

Screening of *Helicobacter pylori* Infection After Gastrectomy for Cancer or Peptic Ulcer

Results of a Cohort Study

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Background: Gastric cancer commonly follows a long-standing inflammation, mainly due to *Helicobacter pylori* (HP) infection. After resection, the stump develops precancerous alterations.

Design: Prospective study of patients undergoing endoscopy from April 1, 2000, through March 31, 2006.

Setting: University departments of Surgery and Experimental Medicine and Pathology.

Patients: One hundred eighty-seven patients receiving upper gastrointestinal tract endoscopy many years after surgery for duodenal ulcer or gastric cancer. Ten to 12 postoperative endoscopic biopsy samples were taken from the remnant stomach.

Main Outcome Measure: The risk of gastric cancer precursor lesions associated with HP infection.

Results: The gastric cancer precursor lesions were more common in the entire HP-positive population (odds ratio [OR], 2.37; 95% confidence interval [CI], 1.25-4.49; $P = .007$). However, HP-positive patients undergoing resection for cancer had a higher risk of the precursor lesions compared with HP-negative patients in the same diagnostic group (OR, 4.20; 95% CI, 1.10-15.96) and all patients undergoing resection for duodenal ulcer (OR, 1.59; 95% CI, 0.44-5.73).

Conclusion: The results of this investigation support the role of HP in gastric carcinogenesis and suggest that the HP eradication therapy might prevent the development of metachronous gastric cancer after gastric resection.

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CANCER OF THE STOMACH IS considered to develop from gastric cancer precursor lesions (GCPLs) such as chronic atrophic gastritis (CAG), intestinal metaplasia (IM), and dysplasia.¹⁻³ Although a long-standing inflammation has always been considered mandatory in the development of gastric cancer, the exact mechanisms of carcinogenesis have remained unknown until the role of *Helicobacter pylori* (HP) infection in the process was first discovered,^{4,5} and several studies have later confirmed the link between HP infection and gastric cancer.⁶

See Invited Critique at end of article

The mucosa of the remaining gastric stump after resection for cancer or for peptic ulcer disease is considered prone to develop GCPLs and cancers⁷⁻⁹ because it is exposed to a new, nonphysiological environment and, probably, to HP.¹⁰⁻¹² We have previously dealt with the histological features related to HP status in intact and re-

sected stomachs.^{13,14} The present study ascertains the prevalence of some histological features and of HP infection after gastric resection for peptic ulcer disease or gastric cancer, the primary outcome being the evaluation of the risk of GCPLs associated with HP infection.

METHODS

One hundred eighty-seven patients (138 were male and 49 were female) who had received gastric resection for peptic duodenal ulcer (group 1; $n = 131$) or advanced gastric cancer (group 2; $n = 56$) were included in this prospective study. All patients were asked for and granted their informed consent for inclusion. Reconstruction of the digestive tract consisted of a Billroth I gastroduodenostomy ($n = 14$) or a Billroth II gastrojejunostomy ($n = 173$). All 187 patients underwent upper digestive tract endoscopy between April 1, 2000, and March 31, 2006, at the endoscopic units of the departments of Surgery Pietro Valdoni and Medical Therapy of the University of Rome La Sapienza, First Medical School. All endoscopies were performed in the setting of postgastrectomy surveillance. None of these patients had received eradicating therapy for HP infection, antibiotics, nonsteroidal anti-

