Intrathoracic anastomotic leakage after gastroesophageal cancer resection is associated with increased risk of recurrence

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ABSTRACT

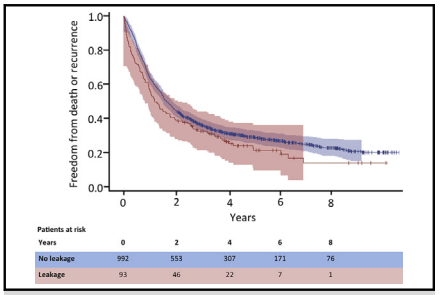
Objective: Intrathoracic anastomotic leakage after intended curative resection for cancer in the esophagus or gastroesophageal junction has a negative impact on long-term survival. The aim of this study was to investigate whether an anastomotic leakage was associated with an increased recurrence rate.

Methods: This nationwide study included consecutively collected data on patients undergoing curative surgical resection with intrathoracic anastomosis, alive 8 weeks postoperatively, between 2003 and 2011. Patients with incomplete resection, or metastatic disease intraoperatively, were excluded. Only biopsy-proven recurrences were accepted.

Results: In total, 1085 patients were included. The frequency of anastomotic leakage was 8.6%. The median follow-up time was 29 months (interquartile range [IQR]: 13-58 months). Overall, 369 (34%) patients had disease recurrence, of which 346 patients died of recurrent gastroesophageal carcinoma. Twenty-three patients were alive with recurrence at the censoring date. In the study period, 333 patients died without signs of recurrent disease.

The overall median time to recurrence was 66 weeks (IQR: 38-109 weeks). Distant metastases were found in 267 (25%), and local disease recurrence in 102 (9%) patients. Overall, 5-year disease-free survival in patients with leakage was 27%, versus 39% in those without leakage ($P = .017$). Anastomotic leakage was independently associated with higher risk of recurrence (hazard ratio [HR] = 1.63; 95% confidence interval [CI]: 1.17-2.29, $P = .004$) and all-cause mortality (HR = 1.57; 95% CI: 1.23-2.05, $P < .0001$).

Conclusions: Intrathoracic anastomotic leakage increased the risk of recurrence in patients who underwent curative gastroesophageal cancer resection. (J Thorac Cardiovasc Surg 2015;150:42-8)



Survival, with and without leakage, after esophagectomy with intrathoracic anastomosis.

Central Message

We found an increased risk of recurrence after intrathoracic anastomotic leakage, after gastroesophageal cancer resection.

Perspective

Anastomotic leakage after esophagectomy for a malignant tumor has a negative effect on the patient through an increased risk of morbidity and mortality. We demonstrate that leakage additionally increases the risk of recurrence. These findings should direct more attention to identification of factors that may contribute to anastomotic leakage in patients undergoing esophagectomy with intrathoracic anastomosis.

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Surgery is a potential curative treatment of cancer in the esophagus or gastroesophageal junction. Long-term survivors who had definitive chemoradiation, even though they are few, make it an alternative to surgical resection.[1,2] One of the most feared surgical complications is anastomotic leakage, which occurs in up to 10% of these patients.[3-9] Anastomotic leakage exerts an obvious negative influence by increasing the risk of immediate morbidity and mortality, but many believe that leakage additionally increases the risk of recurrence.[10] These studies demonstrated a trend, but they failed to show a clear and significant negative effect on long-term survival, presumably because of the small patient cohorts and the inconsistent definitions of leakage.

In contrast, we recently demonstrated a robust negative impact of anastomotic leakage on long-term survival in patients alive 8 weeks after curative gastroesophageal cancer resection with intrathoracic anastomosis, in a large, nationwide study.[11] Whether this increased long-term mortality after an intrathoracic anastomotic leakage can be explained by an increased frequency of cancer recurrence is yet to be

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Abbreviations and Acronyms
CI = confidence interval
HR = hazard ratio
IQR = interquartile range

elucidated. A large study of 8589 patients alive 120 days after curative resection for colonic cancer demonstrated that patients with anastomotic leakage had significantly increased rates of distant recurrence and long-term all-cause mortality, compared with patients without anastomotic leakage.[12] Our hypothesis is that patients surviving an anastomotic leakage after curative resection for cancer in the esophagus, or at the gastroesophageal junction, with intrathoracic anastomosis have an increased risk of cancer recurrence.

METHODS

Patients

The present patient cohort and the surgical procedures used in the current study have been described previously.[11] Analyses were based on data from the Danish Esophageal, Cardia and Stomach Cancer Database. From June 1, 2003 onward, all consecutive patients undergoing curative surgical resection for gastroesophageal cancer (either in the esophagus or at the gastroesophageal junction [Siewert type 1, 2, or 3]) in Denmark have been recorded prospectively in a national database. Information recorded includes: clinical data (age, gender, smoking, alcohol consumption, comorbidity, American Society of Anesthesiologists score, preoperative tumor stage); operative data (surgical approach, type of surgical procedure); pathology (tumor histology and resection margins); and major postoperative complications.

