Does previous fundoplication alter the surgical approach to esophageal adenocarcinoma?§

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Abstract

Objective: The primary aim of this study was to test the widespread assumption that the viability of the gastric fundus is compromised by fundoplication, thereby limiting the use of stomach to reconstruct the upper gastrointestinal tract after esophageal resection. Methods: Between February 1991 and February 2006, a consecutive series of 142 patients with esophageal adenocarcinoma (EADC) underwent esophageal resection. To reconstruct the upper gastrointestinal tract, all patients had a narrow gastric tube (greater curvature of stomach based on the right gastroepiploic artery) transposed through the posterior mediastinum to the left neck where an anastomosis to the cervical esophagus was performed. From a prospective database, 15 patients were identified to have undergone an ‘open’ fundoplication (transabdominal Nissen, n = 11; transthoracic Belsey, n = 4) from 12 to 23 years earlier. Outcomes were compared between patients with EADC who had undergone previous fundoplication, and patients with EADC who never had antireflux surgery. Results: Gastric transposition and cervical esophagogastrostomy were technically feasible in all patients. No significant differences in outcome were found between patient groups. Gastric necrosis developed in only one patient, who had not undergone previous fundoplication. Anastomotic leak rates after esophageal resection and reconstruction were not statistically different based on whether patients had undergone previous fundoplication (2/15, 13.3%) or not (16/127, 12.6%; p = 0.99). Conclusions: With careful attention to surgical technique, previous fundoplication does not preclude the use of stomach to reconstruct the foregut after esophageal resection, refuting the notion that previous antireflux surgery is a relative contraindication to, or alters the approach to esophageal cancer surgery.

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1. Introduction

Epidemiologic, clinical, and experimental studies have now clearly identified gastroesophageal reflux disease (GERD) as a major risk factor for esophageal adenocarcinoma (EADC) and for its premalignant lesion, Barrett esophagus (BE) [1–6]. As antireflux surgery is highly effective at controlling GERD [7], even in patients with BE [8–10], it has been suggested that fundoplication may reduce the risk for progression of GERD and BE to invasive EADC. While this concept is supported in part by experimental studies reporting the normalization of molecular alterations in esophageal epithelia after acid suppression [11,12], and by clinical observations of regression of BE after successful antireflux surgery [13–16], recent population-based studies and meta-analyses have reported that the risk for EADC is not significantly reduced after antireflux surgery [17–20]. Furthermore, EADC has been reported to develop several years after antireflux surgery, particularly in male patients with Barrett esophagus who develop a recurrence of pathologic reflux postoperatively [21].

To date, the technical aspects of esophageal resection and reconstruction for patients presenting with EADC who have undergone previous antireflux surgery have received little consideration. It has been widely assumed that the viability of the gastric fundus is compromised by fundoplication, thereby limiting the use of stomach to reconstruct the upper gastrointestinal tract after esophageal resection. Therefore, the primary aim of this study was to critically evaluate the outcome of patients with EADC who had undergone previous antireflux surgery, with particular emphasis on the technique of upper gastrointestinal reconstruction using the stomach.
2. Materials and methods

2.1. Patients

From February 1991 to February 2006, 142 consecutive patients underwent potentially curative subtotal esophagectomy for primary EADC, performed by a single surgeon (AGC) with a university-based tertiary referral practice. This sequentially accrued series comprised 118 males and 24 females, with a mean age of 62 years (range, 36–85 years). Fifteen patients reported previous open antireflux surgery, performed at other centers from 12 to 23 years earlier. Eleven patients had undergone a transabdominal Nissen fundoplication via a midline epigastric incision, and four patients had undergone a Belsey type fundoplication via a left thoracotomy. No patient had undergone an esophageal lengthening procedure (Collis gastroplasty) or minimally invasive antireflux surgery. All patients had remained clinically asymptomatic with respect to GERD-related symptoms following antireflux surgery.

Routine preoperative staging comprised esophagogastroscopy and biopsy, radiologic contrast studies (barium swallow) and computed tomography (CT) of the chest and upper abdomen. Endoscopic ultrasound (EUS) and positron emission tomography (PET) were not available for staging. All patients were considered to have locally resectable tumors, with no clinical or radiographic evidence of distant visceral metastases. No patient in this series received induction chemotherapy or radiotherapy.