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inflammatory drugs, or chemotherapy in the 4 weeks before the diagnostic procedure. Endoscopic examination of the esophagus, gastric stump, anastomosis, and anastomosed small bowel for approximately 20 cm was routinely performed. A rapid urease test on gastric biopsy specimens from 37 cases, belonging to both groups, was performed at the beginning of the study. However, this test was later abandoned to reduce the number of total biopsy specimens because findings overlapped with the histological results in 36 of 37 cases. Histological microscopic examination was always performed. Most of the study patients had undergone the initial operation in other institutions and had not received any assessment of the HP status before our endoscopy. In any case, to the best of our knowledge, no patient had received any eradicating therapy after surgery. However, we prescribed antibiotic eradicating therapy to any patient we discovered to have positive findings for HP infection (HP positive), with no further HP status assessment at a later stage. Ten to 12 biopsy specimens were routinely taken from the stoma and the peristomal areas, from other areas of residual gastric mucosa along the lesser and greater curvatures, and from any areas showing erythema, erosion, or friability. Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin. Additional sections of biopsy specimens were examined using Giemsa stain for HP detection. All histological slides were blindly reviewed by an experienced gastrointestinal pathologist (I.P.). The histological findings were classified as normal mucosa (NM; no changes in the mucosa), chronic nonatrophic gastritis (NAG; inflammatory cells in the lamina propria, but no loss of glands), CAG (loss of glands of any grade and stromal proliferation between the glands), IM (absorption, goblet, and Paneth cells in the superficial epithelium), and dysplasia (secretive, nuclear, and cytoplasmic abnormalities, excluding reactive, nondysplastic conditions). *Helicobacter pylori* infection, any histological mucosal changes, and inflammation¹ (presence of chronic inflammatory cells in the lamina propria, such as lymphocytes, plasma cells, macrophages, and histiocytes) and its activity¹ (presence of neutrophil granulocyte infiltration in the lamina propria or in intraepithelial foci) were recorded as present or absent. When more histological lesions were present, the case was classified according to increasing severity in the following order: NM, NAG, CAG, IM, and dysplasia. The last 3 (CAG, IM, and dysplasia) were all included in the GCPL group, which was the main focus of our study.

Statistical analysis was performed using the χ^2 test, and $P < .05$ was considered significant. We also used the odds ratio (OR) with a 95% confidence interval (CI), defined as the ratio of the probability that an event (1 specific clinical or histological characteristic) would occur to the probability that it would not. Mean values are expressed as mean (SD). The study was approved by the ethics committee of the University of Rome La Sapienza, First Medical School.

RESULTS

The patients of both groups were divided for statistical analysis according to mean age at endoscopy, mean age at resection, and mean duration of postoperative period. **Table 1** shows sex, age at digestive endoscopy (group 1 mean age, 69.6 [10.0] years; group 2, 69.2 [10.1] years), age at gastric resection (group 1 mean age, 40.8 [12.6] years; group 2, 60.8 [13.9] years), and time elapsed from surgery to endoscopy (group 1 mean interval, 27.8 [11.6] years; group 2, 7.6 [7.4] years). Male sex was prevalent in group 1 (OR, 3.18; 95% CI, 1.60-6.31; $P = .001$). In both groups, there was an even distribution in relation to age at endoscopy, age at resection, and duration of postoperative intervals. Group 2 showed a preva-

Table 1. Characteristics of the Studied Populations^a

Characteristic	Group 1 (n=131)	Group 2 (n=56)
Sex		
Male	106	32
Female	25	24
Age at endoscopy, y		
Range	25-87	37-84
<70	65	27
≥70	66	29
Age at resection, y		
Range	13-72	19-80
<41 ^b	64	
≥41 ^b	67	
<61 ^c		26
≥61 ^c		30
Interval, y		
Range	1-63	1-41
<28 ^b	67	
≥28 ^b	64	
<7 ^c		31
≥7 ^c		25

^aUnless otherwise indicated, data are expressed as number of patients. Group 1 indicates patients undergoing resection for peptic duodenal ulcer; group 2, for advanced gastric cancer.

^bGroup 1 only.

^cGroup 2 only.

Table 2. Prevalence of Histological Findings^a

Histological Findings	No. (%) of Patients		OR (95% CI)
	Group 1 (n=131)	Group 2 (n=56)	
NM	18 (14)	16 (29)	2.51 (1.16-5.39)
NAG	65 (50)	22 (39)	1.52 (0.80-2.87)
CAG	25 (19)	10 (18)	1.08 (0.48-2.44)
IM	18 (14)	3 (5)	2.81 (0.79-9.97)
Dysplasia	5 (4)	5 (9)	2.47 (0.68-8.89)
Inflammation	108 (82)	35 (63)	2.81 (1.39-5.69)
Activity	81 (62)	18 (32)	3.42 (1.76-6.63)
<i>Helicobacter pylori</i> infection	47 (36)	12 (21)	2.05 (0.98-4.26)

Abbreviations: CAG, chronic atrophic gastritis; CI, confidence interval; IM, intestinal metaplasia; NAG, chronic nonatrophic gastritis; NM, normal mucosa; OR, odds ratio.