Only patients undergoing curative surgical resection with an intrathoracic anastomosis, treated between June 1, 2003 and December 31, 2011, were included in the study. Patients who underwent gastrectomy (Siewerts type 3), had an incomplete (microscopically [R1] or macroscopically [R2] remaining cancer in the resected specimen) surgical resection, or had metastatic disease intraoperatively were excluded from the study. Time zero for this study was 8 weeks after esophagectomy; patients who died or experienced a recurrence before 8 weeks were excluded (Figure 1).

Surgical Approach

Four centers in Denmark (population: 5.6 million) are certified to perform gastroesophageal cancer surgery. The following standard surgical technique was used: Tumors located in the esophagus, or at the gastroesophageal junction (Siewerts type 1 or 2), were resected, using the Ivor Lewis procedure consistently throughout the study period; a 2-phase abdominal and right chest approach was used, with subtotal esophagectomy followed by gastric pull-up and a stapled gastroesophageal anastomosis. A 2-field lymphadenectomy with D1+ resection in the abdomen, extended with dissection of the truncal celiac nodes and en-bloc mediastinal lymphadenectomy, including paraesophageal and subcarinal lymph nodes, was mandatory. Cervical lymphadenectomy was not performed, and the lines of resection were placed as far away from the tumor as possible, and $\geq$6 cm from both ends.

Denmark has a long tradition of performing esophageal resection through a right-sided thoracotomy with intrathoracic anastomosis. A neck anastomosis is performed only if the tumor is very proximally located in the esophagus. In all centers, experienced pathologists, who are subspecialists in upper-gastrointestinal cancers, performed the history-pathologic examination of the resected specimens.

Oncologic Treatment

Since January 2009, patients with adenocarcinoma have received perioperative chemotherapy consisting of 3 preoperative cycles of epirubicin (Ellence, Actavis, Dublin, Ireland), oxaliplatin (Eloxatin; Sanofi, Paris, France); and capecitabine (Xeloda; Roche, Basel, Switzerland), followed by surgery after 3 weeks. After recovery, the patient received 3 postoperative cycles. Patients with squamous cell carcinoma received preoperative concomitant chemoradiation (25 fractions with 2 Gy per fraction), and 2 cycles of cisplatin (Platinol; Bristol-Myers Squibb, New York, NY) and fluorouracil (5-FU; Accord Healthcare, Durham, NC), followed by surgery after 8 weeks.

Anastomotic Leakage

Anastomotic leakage was defined as an esophagogastric, anastomotic leak recognized by 1 of the following methods: (1) radiologically, using a water-soluble radiograph contrast medium at day 7 postoperatively, or earlier if suspected; (2) using an acute computed tomography scan performed because of clinical signs of leakage (fever; chest pain; saliva or gastrointestinal content through chest drain); (3) via signs of conduit necrosis (gastrostomy line) or anastomotic dehiscence by upper-gastrointestinal endoscopy in critically ill patients; and (4) from evidence of tracheoesophageal fistula. Patients with contained leaks were categorized as having a leak.

Patients with leakage who underwent thoracotomy were classified as requiring surgical reintervention. Those treated with stenting and/or percutaneous drainage were classified as requiring conservative reintervention. We have previously shown that patients with an asymptomatic leak carry the same risk of death as those with symptomatic leaks.[11]

Disease Recurrence

Patients were followed for 2 years postoperatively with clinical examination. If recurrence was suspected based on clinical findings, a computed tomography or positron emission tomography scan was scheduled. All cases of disease recurrence were verified histologically, using biopsies, and information on disease recurrence was based on data extracted from the Danish Pathology Registry on February 5, 2014. The registry, established in 1997, contains histopathologic information on all biopsies and resected material from patients throughout all of Denmark.

Recurrent disease was classified as local or distant recurrence. Local recurrence was defined as cancer at the anastomotic line, in the gastric conduit, in the mediastinum, or around the celiac trunk in the abdomen. Distant recurrence was defined as metastases in a solid organ, or within the peritoneal or pleural cavity, and patients with both local and distant disease recurrence were classified as having distant recurrence.

Statistical Analysis

Disease-free survival was defined from 8 weeks after esophagectomy until the date of either disease recurrence (date of positive biopsy) or death. February 5, 2014 was the censoring date for investigation of the pathology registry, and the censoring date for survival.

Comparison of survival time, stratified by anastomotic leakage or no leakage, was conducted using the Kaplan-Meier method, and the log-rank test was used to evaluate the statistical significance of the differences. Categoric data were compared using χ^2 analysis or the Fisher exact test. Continuous data are shown as mean $\pm$ SD, or as median and interquartile range (IQR); they were compared using the Mann-Whitney U test.

Cox multiple regression analysis was used to identify independent risk factors for disease recurrence and death. Variables with P values $< .2$, found in univariate analysis comparing patients with or without disease recurrence (gender, age, postoperative tumor stage, lymph node status, histology, oncologic therapy, and anastomotic leakage), were entered into the regression model as forced entry. Patients with missing values were excluded from the regression analysis.

Risk was given as hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were conducted using IBM SPSS, version 19.0,