2.2. Surgical technique

All patients gave full informed consent for surgery. The surgical approach to patients with EADC has been described in detail previously [22,23]. Briefly, subtotal esophagectomy was performed using a right transthoracic (77 patients) or transhiatal approach (65 patients). The extent of resection comprised a complete excision of all primary tumors en bloc with the thoracic and abdominal esophagus, and the lesser curvature of the stomach to achieve a minimum 5 cm distal resection margin. Regional lymph node stations were resected extensively, and mapped to document patterns of metastasis. A narrow tube of the greater curvature of the stomach, based on the right gastroepiploic artery, was created by multiple applications of a linear cutter (Ethicon Endosurgery Inc., Cincinnati, OH) to resect the lesser curve, oversewing the staple line with a running 3-0 silk suture. The gastric tube was transposed through the posterior mediastinum, where an anastomosis of the gastric tube to the cervical esophagus was performed via a left neck incision. From September 1997 onwards, all cervical anastomoses were created using a semimechanical side-to-side technique by application of an endoscopic linear cutter (ETS45; Ethicon Endosurgery Inc., Cincinnati, OH) as reported. [23] A pyloromyotomy was performed routinely to ensure gastric emptying, and all patients had a feeding jejunostomy (J-tube).

The operative strategy for the 15 patients who had undergone previous antireflux surgery was modified as follows. For the eight patients who required a 3-hole (right thoracotomy, laparotomy, left neck incision), a laparotomy was performed initially, in contrast to our usual practice of performing a right thoracotomy first to mobilize the primary tumor and thoracic esophagus. For the remaining seven patients who had undergone previous antireflux surgery and who were judged to be eligible for transhiatal resection, the operative approach did not change substantially. The abdomen was initially entered through the existing midline epigastric incision, and a careful dissection of any adhesions was performed under direct vision. Careful tissue handling and patience was required throughout this initial dissection. An assessment of the right gastroepiploic artery was made early, and this vessel was preserved by a wide (at least 2 cm) lateral dissection of its omental branches. Following mobilization of the gastric body and antrum, a generous Kocher maneuver was performed. Assisted by excellent lighting and retraction of the costal margins, the left triangular ligament was dissected, along with any adhesions between the liver and fundoplication. The left lobe of the liver was retracted to expose the hiatus, and an assessment made of the extent of the fundoplication. Prior to dissection of the fundoplication, any remaining short gastric vessels were identified and ligated, taking particular care to avoid injury to the spleen. By elevating the stomach to enter the lesser sac, the left gastric vessels were identified and individually suture-ligated as close to their origin as possible, thereby ensuring an en bloc resection of all associated nodal tissue. The final step required a careful dissection of the fundoplication, and the identification of the anatomic esophagogastric junction. As described in the preceding section, a narrow gastric tube (based on the right gastroepiploic artery) was created by multiple applications of the linear cutter along the lesser curve. An assessment of the viability of the gastric tube was made after an interval of at least 10 min, prior to transposition to the left neck for esophagogastrostomy.

Contrast studies (water soluble, followed by dilute barium if negative) were performed for all patients between the fifth and seventh postoperative day. If there was no evidence of anastomotic leakage, the nasogastric tube was removed, and clear liquids given. Oral intake progressed daily from liquids to full fluids to semi-solids, and patients were discharged on a soft diet. Anatomic leaks were classified according to severity, as previously reported [23]. Type A comprised clinically asymptomatic, incidental radiographic leaks detected at the time of routine postoperative contrast study. Type B leaks were localized to the neck; all were clinically apparent from increased incisional drainage, and anastomotic disruption was confirmed by radiologic contrast study. Type C (complex cervical) anastomotic leaks were associated with systemic sepsis, mediastinal abscess, pleural effusion and/or empyema.

2.3. Data collection and statistical analysis

Routine clinico-pathologic and outcome data for all patients were recorded in a prospective research database, and follow-up information was complete and available until July 2007. Descriptive statistics were used to summarize data. For categorical variables, comparisons between groups were made by using chi-square tests or Fisher’s exact tests as appropriate. Continuous variables were compared by Stu-
Belsey-type fundoplication performed previously thorough a hospitalization, and ranged from 7 to 63 days (median 17 days). All tumors were located in the left upper quadrant. Gastric transposition and cervical esophagogastronomy was therefore technically feasible in all patients who had undergone previous antireflux surgery.