^aGroup 1 indicates patients undergoing resection for peptic duodenal ulcer; group 2, for advanced gastric cancer.

lence of NM ($P = .02$) and dysplasia, whereas in group 1 NAG, IM, inflammation ($P = .003$), activity ($P < .001$), and HP infection ($P = .05$) prevailed (**Table 2**).

GROUP 1

The biopsy specimens showed a prevailing incidence of NAG and dysplasia in older patients and IM in younger patients ($P = .04$) (**Table 3**). The patients undergoing operation at a younger age had an increased occurrence of NM and IM ($P = .03$), whereas those undergoing operation at an older age had a prevailing incidence of CAG and mononuclear cell infiltration. A longer postoperative period corresponded to an increased incidence of NM and dysplasia, whereas a shorter postoperative interval corre-

Table 3. Histological Findings in Relation to Ages at Endoscopy and Resection and Time Elapsed Since Surgery

Histological Findings	No. (%) of Patients Age at Endoscopy, y			No. (%) of Patients Age at Resection, y			No. (%) of Patients Interval, y		
	<70	≥70	OR (95% CI)	<41	≥41	OR (95% CI)	<28	≥28	OR (95% CI)
Group 1^a									
NM	10 (15)	8 (12)	1.31 (0.48-3.58)	12 (19)	6 (9)	2.34 (0.82-6.68)	7 (10)	11 (17)	1.77 (0.64-4.91)
NAG	29 (45)	36 (55)	1.49 (0.74-2.96)	29 (45)	36 (54)	1.40 (0.70-2.78)	33 (49)	32 (50)	1.03 (0.51-2.04)
CAG	11 (17)	14 (21)	1.32 (0.55-2.96)	8 (13)	17 (25)	2.38 (0.94-5.98)	16 (24)	9 (14)	1.91 (0.77-4.72)
IM	13 (20)	5 (8)	3.05 (1.01-9.12)	13 (20)	5 (7)	3.16 (1.05-9.45)	9 (13)	9 (14)	1.05 (0.39-2.85)
Dysplasia	2 (3)	3 (5)	1.50 (0.24-9.28)	2 (3)	3 (5)	1.45 (0.23-8.99)	2 (3)	3 (5)	1.59 (0.25-9.89)
Inflammation	53 (82)	55 (83)	1.13 (0.46-2.78)	50 (78)	58 (87)	1.80 (0.71-4.52)	58 (87)	50 (78)	1.80 (0.71-9.52)
Activity	40 (62)	41 (62)	1.02 (0.50-2.07)	38 (59)	43 (64)	1.22 (0.60-2.48)	46 (69)	35 (55)	1.81 (0.88-3.70)
<i>Helicobacter pylori</i> infection	25 (38)	22 (33)	1.25 (0.61-2.55)	24 (38)	23 (34)	1.14 (0.56-2.34)	27 (40)	20 (31)	0.48 (0.72-3.04)
Group 2^b									
Histological Findings	No. (%) of Patients Age at Endoscopy, y			No. (%) of Patients Age at Resection, y			No. (%) of Patients Interval, y		
	<70	≥70	OR (95% CI)	<61	≥61	OR (95% CI)	<7	≥7	OR (95% CI)
NM	8 (30)	8 (28)	1.10 (0.34-3.52)	6 (23)	10 (33)	1.66 (0.50-5.46)	10 (32)	6 (24)	1.50 (1.46-4.94)
NAG	9 (33)	13 (45)	1.62 (0.55-4.80)	9 (35)	13 (43)	1.44 (0.48-4.26)	13 (42)	9 (36)	1.28 (0.43-3.79)
CAG	4 (15)	6 (21)	1.50 (0.37-6.02)	6 (23)	4 (13)	1.94 (0.48-7.85)	4 (13)	6 (24)	2.13 (0.52-8.59)
IM	2 (7)	1 (3)	2.24 (0.19-26.22)	2 (8)	1 (3)	2.41 (0.20-28.30)	1 (3)	2 (8)	2.60 (0.22-30.57)
Dysplasia	4 (15)	1 (3)	4.87 (0.50-46.65)	3 (12)	2 (7)	1.82 (0.28-11.87)	3 (10)	2 (8)	1.23 (0.18-8.01)
Inflammation	15 (56)	20 (69)	1.77 (0.59-5.30)	17 (65)	18 (60)	1.25 (0.42-3.74)	18 (58)	17 (68)	1.53 (0.50-4.62)
Activity	10 (37)	8 (28)	1.54 (0.50-4.72)	10 (38)	8 (27)	1.71 (0.55-5.32)	7 (23)	11 (44)	2.69 (0.84-8.54)
<i>Helicobacter pylori</i> infection	8 (30)	4 (14)	2.63 (0.68-10.05)	7 (27)	5 (17)	1.84 (0.50-6.71)	5 (16)	7 (28)	2.02 (0.55-7.38)

