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Management of Gastric Remnant Carcinoma Based on the Results of a 15-Year Endoscopic Screening Program

Frederick L. Greene, M.D.

From the Department of Surgery, University of South Carolina School of Medicine, Columbia, South Carolina

Summary Background Data

Partial gastrectomy for benign peptic ulcer disease is associated with an increased risk of adenocarcinoma of the gastric remnant, especially in patients who are at least 15 years' postgastrectomy. Increasing evidence of mucosal dysplasia is noted on random gastric biopsy and may serve as a histologic marker in the identification of early cancer of the gastric stump.

Methods

From an initial group of 233 patients who underwent gastrectomy for benign peptic ulcer disease between 1960 and 1975, 163 patients began yearly flexible gastroscopy and random mucosal biopsy. Routine histologic studies identified either normal or dysplastic epithelium as well as adenocarcinoma. An average of eight biopsies were taken per endoscopic study. All endoscopic studies were performed by surgical residents under the supervision of one surgical attending.

Results

From July 1980 to June 1995, 145 patients completed annual gastroscopy and random biopsy. A total of 2287 endoscopic studies were performed. Fifteen patients were found to have severe dysplasia. Nine (60%) had associated microscopic evidence of adenocarcinoma. Four additional patients had macroscopic adenocarcinoma on endoscopic examination. All 13 patients with cancer were asymptomatic. Six patients continue surveillance who display moderate-to-severe dysplasia alone. The 13 patients with carcinoma underwent completion gastrectomy (R2 nodal dissection) with no evidence of cancer found beyond the gastric wall. These patients averaged 29 years since their original partial gastrectomy.

Objective

A prospective screening program for gastric remnant cancer was begun to assess the ability to discover early neoplastic changes on random biopsy and to make treatment decisions regarding the efficacy of completion gastrectomy after discovery of carcinoma.

Conclusions

Aggressive annual screening using flexible endoscopy and multiple random biopsy may discover cancer in the gastric remnant and can lead to completion curative gastrectomy in asymptomatic people. Patients who are at least 20 years postpartial gastrectomy for benign disease should be considered for annual endoscopic surveillance.

Table 1. RESULTS OF 15-YEAR SCREENING STUDY, 1980–1995

	Screening Period				
	1980–1985	1985–1987	1987–1988	1988–1994	1994–1995
No. screened	163	163	163	153	145
No. with moderate to severe dysplasia	11	7	9	4	6
No. with remnant cancer	4	2	4	1	2
Postgastrectomy time interval (mean)	14.6	21.5	26.5	28.5	29
Resected with remnant cancer	3*	2	4	1	2
Previous billroth I	3	4	4	2	1
Previous billroth II	8	3	5	2	1
No. with symptoms	0	0	0	0	0

* 1 patient refused completion gastrectomy.

Carcinoma of the gastric remnant after partial gastrectomy for benign peptic ulcer disease was first reported by Balfour[1] at the Mayo Clinic in the early 1920s. More recent reports[2–5] confirm that remnant or "stump" cancer is an unusual, but important, cancer model. The time interval after original gastrectomy is important when considering the epidemiologic diagnosis of disease and the population of patients at risk for neoplastic changes of the remaining stomach.

The development of adenocarcinoma of the gastric remnant is directly related to the postoperative time interval, which is an important consideration to determine surveillance screening in the population at risk. We have reported previously that aggressive flexible esophagogastroscopy not only will identify asymptomatic patients with macroscopic adenocarcinoma of the gastric remnant,[6–8] but effectively can identify patients with moderate-to-severe dysplasia who may be at risk for curable adenocarcinoma, which may be identified on subsequent follow-up gastroscopic examinations.[9,10] After the initiation of our gastric screening protocol in 1980, a report after 8 years of annual endoscopic surveillance, which included random biopsy, showed that severe dysplasia of the gastric remnant developed in nine patients and that four of this group had biopsy-proven microscopic adenocarcinoma.[9] These four patients underwent total gastrectomy and were found to be free of metastatic disease. In addition, four other patients were diagnosed with macroscopic adenocarcinoma during the first 8 years of the surveillance study and underwent total gastrectomy. A report after 14 years of screening recently has been published.[10]

This article details the results of our gastroscopic screening study 15 years after its inception. A total of 145 of the original 163 patients have completed 15 years of surveillance. The results of yearly gastroscopic screening, including random biopsy, are the subject of this article.

