Fate of the esophagogastric anastomosis

Thomas W. Rice, MD,[a] John R. Goldblum, MD,[b] Lisa A. Rybicki, MS,[c] Jeevanantham Rajeswaran, MSc,[c] Sudish C. Murthy, MD, PhD,[a] David P. Mason, MD,[a] and Eugene H. Blackstone, MD[a,c]

Objective: The study objective was to evaluate histopathology of the esophagogastric anastomosis after esophagectomy, determine time trends of histologic changes, and identify factors influencing those findings.

Methods: A total of 231 patients underwent 468 upper gastrointestinal endoscopies with anastomotic biopsy a median of 3.5 years after esophagectomy. Mean age was 59 ± 12 years, 74% (171) were male, and 96% (222) were white. Seventy-eight percent (179) had esophagectomy for cancer, 13% (30) had chemoradiotherapy, and 13% (30) had prior esophageal surgery. The anastomosis was 20 ± 2.0 cm from the incisors. Antireflux medications were used in 59% of patients (276/468) at esophagoscopy. Histopathology was graded as normal (0), consistent with reflux (1), cardia mucosa (2), intestinal metaplasia (3), and dysplasia (4). Repeated-measures nonlinear time-trend analysis and multivariable analyses were used.

Results: Grades 0 and 1 were constant, 5% and 92% at 10 years, respectively. Anti-reflux medication, induction therapy, and higher anastomosis were predictive of less grade 1 histopathology. Grades 2 and 3 increased with time: 12% and 33% at 5 years and 4% and 16% at 10 years, respectively. No variable was predictive of grade 2 or 3 ($P > .15$) except passage of time. No patient's condition progressed to dysplasia or cancer.

Conclusions: The esophagogastric anastomosis is subject to gastroesophageal reflux. To minimize histopathologic changes of reflux, the anastomosis should be constructed as high as possible (closer to incisors) and antireflux medications prescribed. Surveillance endoscopy, if performed, will document a time-related progression of reflux-related histopathologic changes. However, during surveillance, intestinal metaplasia is uncommon and progression to cancer rare. (J Thorac Cardiovasc Surg 2011;141:875-80)

Supplemental material is available online.

The normal esophagogastric junction is a complex, poorly understood, dynamic zone of transition. Direct anastomosis of the stomach to the esophagus at esophagectomy creates an artificial environment, the study of which may increase understanding of the esophagogastric junction and elucidate the long-term impact of esophagectomy. Theoretically, at this anastomosis, histopathologic changes of gastroesophageal reflux disease (GERD) are inevitable, and potential for columnar metaplasia, dysplasia, and carcinoma may be considerable. Since late 2005, esophagoscopy and biopsy were added to routine annual surveillance after esophagectomy for cancer and during postoperative evaluation after esophagectomy for benign diseases. This afforded the opportunity to study histopathologic changes. The purposes of this study were to evaluate histopathology of the esophagogastric anastomosis after esophagectomy, determine time trends of histopathologic changes, and identify factors influencing those histologic findings.

PATIENTS AND METHODS

From January 1, 1989, to January 1, 2009, 1758 patients underwent esophagectomy at Cleveland Clinic; 1564 patients from one surgeon's experience were potential candidates for endoscopic surveillance. From December 22, 2005, to September 4, 2009, 231 of these patients had 468 upper gastrointestinal endoscopies with biopsy; 99% of the procedures (461) were performed by the same surgical endoscopist. Patient characteristics and indications for esophagectomy are listed in Table 1.

Esophagectomy

Esophagectomy (non–vagal-sparing) was accomplished transhiatally in 150 patients and with thoracotomy in 81 patients. Proximal gastrectomy included the gastric cardia. All anastomoses were constructed between the cervical esophagus and the apex of the gastric fundus in an end-to-side fashion via a left cervical incision.[1] A pyloroplasty was constructed in all patients.

Surveillance Endoscopy

Esophagogastroduodenoscopy and biopsy were performed in the outpatient area in all but 2 patients. Conscious sedation was used in all but 3

From the Department of Thoracic and Cardiovascular Surgery,[a] Heart and Vascular Institute; Department of Anatomic Pathology,[b] Pathology and Laboratory Medicine Institute; and Department of Quantitative Health Sciences,[c] Research Institute, Cleveland Clinic, Cleveland, Ohio.

