

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 , $25\text{--}29$, ≥ 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

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