MATERIALS AND METHODS

Using a cohort of patients operated on between 1960 and 1975 at the Dorn Veterans Affairs Hospital affiliated with the Department of Surgery at the University of South Carolina School of Medicine in Columbia, South Carolina, we initially identified 233 patients who in 1980 had undergone previous partial gastric resection for either gastric or duodenal ulcer disease. The description of this patient population and the methodology of gastric screening through August 1994 have been reported previously.[7–10] Of the original group of patients who were operated on, 163 were identified and agreed to undergo at least yearly flexible gastroscopic screening with random biopsy to determine the incidence of mucosal dysplasia and remnant cancer as well as additional problems related to previous gastric resection (Table 1). Of the original group of 163 patients, 145 completed 15 years of annual gastroscopic screening, whereas 18 patients died of causes unrelated to their previous gastric resection.

Endoscopic studies were performed by surgical residents under the supervision of one surgical attending (F.L.G.). Gastroscopic screening was performed using fiberoptic or videoendoscopic equipment. During the last 4 years, videoendoscopy techniques were used routinely. All patients were given both topical and intravenous sedation, and the majority were studied as outpatients. Visualization of the entire esophagus, gastric rem-

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Address reprint requests to Frederick L. Greene, M.D., USC Department of Surgery, Two Richland Medical Park, Suite 402, Columbia, SC 29203.

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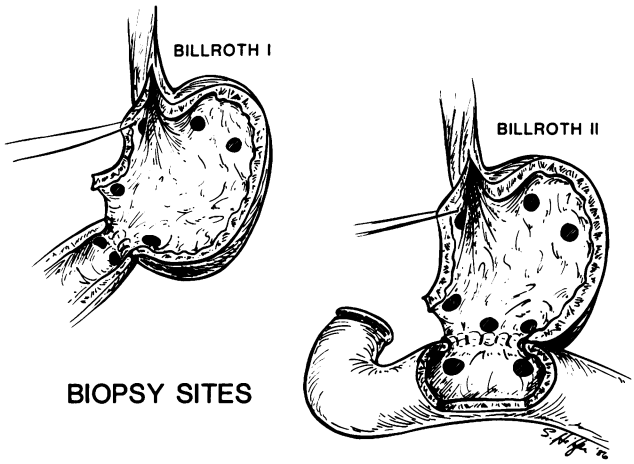

Figure 1. Locations for random biopsy of gastric remnant.

nant, duodenum, and afferent and efferent loops, when applicable, was performed with routine random biopsy using standard biopsy forceps (Fig. 1). Specimens were oriented on filter paper to achieve appropriate flattening of the mucosal surface and were placed in 10% buffered formaldehyde solution for transport to the Pathology Department. All members of the Pathology Department participated in morphologic examination using hematoxylin and eosin staining with review of all findings and grading of dysplasia by members of the department, with specific interests in gastrointestinal disease. An average of eight biopsies were taken during each endoscopic study. Epithelial dysplasia was graded using the standard classification suggested by Savage and Jones.[11] A total of 145 patients completed at least yearly endoscopic evaluation through June 1995. All patients had undergone subtotal gastrectomy with either Billroth I or Billroth II reconstruction, and years since their original gastric resection ranged from 19 to 33. No Roux-en-Y reconstructions were performed in this group. Associated performance of vagotomy was noted when this information was available. Although patients underwent concomitant barium contrast study early in the screening study,[7] this practice was discontinued during the last 10 years of the protocol.

RESULTS

A total of 2287 endoscopic examinations were performed during this prospective screening study. Of 145 patients undergoing repeated annual flexible gastroscopy and random biopsy, 15 were identified as showing severe dysplasia of the gastric remnant (Table 2). Seven patients (46%) had previous Billroth I reconstruction, whereas eight patients (54%) had undergone Billroth II procedures. Only three patients had prior vagotomy with their partial gastrectomy. The 15 patients with dysplasia represented 10.3% of the total group of 145 patients available for screening studies. Associated with severe dysplasia (Fig. 2), 9 of the 15 patients showed histologic evidence of adenocarcinoma in areas of the gastric remnant remote from the dysplastic changes. This represented 60% of the patients who were identified as having severe dysplasia. After being diagnosed as having gastric remnant carcinoma, all nine patients underwent total gastrectomy with conventional (R2) nodal dissection. Results showed limited T_1 or T_2 local disease with no evidence of nodal metastases. The remaining six patients who harbor only moderate-to-severe dysplasia continue to be in a protocol that includes esophagogastroscopy at 6-month intervals.