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Address for reprints: Thomas W. Rice, MD, Cleveland Clinic Department of Thoracic and Cardiovascular Surgery 9500 Euclid Avenue/Desk J4-1 Cleveland, OH (E-mail: ricet@ccf.org).

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GTS

Abbreviation and Acronym
GERD = gastroesophageal reflux disease

patients. Distance from incisors to the anastomosis was 20 ± 2.0 cm (range, 16–30 cm; Figure E1). Gross endoscopic appearance of the anastomosis at esophagoscopy was classified as normal (n = 444, 95%), stricture (13, 2.8%), intestinal metaplasia (9, 1.9%), or nodule (2, 0.4%), but visual endoscopic grading of esophagitis was not done. Biopsies were performed using Radial Jaw 4 biopsy forceps (Boston Scientific, Natick, Mass). Any gross abnormality was biopsied; 3 biopsies were taken from the esophageal side, and 3 biopsies were taken from the gastric side of the anastomosis. At the time of biopsy, 276 of 468 patients (59%) were receiving anti-reflux therapy (primarily proton pump inhibitors and, rarely, H-2 blockers), prescribed for symptoms of reflux.

The median interval between esophagectomy and first biopsy was 2.1 years (25th percentile, 1.2 years; 75th percentile, 4.8 years). Distribution of data collection of graded biopsy outcomes over time is shown in Figure E2.

Histopathology

Histopathologic changes were rated in a stepwise fashion of increasing severity of changes: none (grade 0), changes consistent with reflux (grade 1: reactive, hyperplasia and regeneration, inflammatory), presence of cardia mucosa (grade 2), presence of intestinal metaplasia (grade 3), and dysplasia (grade 4).

Cancer recurrence at the anastomosis developed in only 1 patient during the study (judged a cancer recurrence because of its early occurrence after esophagectomy and lack of evidence of progression from intestinal metaplasia to cancer). The database was approved for use in research by the institutional review board, with patient consent waived.

Statistical Analysis

To assess temporal trend of percentages of each biopsy grade across time after esophagectomy, repeated measurements of biopsy grade were analyzed using a nonlinear logistic mixed model,[2] which resolved several time phases of the temporal pattern of biopsy grade/temporal decomposition. Longitudinal logistic regression[3] for repeated measurements[4] (SAS PROC NLMIXED; SAS Institute Inc, Cary, NC) was used to implement the temporal decomposition model. Overall prevalence of each biopsy grade was estimated by averaging the patient-specific profiles.

Patient-level variables—age, gender, prior hiatal hernia repair, prior esophageal surgery, reason for esophagectomy (cancer vs benign), staged approach (transhiatal vs thoracotomy), type of anastomosis (stapled vs sewn), and induction therapy—and biopsy-level variables—location of anastomosis and use of anti-reflux medication (as a surrogate for reflux symptomology)—were considered in the multivariable analyses. The 2 biopsy-level variables were treated as time-dependent covariables. For grade 1, however, the inability to determine side of origin of grade 2 to 4 changes required analysis as a single finding (Table 2). To carry out this time-dependent multivariable analysis, *exogeneity* was assumed, that is, the time-varying covariable measurements at time **t** were conditionally independent of all preceding response measurements (grades of biopsy outcomes).[3]

Presentation

Continuous variables are summarized by mean ± standard deviation, or 25th, 50th (median), and 75th percentiles for skewed data. Categoric data are summarized by frequencies and percentages. All analyses were performed using SAS statistical software (SAS v9.1; SAS, Inc). Uncertainty is expressed by confidence limits equivalent to ± 1 standard error (68%).

RESULTS

Histopathologic Changes

Of the 468 biopsies, 48 (10%) were classified as normal (grade 0; Table 2). The majority (407 [87%]) showed changes consistent with reflux (grade 1). These changes were more pronounced on the esophageal side of the anastomosis (75%) versus the stomach side (55%). Columnar epithelium was found in 28% of biopsies, predominantly gastric cardia (grade 2). Only 8.7% of patients were found to have intestinal metaplasia. No biopsy showed dysplasia (grade 4) or cancer.

