Study protocol.

Official Title of the study:

Severe complications after gastrectomy for esophagogastric junction and gastric cancer.

Document date: April/1/2019

Introduction

Gastric cancer (GC) is the fifth most common cancer[1], with more than 900,000 new cases every year, and the third leading cause of cancer-related death worldwide[2].

Surgery and adjuvant treatment are the main treatment modalities for GC. Postoperative morbidity rates after gastrectomy vary across different studies, but total morbidity is more than 20–30% in most studies[3–8]. In a previous study by our group, morbidity was present in 31% of 1066 gastrectomies [9].

Data on postoperative morbidity predictors are heterogeneous. Patient (age, comorbidity, body mass index, serum albumin), tumor (local invasion and location), and surgery (open approach, total gastrectomy, lymph node dissection, and multi-organ resection) variables are described as potential factors for higher morbidity[3–5,8].

In our previous study, we did not have data on complication severity because this type of score did not exist at the beginning of that study[9]. In the past decade, complication severity has gained great importance, and use of the Clavien-Dindo classification has been widely adopted[10]. However, only a few studies have evaluated postoperative morbidity predictors according to complication severity for gastrectomy[6,7].

The aim of this study to identify predictors of severe postoperative morbidity after gastrectomy for gastric cancer (GC) and esophagogastric junction (EGJ) cancer and to evaluate long-term survival according to complications.

Material and methods

This is a retrospective cohort study. We collect patients' demographics, tumor and surgery characteristics, and postoperative morbidity. All consecutive patients treated with a gastrectomy for GC or EGJ cancer are included. Only patients with stomach or EGJ adenocarcinoma are selected, and patients with other histology are excluded.

Preoperative assessment

The preoperative assessment is an upper gastrointestinal endoscopy, biopsy, complete blood count, liver function tests, electrocardiogram, and nutritional evaluation. Preoperative imaging is a thorax-abdomen-pelvis computed tomography (CT) scan.

Operative procedure

Epidural analgesia is routinely employed in open surgery. Depending on the tumor's location, a total or subtotal gastrectomy is indicated. Surgery includes omentectomy with bursectomy and D2 lymph node dissection, according to the Japanese classifications in patients with curative gastrectomy[11]. Multi-organ resection, including spleen, pancreas, colon, and liver, is performed in cases of direct tumor invasion. Partial distal esophagectomy with a transhiatal approach and mediastinal anastomosis is employed for Siewert types II and III cancers, with frozen section intraoperative biopsy to confirm an R0 resection. Partial distal esophagectomy is considered a multi-organ resection when more than 2 cm of the esophagus was resected. Routine cholecystectomy is performed in curative cases and was not considered a multi-organ resection. A reconstruction, using Roux-en-Y, is performed after a total gastrectomy; Roux-en-Y or Billroth II is used for subtotal gastrectomy. Esophagojejunal anastomosis is performed with a circular stapler and a second layer of running monofilament suture. One or two prophylactic drains are used routinely[9]. A laparoscopic approach is employed in patients with clinical early GC who are not candidates for endoscopic resection and patients with advanced GC without clinical invasion of adjacent structures and with lymph node metastases only in the perigastric area[12].

Postoperative management

Patients start early respiratory and physical therapy the day following surgery. An oral contrast study is performed on postoperative day 5–7 for total gastrectomy; after this study, the patient starts an oral diet and prophylactic drains are removed.

Esophagogastric junction (EGJ) cancer is classified according to Siewert classification[13]. In this study, only EGJ cancer Siewert types II and III are included. Patients are staged using *TNM Classification of Malignant Tumors*, seventh edition[14].

Complication assessment

Severe 30-day or in-hospital morbidity is defined as a Clavien-Dindo score $\geq$ 3[10]. The complication data is collected by each attending surgeon and together at a monthly conference. Complications detected upon readmission are also included in this study.

The complications are grouped into three categories: intraabdominal, wound–abdominal wall, and medical complication. We consider an esophagojejunostomy leak as the appearance of contrast outside the anastomosis, using an oral contrast study or CT scan, or by direct evaluation at reoperation. We consider a duodenal stump leak as the discharge of bile-containing liquid in drains or by direct evaluation at reoperation. A pancreatic fistula is considered as a drain output of any volume on or after postoperative day 3 with an amylase greater than three times the serum level.

Follow-up

Standard follow up is at three-month intervals for two years, then at six-month intervals for three years, and yearly thereafter. Follow-up consists of physical examination, a complete blood count, liver-function testing, chest x-ray, abdominal ultrasound and CT-scanning, as clinically indicated. Patients are planned to have a minimum of 5 year follow-up.

Outcomes:

The primary outcome of the study is severe 30-day or in-hospital morbidity.

The secondary outcome is long-term 5 year survival.

Sample size

Using previously published data and given a 0.05 alpha level, a percentage of unexposed outcome of 10.8%, and OR 4.28, a sample size of 116 patients would yield at least 80% statistical power.

Statistical analysis

Continuous variables are described by means and standard deviations or medians and interquartile range. Categorical variables are described with frequencies and percentage.

The following factors are analyzed: age, sex, comorbidity, American Society of Anesthesiologists (ASA) physical status, tobacco and alcohol consumption, body mass index (BMI), hematocrit, serum albumin level, tumor location, the use of preoperative chemotherapy, laparoscopic or open surgery, total or subtotal gastrectomy, duodenal stump closure, multi-organ resection, lymphadenectomy, reconstruction method, T status, lymph node metastasis, and resection margin. The T stage was grouped by T1–T2 and T3–T4 for analysis. Univariate and multivariate analyses are performed to identify predictors of severe postoperative morbidity; and predictors of long-term survival. All variables associated with severe morbidity with p <.05 in the univariate analysis are subsequently entered into a Cox multivariate regression model with backward elimination. Significance is set at two-sided p <.05. All analyses are performed using the statistical SPSS IBM Statistics software program, version 22.

The local ethics committee approved this study. Informed consent of patients is waived because of the retrospective nature of the study. The study was designed in line with the PROCESS criteria[15].

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