Since the most recent report of this surveillance protocol, which included results through August 1994,[10] 2 additional patients have been discovered to harbor severe dysplasia and are added to the 13 patients identified during the first 14 years of screening. These two patients averaged 28.5 years since their original gastric resection. A total of nine patients now have been detected who have asymptomatic localized adenocarcinoma of the gastric remnant identified on the basis of associated severe dysplasia. Four patients have been found during the 15-year study who had gross evidence of adenocarcinoma of the gastric remnant but remained asymptomatic. Since 1991, routine evaluation for *Helicobacter pylori*, using urease testing or culture techniques, has not shown an association with either dysplasia or remnant cancer. A total of 13 patients (7.9%) have, thus, been identified with adenocarcinoma in the original screened population. Six patients have been identified as having only

Table 2. OVERALL RESULTS OF 15-YEAR SCREENING PROGRAM

Total patients screened	145
Interval since original gastric resection	
Range	19–34 years
Mean	26.5 years
Total gastroscopic procedures	2287
Total patients with moderate to severe dysplasia	13 (8.5%)
Previous billroth I	6 (40%)
Previous billroth II	9 (60%)
Total gastric remnant cancers associated with dysplasia (intraepithelial cancer)	9 (60%)
Gastric remnant carcinoma (macroscopic)	4
Total gastric remnant cancers	13 (6.7%)
Asymptomatic when screened	13 (100%)
Resected for cure	12 (90.9%)
Ongoing screening with moderate to severe dysplasia	6

* 1 patient refused surgery.

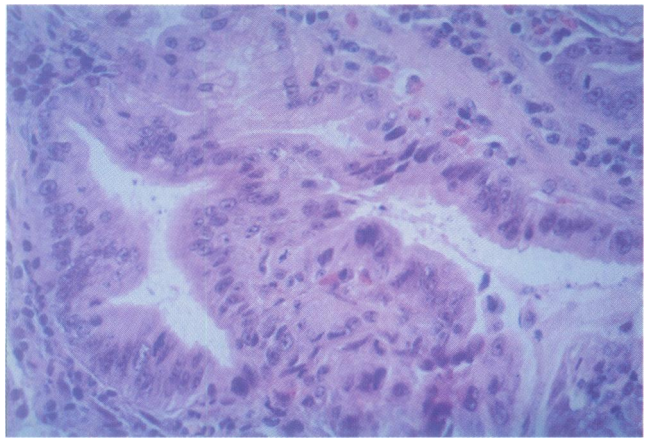

Figure 2. Hematoxylin and eosin slide showing severe dysplasia and intraepithelial cancer from random biopsy. (magnification ×300)

moderate-to-severe dysplasia on random biopsy and have not undergone further gastric resection. No complications from either endoscopic manipulation or biopsy were noted in the 2287 examinations performed.

DISCUSSION

Our screening program for the early diagnosis of carcinoma of the gastric remnant was initiated in 1980 because of the belief that the early endoscopic recognition in the asymptomatic patient would be the only effective means to achieve an improved long-term outlook. Sowa et al.[12] in Japan reported that 61% of their patients were asymptomatic when identified as having remnant cancer during screening. Once patients are symptomatic with adenocarcinoma of the gastric remnant, the likelihood of cure, even after aggressive resection, is remote. During the past 15 years, we have noted the increased association of carcinoma of the remnant in our group of patients with postgastrectomy and have identified the likelihood of progression of mucosal change from dysplasia to adenocarcinoma.

The results of our study further confirm the benefit of endoscopic screening over barium contrast studies in the identification of neoplastic lesions of the gastric remnant. Early in our screening study,[7] all patients underwent upper gastrointestinal barium studies as well as endoscopic procedures. Universally, the barium studies underestimated mucosal findings in the gastric remnant and did not identify lesions in any of our patients with early gastric remnant carcinoma. Radiographic identification may only show positive results in patients who are symptomatic and who, therefore, may not be amenable to curative resection.