Time-Trend Analysis

Biopsies could show more than 1 grade of change. Thus, each grade was analyzed separately.

Grade 0: Normal. Temporal trend yielded an almost constant phase (Figure 1). Percentages of patients with grade 0 were relatively constant at 5% (Figure 1).

Grade 1: Reactive, hyperplasia and inflammatory, regenerative. Temporal trend yielded an almost constant phase. Percentages of patients with grade 1 were relatively constant at 92% (Figure 2), but grade 1 features were somewhat more common on the esophageal side of the anastomosis than the gastric side (Figure E3). Patients not receiving anti-reflux medicine at the time of biopsy (Table 3, $P = .01$), those not receiving induction therapy ($P = .02$), and those with lower location of the anastomosis (farther from the incisor teeth) ($P = .02$) had increased likelihood of grade 1 changes. No other variable was found to predict a higher likelihood of grade 1 changes ($P > .01$).

Grade 2: Cardia mucosa. Temporal trend yielded an early peaking and late slow rising phase (Figure 2). Percentages of patients with grade 2 changes increased from 20% at 1 year to 24% by 2 years, decreased to approximately 12% by year 5, and increased to 33% by year 10 (Figure 2). No other variable predicted higher likelihood of having cardia mucosa ($P > .1$).

Grade 3: Intestinal metaplasia. Temporal trend yielded a slightly increasing phase. Percentages of patients with intestinal metaplasia increased steadily from 0.68% at 1 year to 16% at 10 years (Figure 2). No variable predicted a higher likelihood of intestinal metaplasia at biopsy ($P > .1$).

Grade 4: Dysplasia. No patient was found to have dysplasia.

DISCUSSION

Principal Findings

Grade 1: Reactive, hyperplasia and inflammatory, regenerative. It is inevitable that the esophagogastric anastomosis will be subjected to gastroesophageal reflux. Despite a relatively normal endoscopic appearance, histopathologic changes associated with gastroesophageal reflux predominated in our patients; these changes remained

TABLE 1. Patient characteristics and indications for esophagectomy (n = 231)

Variable	No. (%)
Demographic	
Male	171 (74)
White	224 (97)
Age (y), mean ± SD	59 ± 12 (25–84)
Prior esophageal surgery	30 (13)
Prior hiatal hernia repair	25 (11)
Reason for esophagectomy	
Cancer	179 (78)
Induction therapy	30 (13)
Benign	52 (22)
Achalasia	30 (13)
GERD/failed anti-reflux surgery	19 (8.2)
Diverticulum	2 (0.9)
Benign tumor	1 (0.4)
Surgical approach	
Thoracotomy	81 (35)
Transhiatal	150 (65)

GERD, Gastroesophageal reflux disease; *SD,* standard deviation.

TABLE 2. Histopathologic findings

Variable	468 Biopsies no. (%)	231 Patients no. (%)
Esophageal side of anastomosis		
Grade 0	77 (16)	16 (6.9)
Grade 1	350 (75)	195 (84)
Reactive	71 (15)	62 (27)
Hyperplasia and regeneration	110 (24)	87 (38)
Inflammatory	291 (62)	172 (74)
Stomach side of anastomosis		
Grade 0	187 (40)	60 (26)
Grade 1	259 (55)	160 (69)
Reactive	26 (5.6)	22 (9.5)
Hyperplasia and regeneration	18 (3.8)	16 (6.9)
Inflammatory	257 (55)	160 (69)
Either side of anastomosis		
Grade 0	48 (10)	6 (2.6)
Grade 1	407 (87)	137 (59)
Reactive	82 (18)	68 (29)
Hyperplasia and regeneration	116 (25)	92 (40)
Inflammatory	375 (80)	210 (91)
Grade 2 cardia mucosa	103 (22)	76 (33)
Grade 3 intestinal metaplasia	28 (6.0)	20 (8.7)
Grade 4 dysplasia	0 (0)	0 (0)
Other pathologic findings		
Fungus	22 (4.7)	19 (8.2)
Eosinophils	22 (4.7)	19 (8.2)

constant at 92% from 1 year after esophagectomy. Three other studies have evaluated these changes.[5-7] The reported non–time-related prevalence was 70%[5] and 88%[6] for intrathoracic anastomoses and 63% for cervical anastomoses.[6] After esophagectomy with cervical anastomosis in patients with achalasia, da Rocha and colleagues[7] reported esophagitis in 46% at 1 year, 72% at 5 years, and 70% at 10 years; the prevalence of gastritis was 20%, 31%, and 40% at 1, 5, and 10 years, respectively.

