Diagnostic Variation and Outcome for High-Grade Gastric Epithelial Dysplasia

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Hypothesis: High-grade dysplasia (HGD) of the gastric epithelium is associated with high prevalence of invasive carcinoma, and distinction by endoscopic biopsy is difficult.


Setting: Tertiary care center.

Patients: Consecutive sample of 22 patients with initial diagnosis of gastric HGD by endoscopic biopsy. Biopsy specimens were separately reviewed by 3 experienced pathologists. Clinical management was individually decided.

Main Outcome Measures: Strength of interpathologist agreement (κ) and final pathological diagnosis.

Results: The diagnosis was revised to intramucosal carcinoma in 14% to 32% of patients or suspicious for invasive carcinoma in 23% to 41%. The strength of agreement between any 2 pathologists for distinguishing between dysplasia and invasive carcinoma was fair (κ=0.35-0.36). A diagnosis of intramucosal carcinoma or suspicious for invasive carcinoma by 2 pathologists correlated strongly with subsequent detection of invasive carcinoma. Three patients underwent gastrectomy for HGD, and invasive carcinoma was detected in all (2 patients, T1 N0; 1 patient, T2 N0). Six patients had invasive carcinoma on endoscopic surveillance at a median of 15 months (range, 3-34 months) after diagnosis of HGD and underwent endoscopic mucosal resection (2 patients, T1 NX), gastrectomy (2 patients, T1 N0), or no resection (2 patients). Another patient had metastatic gastric adenocarcinoma despite having a diagnosis of only HGD by endoscopy. Seven patients (32%) died of unrelated causes, without invasive carcinoma, at a median of 19 months (range, 1-38 months). Three patients were alive with persistent HGD at 26 to 61 months. Two patients had no dysplasia on follow-up.

Conclusions: Experienced pathologists often disagreed in distinguishing invasive carcinoma from HGD in gastric biopsy specimens. One third of patients with gastric HGD died of causes unrelated to cancer. Invasive carcinoma was detected in 67% of the remainder.

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Within the gastrointestinal tract, dysplasia refers to phenotypically neoplastic epithelium that is limited to glandular structures inside the epithelial basement membrane. The diagnosis is based on atypical cellular features, abnormal differentiation, and disorganized architecture of epithelial cells. Dysplasia has been extensively discussed in the context of ulcerative colitis and Barrett esophagus. Gastric epithelial dysplasia (also called noninvasive gastric neoplasia) is less well recognized as the penultimate stage of a multistep process in the pathogenesis of intestinal-type gastric adenocarcinoma and involves progression through superficial gastritis, chronic atrophic gastritis, and intestinal metaplasia. With systematic, prospective follow-up, invasive adenocarcinoma (ie, invasion of neoplastic cells through the basement membrane and into the lamina propria) is endoscopically detected in up to 8% of patients with low-grade gastric epithelial dysplasia and a policy of surveillance is appropriate for this population. In contrast, the natural history of progression and clinical management of high-grade gastric dysplasia remain controversial. The controversy is partly because of interpathologist variation in the distinction of high-grade dysplasia (HGD) from carcinoma. For example, Japanese pathologists attach more importance to nuclear features as well as glandular structures than to invasion and diagnose carcinoma in up to 90% of cases for which Western pathologists would use the term...
**METHODS**

All patients with a histopathological diagnosis of HGD or severe gastric epithelial dysplasia in endoscopic biopsy specimens, between 1996 and 2001 at a single institution (St James’s University Hospital, Leeds, England), were identified. Cases of HGD or severe dysplasia adjacent to invasive carcinoma were excluded. There was no screening program for gastric neoplasia, and the initial endoscopy had been performed for investigation of a variety of symptoms. During this study period, gastric epithelial dysplasia had been graded on either a 2-tier system (low grade or high grade) or a 3-tier system (mild, moderate, or severe). If the 3-tier system had been used, only the severe category was included in this study.