As summarized in Table 2, no statistically significant differences ($p > 0.05$) were found between patients presenting with EADC who had undergone previous fundoplication and the 127 patients who had never undergone antireflux surgery with respect to age, operative approach and extent of resection, tumor grade, stage, disease-free and overall survival, hospital stay or postoperative complications. Gastric necrosis developed in only one patient who had not undergone previous fundoplication. Neither the severity nor overall number of anastomotic leaks after esophageal resection and reconstruction were statistically different between groups: 13.3% (2/15) for patients who had undergone previous fundoplication versus 12.6% (16/127) for patients who had never undergone antireflux surgery ($p = 0.99$). Similarly, no significant difference in anastomotic stricture rates was seen between groups: 20.0% (3/15) for patients who had undergone previous fundoplication versus 11.8% (15/127) for patients who had never undergone antireflux surgery ($p = 0.41$).

4. Discussion

Regardless of current levels of evidence supporting [11–16] or disputing [17–20] the use of antireflux surgery to reduce the risk of esophageal malignancy, antireflux surgery is still widely used in clinical practice to treat GERD [7]. Therefore, it is quite possible that in future years an increasing proportion of patients presenting with EADC may well have a history of previous fundoplication, and that this will not be an altogether uncommon clinical scenario. On the basis of results from this study, prior antireflux surgery should therefore not necessarily exclude a patient with EADC from surgery, or the possibility of using the stomach to reconstruct the upper gastrointestinal tract.

As summarized in Table 2, outcomes for patients with a history of previous fundoplication who undergo esophageal resection and reconstruction using stomach were similar to patients who never had antireflux surgery. As the widespread assumption was that a previous fundoplication would potentially compromise the vascularity of the gastric fundus, we focused on evaluating postoperative complications, which would most likely reflect viability of the gastric tube. Only one patient in this series developed gastric necrosis, but this individual had not undergone prior antireflux or upper abdominal surgery. As occult ischemia of the partially devascularized gastric fundus after mobilization has been implicated as a major etiologic factor underlying anastomotic failure, we specifically evaluated esophagogastric anal-
stomotic leak and stricture rates; no differences were seen for patients who had undergone previous fundoplication and those who had not. It is interesting to speculate whether prior ligation of the short gastric vessels (for fundoplication) contributes to ischemic conditioning (delay phenomenon), thereby increasing perfusion to the gastric fundus over time, as proposed by Urschel et al. [24].

With respect to anastomotic leak rates reported in this series, it should be noted that all patients underwent cervical esophagogastrostomy via a left neck incision. Furthermore, all patients underwent postoperative contrast studies (water soluble followed by dilute barium) to assess the integrity of the anastomosis. As noted in Table 1, we identified five incidental leaks (type A), which although not clinically significant, would otherwise have been missed. Otherwise, patients in this series appear to have outcomes comparable to that reported in larger series from high-volume centers (Table 1).

It should also be noted that no conclusions can be made from this study with respect to the frequency of EADC arising after fundoplication. The number of patients who were identified as having undergone previous antireflux surgery simply reflected referral patterns. However, a recent review by Csendes et al. [21] has attempted to address the risk of developing EADC after antireflux surgery. Following a comprehensive review of published literature worldwide over 23 years (1980—2003), it was concluded that EADC appears to develop in male patients several years after antireflux surgery, and who experience a recurrence of GERD symptoms. While such patients in our series were also exclusively male, with a long interval (12—23 years) between fundoplication and the diagnosis of EADC, all remained asymptomatic with respect to GERD symptoms. However, as lack of reflux symptoms does not necessarily indicate that GERD is controlled, and as objective studies to evaluate acid (24 h pH) and/or bile reflux (Bilitec) were not performed on these patients, it is quite possible that these patients did have pathologic gastroesophageal reflux despite apparently successful previous antireflux surgery. To explore this further, we compared the molecular profiles of two inflammation-
related biomarkers (cyclooxygenase-2, COX-2 [25]; and inducible nitric oxide synthase, iNOS [6]), in tumors from the 11 patients who had undergone a previous Nissen fundoplication and the 11 matched EADCs from patients who never had antireflux surgery (data not shown). Compared to patients who had never undergone antireflux surgery and who were clinically asymptomatic with respect to GERD symptoms, significantly fewer tumors from patients who had undergone Nissen fundoplication overexpressed COX-2 and iNOS mRNA and protein, suggesting that the previous fundoplication had indeed been effective. The biologic significance of these observations is the subject of ongoing investigation in our laboratory.