Grade 2: Cardia mucosa. Native cardia mucosa is resected at esophagectomy; therefore, this anastomotic finding represents metaplasia of esophageal mucosa, gastric mucosa, or both. Prevalence of columnar epithelium (cardia mucosa or intestinal metaplasia) increased with time. This change was present in one third of our patients at 10 years. Seven studies examined these changes in a non–time-related manner.[5,6,8-12] Prevalence of cardia mucosa at a median of 36 months ranged from 10%[6] to 50%.[11] In one-time evaluations, the prevalence was 28%[9] and 50%.[10]

Grade 3: Intestinal metaplasia. Intestinal metaplasia was uncommon; its prevalence in our patients increased with time to 16% at 10 years. Six studies have examined this change.[5,6,8-11] Prevalence ranged from 13.5% at a median of 489 days[8] to 27% at a median of 61 months.[10]

Two studies did not differentiate between grade 2 and grade 3 changes and reported the finding of columnar epithelium.[7,12] Bax and colleagues[12] reported columnar epithelium in 40% of patients at a mean of 59 months. In patients with achalasia, da Rocha and colleagues[7] found columnar epithelium in none at 1 year, 30% at 5 years, and 58% at 10 years.

Grade 4: Dysplasia and cancer. Neither dysplasia nor cancer was seen in our patients, mirroring the findings of Oberg and colleagues[9] and Bax and colleagues.[12] Lord and colleagues[11] reported 1 patient who progressed to dysplasia and developed carcinoma 42 years after esophagectomy. da Rocha and colleagues[7] found 5 cancers (3 squamous cell carcinomas and 2 adenocarcinomas) in patients with achalasia. The 2 patients with adenocarcinomas at 13 and 19 years after esophagectomy progressed from intestinal metaplasia.

Predictors of Histopathologic Changes

Construction of the anastomosis as high as possible (closer to the incisors), preoperative use of induction therapy, and postoperative use of anti-reflux medication were associated with fewer grade 1 changes in our patients. Patients receiving induction therapy are least likely to have grade 1 changes, perhaps explained by cytotoxic effects on the gastric mucosa. No predictors of histopathologic reflux-related changes have been reported by others.

Time since esophagectomy was the only factor associated with developing columnar epithelium; this makes the findings from this study particularly relevant to those whose esophagectomy was for benign disease or early-stage grade 1 cancers. Time after esophagectomy was also the only reported predictor of intestinal metaplasia in 2 studies.[7,10] Magnitude of acid and bile exposure has been variably reported to be associated with developing columnar epithelium: an association with both,[5] with acid but not

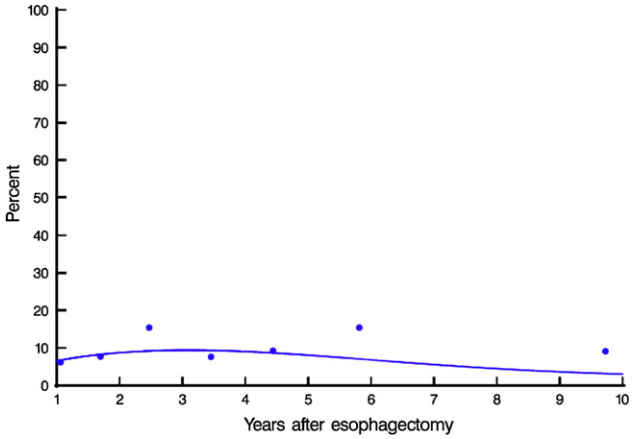

FIGURE 1. Time trend of normal biopsies (grade 0) after esophagectomy. Symbols represent data grouped within time frames without regard for repeated assessment, simply to provide crude verification of model fit.