A number of retrospective studies have supported the increased association of carcinoma occurring in the stomach after gastric acid suppression surgery.[2,3,13–16] Using a schema proposed by Correa,[17] it is postulated that the raised gastric pH associated with both Billroth I and Billroth II reconstruction may be conducive to the proliferation of anaerobic bacteria that colonize the stomach and transform dietary or endogenous nitrates to nitrites. These substances produce additional N-nitroso compounds, which act as carcinogens. This neoplastic environment has been produced in the animal model.[18,19] In addition, the development of "chemical" atrophic gastritis in the gastric remnant leads to colonization of the mucosa by bacteria, which, in turn, may include *H. pylori*.[20,21] This gram-negative microaerophilic spiral bacteria may be associated with several chronic inflammatory conditions of the stomach, which include chronic atrophic gastritis, a known precursor of gastric carcinoma. *H. pylori* may well act as a promoter of carcinogenesis and may be an important organism to identify because of its association with both the diffuse and intestinal types of gastric cancer.[22,23] Although recent studies have estimated that *H. pylori* infection may contribute up to 60% of the risk for gastric carcinoma,[23] we have not found this organism to be specific in those patients in whom either dysplasia or adenocarcinoma of the gastric remnant develops (unpublished data, 1994).

Yamamoto et al.[24] showed the significant association of Epstein–Barr virus and gastric remnant cancer. Using hybridization techniques to study paraffin sections of 48 cases of remnant cancer, these workers found that Epstein–Barr virus was significantly more common in gastric remnant cancer than in adenocarcinoma of the intact stomach. Further study is needed to support the causal role for Epstein–Barr virus in remnant cancer.

In the 15 years of our screening study, we essentially have had equal numbers of patients with Billroth I and Billroth II reconstructions identified as having both severe dysplasia and early adenocarcinoma, although others have reported a higher incidence after Billroth II reconstruction.[16,25,26] Because no Roux-en-Y reconstructions were performed, an assessment of the protective effect of this maneuver is not possible. Prior vagotomy has not been a reliable association for adenocarcinoma of the gastric remnant, although this association has been reported previously as an independent risk factor for gastric cancer.[27] Our study gives further impetus to the time course after initial gastric resection because patients who are at least 15 years' postresection should be entered into a screening protocol. The longer the patient remains asymptomatic after gastric resection, the more likely will findings of moderate-to-severe dysplasia be observed. Because our study was done within the setting of a Veterans Affairs hospital, all of our patients are men. Although we cannot definitively comment on the applicability of long-term screening of female patients, previous

studies have shown that the risk of remnant carcinoma is equal in men and women.[26]

A report of approximately 6500 Swedish patients who have been observed for 25 to 33 years after partial gastrectomy shows that the length of interval after gastrectomy is of significance and that patients who are at least 20 years' postresection are at risk for gastric remnant cancer.[26] Studies that report to show no increased risk of adenocarcinoma in patients who are postresection may not have included a subset of patients who are remote enough from their original gastrectomy. It is clear that younger patients who are followed for at least 20 to 30 years may be at significant risk from this neoplasm.[5,16,25]

The 145 patients who have reported for annual gastroscopic screening have proved to be a rather reliable cohort and surprisingly have been rather amenable to yearly gastroscopy and biopsy when told of the potential benefits of early cancer detection. As reported previously,[7-10] random biopsy and careful endoscopic visualization serve as important techniques in the identification of both dysplasia and early adenocarcinoma. We continue to follow six patients who have evidence of moderate-to-severe dysplasia, but who have not undergone completion gastrectomy. It remains unclear as to the time course and eventual outcome in this subset of patients in that the risk–benefit equation may not yet weigh toward recommending completion gastrectomy, as has been suggested by others.[3] We think, however, that this represents a "high-risk" group and, therefore, have modified our screening approach to offer semiannual gastroscopy with random biopsy to these patients. In addition, these six patients have been informed that they indeed represent a high-risk group and that eventual completion gastrectomy may be indicated.

It has been suggested by Japanese workers that advanced gastric cancer may be preceded by dysplastic lesions by 5 to 10 years.[28] It may be reasonable to use a similar approach in these patients as originally reported regarding the concept of "precancer" as it applies to chronic ulcerative colitis.[29] The critical problem, however, is in the histologic recognition of changes that may in fact be early intraepithelial cancer in the colon. The drawback to the concept of precancer as it applies to ulcerative colitis is that most pathologists do not have the training to recognize these early, subtle changes. The difficulty in interpretation of gastric dysplasia after previous gastrectomy is heightened by the overall inflammatory changes that are secondary to reflux bile gastritis, which occurs in all patients.[29] Over the 15 years of our screening study, our pathology staff has benefitted by the opportunity of reviewing these histologic specimens and has become quite facile in the identification of dysplasia *versus* inflammation alone.