For the present study, all cases of HGD or severe dysplasia were identified and representative sections were selected by 1 pathologist (pathologist 1 [N.S.]). These representative slides were then independently reviewed by 2 other pathologists (pathologists 2 and 3 [C.S.V. and J.I.W.]). The pathologists were of attending status for 8, 10, or 15 years, respectively, and specialized in gastrointestinal histopathology. The initial diagnosis of HGD or severe dysplasia had been made by pathologist 1 in 6 cases, by pathologist 2 in 7 cases, by pathologist 3 in 6 cases, or by another pathologist in 3 cases (Table 1). For the present study, all 3 pathologists were blind to the identity of the initial pathologist. All cases were separately reclassified by each pathologist as low-grade dysplasia (LGD), HGD, suspicious for invasive carcinoma, or intramucosal carcinoma (IMC), strictly according to criteria proposed by the Vienna system of nomenclature. The combination of the 3 separate pathological evaluations was used to assign a “majority diagnosis” to each case.

The majority diagnosis was termed noninvasive neoplasia (ie, a diagnosis of LGD or HGD by 2 of the 3 pathologists) or invasive neoplasia (ie, a diagnosis of suspicious for invasive carcinoma or IMC by 2 of the 3 pathologists).

Clinical management, following the initial diagnosis of HGD or severe dysplasia, was individually decided in each case by the responsible health care professional. There was no institutional protocol for endoscopic surveillance or resection of HGD, but several of these patients had been discussed and joint decisions had been made at a multidisciplinary meeting of upper gastrointestinal surgeons, gastroenterologists, pathologists, and radiologists. Radiological staging with computed tomography scanning or endoscopic ultrasound scanning was conducted in selected cases, but this information was not routinely incorporated into the decision-making process.

The pathological or clinical final outcome for each patient up to December 2003 was determined by review of case records, including surveillance endoscopy reports and pathology reports, and communication with family physicians. Pathological outcomes were recorded as (1) apparent regression of dysplasia; (2) persistent HGD; or (3) invasive carcinoma. The interval between the initial diagnosis of HGD or severe dysplasia and the final pathological or clinical outcome for this series of patients with an initial diagnosis of HGD or severe dysplasia was documented.

### Table 1. Revised Classification of Specimens With Initial Diagnosis of High-Grade or Severe Dysplasia of the Gastric Epithelium and Clinical Pathological Outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial Diagnosis of HGD Made by</th>
<th>Path 1</th>
<th>Path 2</th>
<th>Path 3</th>
<th>Majority Diagnosis</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
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<td>SIMC</td>
<td>HGD</td>
<td>IMC</td>
<td>Inv</td>
<td>AWHGD</td>
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<td>2*</td>
<td>Another</td>
<td>HGD</td>
<td>IMC</td>
<td>SIMC</td>
<td>Inv</td>
<td>Cancer</td>
</tr>
<tr>
<td>3</td>
<td>Path 1</td>
<td>IMC</td>
<td>IMC</td>
<td>IMC</td>
<td>Inv</td>
<td>Cancer</td>
</tr>
<tr>
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<td>SIMC</td>
<td>Inv</td>
<td>Cancer</td>
</tr>
<tr>
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<td>Path 2</td>
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<td>IMC</td>
<td>IMC</td>
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<td>Cancer</td>
</tr>
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<td>6*</td>
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<td>IMC</td>
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<td>Cancer</td>
</tr>
<tr>
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<td>Path 3</td>
<td>HGD</td>
<td>SIMC</td>
<td>SIMC</td>
<td>Inv</td>
<td>Cancer</td>
</tr>
<tr>
<td>8</td>
<td>Path 1</td>
<td>HGD</td>
<td>HGD</td>
<td>SIMC</td>
<td>Non-inv</td>
<td>No dysplasia</td>
</tr>
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<td>9</td>
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<td>LGD</td>
<td>LGD</td>
<td>HGD</td>
<td>Non-inv</td>
<td>No dysplasia</td>
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<td>HGD</td>
<td>Non-inv</td>
<td>AWHGD</td>
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<td>Non-inv</td>
<td>AWHGD</td>
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<td>HGD</td>
<td>Non-inv</td>
<td>Cancer</td>
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<tr>
<td>13*</td>
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<td>LGD</td>
<td>SIMC</td>
<td>Non-inv</td>
<td>Cancer</td>
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<td>SIMC</td>
<td>LGD</td>
<td>Non-inv</td>
<td>Cancer</td>
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<tr>
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<td>LGD</td>
<td>LGD</td>
<td>Non-inv</td>
<td>DOC</td>
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<tr>
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<td>HGD</td>
<td>SIMC</td>
<td>Inv</td>
<td>DOC</td>
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<tr>
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<td>IMC</td>
<td>IMC</td>
<td>Inv</td>
<td>DOC</td>
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<td>SIMC</td>
<td>HGD</td>
<td>Inv</td>
<td>DOC</td>
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<td>SIMC</td>
<td>SIMC</td>
<td>Inv</td>
<td>DOC</td>
</tr>
<tr>
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<td>Path 2</td>
<td>HGD</td>
<td>HGD</td>
<td>HGD</td>
<td>Non-inv</td>
<td>DOC</td>
</tr>
<tr>
<td>22</td>
<td>Path 2</td>
<td>SIMC</td>
<td>IMC</td>
<td>IMC</td>
<td>Inv</td>
<td>DOC</td>
</tr>
</tbody>
</table>