Abbreviations: CAG, chronic atrophic gastritis; CI, confidence interval; IM, intestinal metaplasia; NAG, chronic nonatrophic gastritis; NM, normal mucosa; OR, odds ratio.

^aGroup 1 indicates patients undergoing resection for peptic duodenal ulcer (n = 131). Percentages have been rounded and may not total 100.

^bGroup 2 indicates patients undergoing resection for advanced gastric cancer (n = 56). Percentages have been rounded and may not total 100.

sponded to an increased incidence of CAG, inflammation, and activity.

GROUP 2

Younger age at endoscopy was associated with a higher prevalence of IM, dysplasia, neutrophil granulocyte infiltration, and HP infection, whereas older age at endoscopy was associated with a higher rate of NAG, CAG, and inflammation. A prevalence of GCPLs was found in younger cases (OR, 1.54; 95% CI, 0.50-4.72) (Table 3).

Patients undergoing operation at an older age had more frequent NM, whereas those undergoing resection at a younger age presented with CAG, IM, dysplasia, neutrophil granulocyte infiltration, and HP infection. Patients undergoing resection at a younger age had more frequent findings of GCPLs (OR, 2.40; 95% CI, 0.76-7.60).

A shorter postoperative interval was related to prevalence of NM, with longer intervals related to prevalence of CAG, IM, inflammation, activity, and HP infection. The occurrence of GCPLs was related to longer postoperative intervals (OR, 1.91; 95% CI, 0.61-5.96).

INFLUENCE OF HP INFECTION

All HP-positive cases showed a higher prevalence of CAG (P = .02), IM (P = .09), inflammation (P < .001), and activity (P < .001), whereas HP-negative cases showed a preva-

lence of dysplasia. A prevalence of GCPLs was found in HP-positive cases (OR, 2.37; 95% CI, 1.25-4.49; P = .007) (Table 4).

The HP-negative cases in group 2 showed an increased occurrence of NM and dysplasia, whereas those of group 1 showed higher rates of IM (P = .06), inflammation (P = .03), and activity (P = .001).

The HP-positive cases in group 1 showed a nonsignificant increase of NAG and inflammation, whereas those in group 2 evidenced a higher risk of GCPLs (OR, 1.59; 95% CI, 0.44-5.73). The HP-positive cases in groups 1 and 2 showed an increased incidence of GCPLs, inflammation, and activity compared with HP-negative patients (Table 5).

COMMENT

To the best of our knowledge, this is the first study to compare mucosal lesions and HP status in the gastric stump after partial gastrectomy for duodenal ulcer and gastric cancer. It could be argued that it is difficult to compare gastric lesions in patients undergoing resection for benign and malignant illnesses because the mucosal baseline conditions are in many aspects different. Most gastric cancers arise from an atrophic and metaplastic mucosa,¹⁵ unlike peptic duodenal ulcer.¹⁶⁻²⁰ In addition, ages at resection and, therefore, duration of the postoperative follow-up are substantially different in the cases of