The study by Rugge[30] supports the concept that dysplastic lesions in the stomach were associated with atrophic gastritis and progressed to carcinoma in direct proportions to the histologic severity of the dysplastic lesion. Fourteen of the 93 patients studied showed evolution to gastric carcinoma and 86.9% of these patients had their cancer detected at an early stage.

A recommendation for screening patients undergoing previous gastrectomy still may be challenged because of the small number of patients affected and the potential cost of such a screening program. Staël von Holstein et al.[31] found increased numbers of remnant cancer in an endoscopically screened group but report no increase in survival when compared with the unscreened control group having previous gastric resection. As Staël von Holstein et al.[32] have concluded, the appropriate course is to perform total gastrectomy for gastric remnant cancer because the entire remaining remnant is at risk for neoplastic transformation. If partial resection of the remnant is performed, 30% of patients may have tumor recurrence.[32]

The results of our 15 years of intensive gastroscopic screening with random biopsy suggest that a significant benefit may be achieved by limiting annual screening to patients who are at least 15 years' postgastric resection and who are identified as showing moderate-to-severe dysplasia on random biopsy. Our study clearly has shown that patients with early gastric remnant carcinoma benefit greatly by resection when limited disease is diagnosed. Pointner et al.[33] recently reported the improved prognosis when resection is performed for early stage gastric remnant cancer. Although costs, both in terms of economic impact and procedural risks, are important concepts, the ability to cure a patient when a potentially life-threatening neoplasm is discovered is in itself rewarding and, in our opinion, has justified the last 15 years of our screening effort.

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Discussion

DR. JOHN L. SAWYERS (Nashville, Tennessee): Dr. Haller, Dr. Copeland, Fellows, and Guests. Dr. Greene's presentation attempts to shed more knowledge regarding a longstanding controversy as to whether the risk of gastric cancer is greater after resection for benign disease than the risk of gastric carcinoma developing in a normal unoperated stomach. It would appear that this controversy has been settled.

In the first 15 years of gastric resection, there is a decrease in the incidence of adenocarcinoma of the stomach. Beginning after 15 years, there becomes a marked increase, so that the relative risk is two- to threefold after 20 years.

Stump cancer is reportedly four times higher after a Billroth II than after a Billroth I procedure, although this was not the case in Dr. Greene's report. An increase in bile reflux after a Billroth II procedure is blamed for this difference.

The incidence of stump cancer is also greater after gastric resection for gastric ulcer than after gastric resection for duodenal ulcer. Patients having only sutured closure for a perforated peptic ulcer did not have an increased risk of stump cancer, so it may be that the gastric operation and not peptic ulcer disease is a precursor for gastric carcinoma.

There have been three major reports, not including Dr. Greene's, in the 1990s that suggest an increased risk for the development of gastric remnant cancer after 10 to 20 years, more frequently after the Billroth tube gastrectomy.

Cancer has also been reported after other operations for peptic ulcer disease, including proximal gastric vagotomy. Dr. Greene has suggested that endoscopic surveillance for gastric stump cancer should find early gastric cancers which, when treated by completion gastrectomy, would lead to improved survival. I would like to know what his survival results are.

I would also like to ask Dr. Greene some questions regarding his study. First, has he done a cost analysis of endoscopic surveillance for gastric stump cancer?

He performed 2287 endoscopies with an average of 8 random biopsies. I wonder in this era of managed care if such surveillance will be authorized?

Does he think that there is an environmental influence which may cause a geographic distribution of stump cancer. The incidence of gastric stump cancer is higher in most studies from Europe. But in a study done at the Mayo Clinic in Olmsted County, Minnesota, stump cancer was found in only two patients, and it was thought that gastric cancer was no more prevalent among patients with prior gastric operations for benign disease than among the general population.

Would he elaborate on his studies regarding the presence of *Helicobacter pylori*? Researchers at Vanderbilt University Medical Center have discovered a distinct strain of bacteria responsible for most cases of stomach cancer. A gene called CAG-A has been found in certain *H. pylori* organisms. It appears that patients infected with *H. pylori* with CAG-A positive strains of the bacteria are more at risk for the development of malignant