectomy.

complications (Wald chi-square, 3.0; $P = .271$), length of hospital stay (Wald chi-square, 2.5; $P = .280$), overall survival (Wald chi-square, 0.3; $P = .835$), or disease-free survival (Wald chi-square, 1.0; $P = .603$).

DISCUSSION

The results of the present study indicate that unintentional preoperative weight loss of $\geq 10\%$ before esophageal cancer resection is followed by worse overall 5-year survival but does not influence the risk of postoperative complications or length of hospital stay.

Among the strengths of the present study were the prospective collection of data in a predefined study form, which decreased the risk of systematic errors resulting from misclassification. Furthermore, an independent data manager, not involved in care of the patients, collected the clinical information, which further decreased the risk of biased data collection. Information about important clinical variables was available, which facilitated adjustment for potential confounding. Among the weaknesses of the study was the risk of residual confounding, which is an issue in observational studies owing to the lack of randomization. Another potential weakness of the study was patient selection, because only patients who were well enough to undergo surgery were included. This might imply that patients who were severely malnourished, were severely overweight, or had many concurrent diseases were considered too frail to

TABLE 4. Effect of preoperative >10% weight loss before esophageal cancer diagnosis on overall and disease-free survival and hospital duration after esophagectomy

Variable	HR	95% CI	P value
Overall 5-y survival*	1.34	1.02-1.74	.03
Length of hospital stay	1.09	0.89-1.35	.41

HR, Hazard ratio; CI, confidence interval. *Occurrence of an event means death.

undergo surgery. Moreover, the recall of the patients' estimated weight 3 months before the diagnosis might have increased the likelihood of misclassification. However, a recent study has suggested that a patient's estimated weight is as accurate as a measured weight at the outpatient clinic.¹⁶ Another potential weakness was the lack of objective measurements of malnutrition (eg, serum albumin and C-reactive protein levels). We also did not have information on interventions to prevent weight loss after the diagnosis of esophageal cancer. Moreover, no detailed information was available on the patients' nutritional intake, which could be of concern, because patients often adjust their diet after having developed eating difficulties before seeking medical attention.² When adjusting for confounding factors, the tumor stage was classified according to the 6th version of the Union for International Cancer Control-TNM classification. We realize that this classification has some limitations compared with the 7th version of the TNM classification. However, in the present cohort, not all the information required for staging using the 7th edition (eg, number of resected lymph nodes) was available. Thus, we were unable to analyze the results using the 7th revised staging system. Also, we used the histopathologic TNM stage and not the clinical TNM stage, which has some limitations. The clinical TNM stage does not take into account downstaging after preoperative chemoradiotherapy. However, only the vast minority of our cohort underwent preoperative chemoradiotherapy.

It has generally been believed that severe weight loss before surgery in patients with cancer increases the risk of infectious and noninfectious complications. Hence, the optimization of nutritional status by parenteral and enteral feeding aimed at reducing postoperative morbidity and mortality has frequently been deployed. The results of the present study, however, have shown that patients with esophageal cancer who had lost >10% body weight in the 3 months before the diagnosis were not at an increased risk of postoperative complications.

Increased overall 5-year mortality was found among patients who had lost >10% weight before esophageal cancer surgery. This is a novel finding specifically regarding esophageal cancer surgery, but reduced survival has been described for general abdominal surgery.^{4,17,18} Although the mechanism behind this is unclear, reduced immune function in malnourished patients might be associated with a reduced chance of survival.⁴

The results of the present study pose the question of whether it is useful to halt additional weight loss after diagnosis and correct weight loss before patients undergo surgery, after some interval of delay. Some evidence has shown that patients with an increased risk of severe malnutrition, such as severe weight loss (>10%), a low BMI (<18 kg/m²), or increased inflammatory parameters, might benefit from nutritional support and the involvement of

dietitians before surgery.¹⁹ However, patients who did not have severe weight loss did not seem to benefit strongly from preoperative nutritional support.¹⁹

Earlier studies have suggested that the BMI per se is not associated with a risk of postoperative complications or survival after esophagectomy.^{10,12,20} In the present study, we evaluated the percentage of preoperative weight loss, rather than the BMI, because patients with esophageal cancer and a high BMI are often malnourished owing to severe weight loss.¹¹ Additionally, weight loss, even without taking the BMI into account, can be a good indicator of disease-related malnutrition.^{13,21} The >10% weight loss cutoff was determined from studies in which weight loss of ≤10% was not associated with an increased incidence of postoperative complications²¹ but >10% was considered to represent a severe nutritional risk.¹³ This is in contrast to the findings of the present study, in which we did not observe an increased risk of complications after surgery. This could have been because most studies have investigated major abdominal surgery, including a mix of oncologic operations, and our study focused on patients with esophageal cancer.

In conclusion, patients with esophageal cancer who experience weight loss of >10% in the 3 months before diagnosis had no increased risk of postoperative complications or longer hospital stay. However, they had increased 5-year overall mortality after surgery. These results highlight the need for studies to test whether improving the nutritional status in malnourished patients with esophageal cancer before esophagectomy is beneficial from a prognostic viewpoint.

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