Table 4. Prevalence of Histological Findings in Relation to HP Status^a

Histological Findings	No. (%) of Patients		OR (95% CI)	No. (%) of Patients		OR (95% CI)
	Group 1 (n=131)			Group 2 (n=56)		
	HP+	HP-		HP+	HP-	
NM	0	18 (21)	...	0	16 (36)	...
NAG	25 (53)	40 (48)	1.25 (0.61-2.55)	5 (42)	17 (39)	1.13 (0.30-4.15)
CAG	13 (28)	12 (14)	2.29 (0.94-5.55)	4 (33)	6 (14)	3.16 (0.72-13.87)
IM	8 (17)	10 (12)	1.51 (0.55-4.15)	2 (17)	1 (2)	8.6 (0.70-104.47)
Dysplasia	1 (2)	4 (5)	4.6 (0.49-42.86)	1 (8)	4 (9)	1.1 (0.11-10.87)
Inflammation	46 (98)	62 (74)	16.32 (2.12-125.53)	11 (92)	24 (55)	9.10 (1.08-77.24)
Activity	43 (91)	38 (45)	13.01 (4.28-39.52)	11 (92)	7 (16)	58.14 (6.43-125.15)

Abbreviations: Ellipses, not calculable; minus sign, negative; plus sign, positive. Other abbreviations: See Table 3.

^aGroup 1 indicates patients undergoing resection for peptic duodenal ulcer; group 2, for advanced gastric cancer.

benign or malignant conditions, because of a shorter likelihood of survival and follow-up time in the neoplastic population. In addition, although HP infection plays a critical role in malignancy and peptic ulcer disease, a number of other etiological factors are involved in gastric cancer.²¹ In any case, the residual mucosa in the gastric stump is considered at risk and precancerous as such, independent of indication for surgery.²² We determined HP status by means of conventional histological patterns, although more sensitive methods for detecting HP do exist,^{23,24} which could explain a higher prevalence of HP infection reported by others.^{9,25-28} The maximal accuracy of histological analysis in detecting HP infection is obtained with a satisfactory number of biopsy specimens, optimal specimen processing, adequate staining, and an experienced observer.²⁹ Our study fulfilled all these conditions. Theoretically, the patchy nature of HP infection might bias the results of biopsy-based histological studies; however, we have minimized this risk by taking 10 to 12 biopsy specimens. In addition, the use of 2 staining methods has reduced the likelihood of false-negative results.³⁰⁻³³ Many factors render the mucosa of the gastric stump a progressively inhospitable environment for HP. Biliopancreatic reflux is regarded as the main cause of inhospitality to HP after gastric resection, and most of our patients received a Billroth II gastric resection, which particularly favors this reflux.^{26,34-36}

Patients in group 2 had undergone resection for advanced cancer; therefore, it is possible that, at surgery, the mucosa adjacent to the tumor had already become inhospitable to HP. In addition, although some patients in both groups may have undergone operation for an HP-negative condition such as duodenal ulcer caused by non-steroidal anti-inflammatory drugs³⁷ or gastric cancer developed without the promoter effect of HP infection,³⁸ this could not be ascertained in our study, which did not investigate preoperative HP status.

Therefore, HP-positivity in our patients might indicate expression of a persistent or newly developed infection. In relation to mucosal alterations, we took into account their presence or absence, rather than their severity, to make the results easier to compare. There is a chance that some of the morphological changes of the residual mucosa were already present at surgery in relation to the causative disease and that, in the postoperative period, these lesions persisted, pro-

Table 5. Odds of GCPLs, Inflammation, and Activity in *Helicobacter pylori*-Positive Cases With Respect to Negative Cases

	HP+, OR (95% CI)	
	Group 1	Group 2
GCPLs	1.90 (0.93-4.09)	4.20 (1.10-15.96)
Inflammation	16.32 (2.12-125.50)	9.10 (1.08-77.24)
Activity	13.01 (4.28-39.52)	58.14 (6.43-525.15)

Abbreviations: CI, confidence interval; GCPLs, gastric cancer precursor lesions; OR, odds ratio; plus sign, positive.

^aGroup 1 indicates patients undergoing resection for peptic duodenal ulcer; group 2, for advanced gastric cancer.

gressed, and/or even regressed in relation to HP status³⁹⁻⁴³ and undefined other multiple factors.⁴⁴ However, it was impossible for us to retrospectively ascertain the status of the gastric mucosa at the time of surgery. We observed that the prevalence of mucosal lesions in both groups was irregularly related to the time. Group 1 showed a higher risk for IM in younger patients at endoscopy and at gastric resection, whereas group 2 showed a higher risk for IM and dysplasia in the same cases. A longer postoperative period was related to an increased incidence of almost all mucosal lesions in group 2, whereas a longer postoperative period implied only an increased incidence of dysplasia in group 1. Other authors, however, have observed that time is an important factor ruling IM and CAG.^{43,45-47}