bile,[9] and with neither.[10] Columnar epithelium before esophagectomy was associated with developing it postoperatively.[9] Both intestinal metaplasia before esophagectomy and lower level of anastomosis were associated with development of intestinal metaplasia.[6]

Strengths and Limitations

This is a single-institution prospective study based on histopathologic changes and not visual assessment of the anastomosis. However, sampling error during biopsy may underestimate the prevalence of these histopathologic changes. All anastomoses were performed through a cervical incision. Although the majority were within 20 cm of the incisors, there was a range, allowing this factor to be assessed. Anti-reflux medications were not randomly prescribed but used for symptom control, which may affect the association with histopathologic reflux changes. Failure to identify associations with columnar epithelium may be related to the size of the study population, large by current studies, but possibly too small to detect associations.

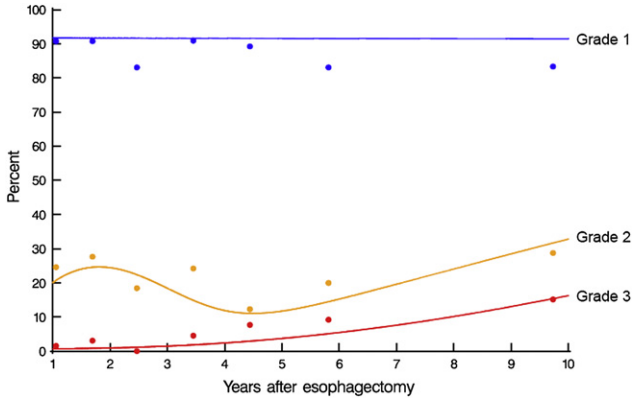

FIGURE 2. Time trend of histopathologic changes at esophagogastric anastomoses. Combined esophageal and gastric findings. Grade 1 = changes consistent with reflux. Grade 2 = presence of cardia mucosa. Grade 3 = presence of intestinal metaplasia. Depiction is as in Figure 1.

TABLE 3. Risk factors associated with higher likelihood of grade 1, 2, and 3 changes

Risk factor	Estimate ± SE	*P*
Grade 1 changes		
Overall		
Female	0.63 ± 0.56	.3
Prior hiatal hernia repair	0.0013 ± 0.81	>.9
Prior surgery	1.6 ± 1.1	.16
Older*	1.1 ± 0.58	.06
No anti-reflux medication	–1.1 ± 0.42	.01
Anastomosis farther from incisors†	–5.6 ± 2.4	.02
No induction therapy	–1.3 ± 0.54	.02
Stapled anastomosis (vs sewn)	–0.16 ± 0.72	.8
Malignant (vs benign)	–0.21 ± 0.81	.8
Surgical approach		
Thoracotomy (vs transhiatal)	–0.072 ± 0.46	.9
Grade 2 changes		
Overall		
Female	–0.31 ± 0.48	.5
Younger*	–0.41 ± 0.52	.4
Prior surgery	0.32 ± 0.64	.6
Anti-reflux medication	0.33 ± 0.35	.3
Anastomosis farther from incisors‡	0.31 ± 2.04	.9
Induction therapy	–0.15 ± 0.59	.8
Stapled (vs sewn)	–0.47 ± 0.98	.6
Surgical approach		
Thoracotomy (vs transhiatal)	0.068 ± 0.41	.9
Late phase		
Malignant (vs benign)	–0.65 ± 0.41	.11
Prior hiatal hernia repair	–1.2 ± 0.80	.14
Grade 3 changes		
Overall		
Female	–0.35 ± 0.86	.7
Older*	1.2 ± 0.88	.2
Anti-reflux medication	1.03 ± 0.68	.13
Anastomosis farther from incisors‡	2.02 ± 3.4	.6
Malignant (vs benign)	0.42 ± 0.95	.7
Stapled (vs sewn)	–0.16 ± 1.003	.9

SE, Standard error. *$(Age/60)^2$, squared transformation. †(20/location of anastomosis), inverse transformation. ‡Log(location of anastomosis), logarithmic transformation.