In summary, with careful attention to surgical technique, this study found that previous fundoplication did not preclude the use of the stomach to reconstruct the foregut after esophageal resection, refuting the notion that prior antireflux surgery is a relative contraindication, or substantially alters the approach to esophageal cancer surgery.

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execution of the gastric pull-up after esophagectomy, which was the primary aim of the study, and, secondarily, whether in the long run the fundoplication can modify the etiology, i.e. the biological origin of the adenocarcinoma for which they received the second operation. The answer to the first question is clear: a previous fundoplication does not impair the gastric pull-up after esophagectomy. Secondarily, they speculate that the fundoplication may have modified the biology of the adenocarcinoma occurred years after the antireflux operation and render these cases different than others. In few words, these adenocarcinomas would not have been caused by chronic GERD.

The study was done on a relatively small number of patients. Furthermore we don’t know whether the fundoplication was effective or not because we don’t have a previous follow-up of the patients in terms of GERD control, although I understand the reason why the pH recording was not performed. Finally three wraps were disrupted. So we don’t know if the function in terms of cardiac competence in this small number of patients had been really effective or not.

Dr Casson: This really started out as just a technical review of our experience with fundoplication in this setting, and I would agree with you, there are very small numbers here. I would be interested to see how many others have operated on people with antireflux surgery. I would just stress that all patients had antireflux surgery well over a decade ago, and certainly clinically none of them had any suggestion of reflux symptoms, admittedly, none had 24 h pH monitoring at the time of presentation, but this was also the reason we wanted to look at the biomarkers. The point I want to make is that there was reduced expression at the mRNA and protein level in the majority of folks that had had previous antireflux surgery, and that suggests that the fundoplication was in fact doing its job and reducing the inflammation-related background. And we would throw out as a theory that the development of the tumors in this group may actually be along quite different pathways to what we normally see.

Dr J. Jeyasingham (Bristol, UK): I agree with the discussant that the numbers are small, and also in your antireflux procedure, the fundoplication, you didn’t have any patients who had a short esophagus elongated with a Collis-Belsey or Collis-Nissen gastroplasty. That would have certainly interfered with the possibility of a gastric tube construction, or if there had been any drainage procedures associated with the antireflux operation previously. Now, accounting for the causation, what is the explanation you have for the difference in the expression of RNA, Cox-2, and other molecular factors? Do you have an explanation?

Dr Casson: Just one comment. First of all, we actually had reported many years ago the development of an adenocarcinoma in a Collis gastroplasty, and Donna Maziak wrote this up at the University of Toronto back in the mid 90s. My personal feeling is that these are really gastric cancers, not esophageal. So that was not included in this series, because we did, really, a gastric operation for that.

And, I really don’t know the molecular cause for this. The primary point of this study was really a technical review of our experience with antireflux surgery and resection. I think this is an area of significant work we have got left to do in the lab to try to define these molecular pathways. So in answer to your question, I don’t know what they are.

Dr T. Lerut (Leuven, Belgium): It was a nice study, especially in relation to the biology of those tumors. You said they were all type I. May I assume that they were all Barrett carcinomas then, or did you look at the cytokeratin expression to see whether they were more gastric type or real intestinal metaplasia from Barrett’s?

Dr Casson: We did not look at the cytokeratin markers. They were all from the tubular esophagus, and about 60% of all cancers in this series had a definable columnar mucosa. The ones that didn’t, the 40%, we have a list of other criteria that must be fulfilled to define that they were primary esophageal, and all of them clearly were. We didn’t have a messy series here with cardiac cancers. These were all true esophageal adenocarcinomas.

Dr Lerut: Just a technical question. Forty-six percent of your patients were treated by a transhiatal approach, and you said that all patients had a two-field lymphadenectomy. How do you do that in a transhiatal approach?

Dr Casson: I had the same discussion with Dr Orringer last week. You can do quite a wide dissection transhiatally, and we clip very widely, we get into the pleura, and I will call it a two-field.