Lymphocyte and leukocyte infiltration of the lamina propria had a similar prevalence in the HP-positive cases of both groups, although there was a 4-fold risk of inflammation in group 1 compared with group 2 (Table 4). The HP-negative cases in group 1 showed a 2-fold and 4-fold risk of inflammation and activity, respectively, compared with HP-negative patients in group 2 (Table 4). These findings suggest that, apart from infection, environmental or lifestyle factors play a role in the development of some morphological changes.^{38,48}

The resected stomach, because it is a precancerous condition, offers the unique opportunity to study the factors involved in gastric carcinogenesis. Our research considered some of these factors and showed no significant role of mucosal changes in relation to age (at endoscopy and at resection) and duration of postoperative period,

although a longer postoperative period was related to more advanced lesions in group 2. In this study, however, the role of the disease leading to surgery on the residual mucosa lesions was evident. The prevalence of dysplasia in HP-positive patients was 4 times higher in group 2 compared with group 1, and HP-negative patients in group 2 presented a 2-fold risk of dysplasia compared with group 1 (Table 4). In addition, the role of infection was considerably significant. The risk of GCPLs, inflammation, and activity in HP-positive patients was notably increased compared with HP-negative patients (Table 5). This is the most significant finding of our study and proves that there is a link between HP infection and gastric carcinogenesis. Table 5 shows a wide range of 95% CIs for inflammation and activity, which suggests that more data should be collected to draw any conclusion in relation to the importance of HP positivity after gastric resection. However, the Asian and European guidelines strongly recommend HP eradication therapy after gastric resection,^{49,50} although it has been observed that therapy significantly decreases inflammation and activity, whereas glandular atrophy and IM persist unchanged.^{15,45,51,52} In any case, according to the results of our research, we strongly recommend HP status assessment and possible HP infection eradication therapy after gastric resection for malignant or benign disease.

CONCLUSIONS

The remnant mucosa after gastric resection for duodenal ulcer and gastric cancer is often a favorable environment for HP infection, which increases the risk of GCPLs, inflammation, and activity, in particular in patients who received surgery for gastric cancer. The eradication of HP infection from the gastric stump, therefore, may prevent the development of metachronous gastric cancer after partial gastrectomy. Given the relative ease of such an eradication, this should always be recommended after partial gastrectomy. The important question is, will eradicating the bacteria result in normalization of the reported histological abnormalities and reduce the risk of cancer in the gastric stump? In our opinion, it might, although we have no data to support this hypothesis, which, therefore, could be the basis for future research.

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INVITED CRITIQUE

Gastric Remnant Cancer

Is Elimination of the Bug the Answer?

Giuliani et al provide incremental information suggesting that HP infection is an integral factor in the development of GCPLs and, maybe, subsequent gastric cancer. This association was present regardless of whether the indication for gastric resection was ulcer disease or gastric cancer. Thus, the mere presence of a mucosal field defect in patients who underwent resection for cancer cannot explain the propensity toward malignant transformation. Although the data suggest that patients with HP infection are indeed at risk for the development of premalignant lesions, it is also clearly evident that HP-negative patients were at significant risk of GCPLs and thus, likely, gastric cancer. Hence, the development of gastric cancer does not necessarily follow the sequential progression of HP infection, chronic inflammation, GCPL development, and, finally, gastric cancer. Therefore, if a field defect does not explain cancer development and the presence of HP infection is not solely explanatory, what are the key elements of gastric cancer development in this setting? Perhaps chronic inflammation is the common denominator. Although the associations identified by the authors are helpful, simple treatment for HP infection and/or a surveillance program clearly

will not eliminate the development of gastric cancer in the remnant stomach. As the authors point out, the investigative community must perform more in-depth studies to identify not only clinical associations but also mechanistic causality through rigorous basic science studies. In recent years, the surgical community has gravitated toward important but limited clinical studies to identify clinical associations of disease development. This study highlights the potential benefits derived from such clinical work but also is a clear reminder that, as a surgical investigative community, we must perform hypothesis-driven basic science that seeks further understanding of the underlying mechanisms of cancer development and the role of HP infection and chronic inflammation.

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