CONCLUSIONS

The esophagogastric anastomosis is inevitably exposed to reflux. Careful surgical technique, including a high stapled anastomosis, and postoperative management, including medical treatment of GERD, may minimize histopathologic reflux changes. With time, columnar mucosa will develop in a minority of patients, and intestinal metaplasia will develop in even fewer patients. Progression of intestinal metaplasia to dysplasia or cancer seems rare. Therefore, annual surveillance endoscopy is of limited

value, particularly in asymptomatic patients (ie, those not taking anti-reflux medication). Rather, endoscopy should be directed toward detection of cancer recurrence and diagnosis of symptoms.

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Discussion

Dr Farzaneh Banki *(Houston, Tex)*. I thank Drs Milliken and Bremner for the opportunity to discuss this article and congratulate Dr Rice and colleagues on providing the largest series with long-term follow-up that elucidates the fate of gastroesophageal anastomosis and mucosal changes in esophageal remnant after esophagectomy.

This study has multiple clinical implications, including the need for surveillance and use of proton-pump inhibitor after esophagectomy, and once again proves that cardiac mucosa is an acquired metaplastic epithelium that arises from squamous mucosa in response to gastric acid. I have 3 questions.

In your study, the curve for development of cardiac mucosa is biphasic, so there is an early and a late development of cardiac mucosa, but the development of intestinal metaplasia is linear and increases with time. Although one can explain the early development of cardiac mucosa by acute exposure of the esophageal remnant to acid and bile, and the late development by chronic exposure and by the fact that despite vagotomy the stomach regains its capacity to produce acid with time, how do you explain the decline between 2.5 and 4.5 years in development of cardiac mucosa in your study?

Dr Rice. I think it is explained by sampling error. If you don't biopsy the columnar mucosa, you are not going to find it. We tried to do another analysis on reaching the greatest change, but that became very confusing to present.

Dr Banki. Prior studies with a small number of patients have shown that presence of intestinal metaplasia in the esophagus before esophagectomy is an important predictive factor for development of intestinal metaplasia in esophageal remnant after esophagectomy. Have you considered that as a factor in your multivariate analysis?

Dr Rice. That variable was not considered. We hope that benign versus malignant indication would be a surrogate. I would remind you that the studies on intestinal metaplasia, and it is a variable factor (yes in some studies and no in others), were done mostly in patients with low intrathoracic anastomosis, and we have no idea about the surgical margin. Indeed, if you don't take out the Barrett's and you do your first biopsy, you are going to find Barrett's because your operation was incomplete—another reason to go high in the neck. But you are absolutely right, we should probably add to our analysis the presence of Barrett's mucosa before the esophagectomy.

Dr Banki. Have you changed your yearly surveillance protocol for endoscopy and routine biopsies and the use of proton-pump inhibitors in your patients after esophagectomy as a result of this article?

Dr Rice. I still use proton-pump inhibitors for symptoms, but I have a low tolerance to use them. Of course we are going to do our surveillance for cancer recurrence, but I think surveillance for cancer progression is probably not wise. Maybe if you are going to do it every 5 years, it may be a good way to check for progression of Barrett's at the anastomosis.

Dr Ross Bremner (*Phoenix, Ariz*). Tom, have you considered doing an anti-reflux procedure? Glyn Jamieson and his group in Australia just published some compelling data on a prospective study they did with a high intrathoracic anti-reflux procedure that showed no difference in dysphagia but a remarkable difference in reflux. Is that something you would consider doing?

Dr Rice. Do you mean a fundoplication about a low anastomosis?

Dr Bremner. Actually just do an anti-reflux high up in the chest.

Dr Rice. I try to use full gastric tube, full gastric remnant, whenever I can, but usually there is not enough stomach in the neck to do that anti-reflux procedure.

Dr Steve Demeester *(Los Angeles, Calif)*. Tom, those are nice data, important data. What was the longest length of columnar mucosa that you saw develop over time in these patients?

Dr Rice. We did not rely on the measurement of columnar mucosa. Most of the columnar mucosa we found was on histopathologic biopsy, but we did see a few cases endoscopically of approximately 1 cm.

Dr Demeester. So most of the time the anastomosis appeared relatively normal.

Dr Rice. Yes, to my eye it appeared relatively normal and the reflux changes were histopathologic, and surprisingly, a number were ulcerative when things looked reasonably okay.

Dr Demeester. Good, and then just a follow-up question on that. In light of this, the Cleveland Clinic, in particular John (Goldblum), has been a big proponent that all cardiac mucosa intestinal

metaplasia at the gastroesophageal junction in its normal location is a *Helicobacter pylori*–related phenomenon. Has this altered his thinking at all seeing these data?

Dr Demeester. You will have to talk to John, but we discuss this frequently. His belief is that the cardia mucosa in its normal position at the esophagogastric junction, which of course we excise during this operation, is normal mucosa, and when we find it anywhere else it is metaplastic. Certainly with some of the findings we observed, it is hard to tell where the columnar mucosa was at that anastomosis, but one could believe that some of it was on the gastric side of the anastomosis. So we are learning about the esophagogastric junction and the esophagogastric anastomosis.

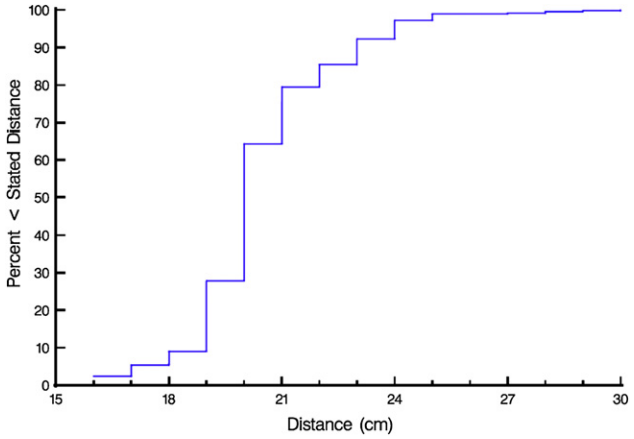

FIGURE E1. Cumulative distribution of distance from incisors to anastomosis.

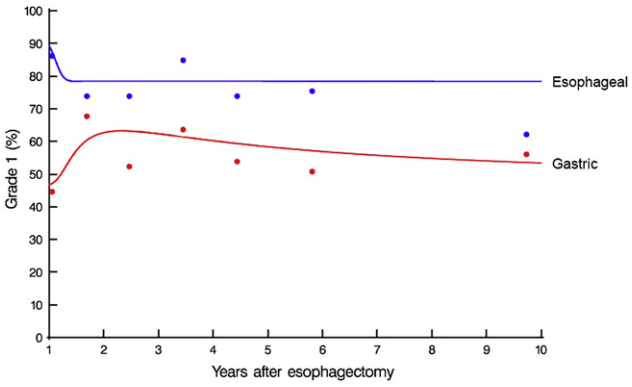

FIGURE E3. Time trend of grade 1 changes at esophageal and gastric sites. Symbols represent data grouped within time frames without regard for repeated assessment, simply to provide crude verification of model fit.

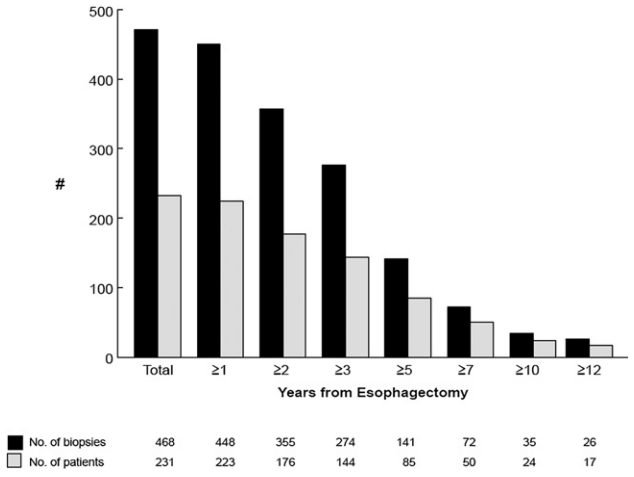

FIGURE E2. Number of patients with biopsies available at and beyond various time points, and number of biopsies available for analysis (*black bars* = biopsies; *grey bars* = patients).