*Abbreviations: another, another pathologist; AWHGD, alive with HGD; DOC, died of unrelated cause; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; Inv, invasive neoplasia; LGD, low-grade dysplasia; non-inv, noninvasive neoplasia; path 1, pathologist 1; path 2, pathologist 2; path 3, pathologist 3; SIMC, suspicious for invasive carcinoma.
*Patients who underwent gastrectomy following initial diagnosis of high-grade or severe dysplasia.
plasia and the final pathological outcome was determined. Pa-
tient follow-up after detection and treatment of invasive car-
cinoma was not included in this study.

The statistics software program SPSS version 11 (SPSS Inc, Chi-
cago, Ill) was used for statistical analysis. Summary statistics were
expressed as median (range). To examine interpathologist agree-
ment, LGD and HGD were grouped together as noninvasive neo-
plasia. Suspicious for invasive carcinoma and IMC were grouped
as invasive neoplasia. The proportion of cases in which any pair
of pathologists agreed in distinguishing noninvasive neoplasia from
invasive neoplasia was determined. The
\( \chi^2 \) test was used to examine the strength of cor-
rrelation between a majority diagnosis of noninvasive neoplasia
or invasive neoplasia and final detection of invasive carcinoma.

RESULTS

There were 22 patients, comprising 14 men and 8 women,
with a median age of 76 years (range, 56-87 years). Two

patients had previously undergone a distal gastrectomy and Billroth II reconstruction for peptic ulcer disease. In
all cases, HGD or severe dysplasia had been detected on
biopsy specimen of an endoscopically visible lesion (15
patients, ulcer; 4 patients, polyp; 3 patients, gastritis). The
lesions were located in the antrum (19 patients), prox-
imal stomach (1 patient), body (1 patient), or gastroje-
junostomy (1 patient). At histological examination, as-
associated Helicobacter pylori infection (3 patients [14%]),
testinal metaplasia (17 patients [77%]), or glandular
atrophy (11 patients [50%]) was noted. Information about
previous H pylori eradication or proton pump inhibitor
therapy was not available.

The initial diagnosis of HGD or severe dysplasia was
revised to LGD, HGD, suspicious for invasive carcinoma,
or IMC by pathologist 1 in 2 (9%), 12 (54%), 5 (23%),
or 3 (14%) cases, respectively; by pathologist 2 in 4 (18%),
7 (32%), 5 (23%), or 6 (27%) cases, respectively; and by
pathologist 3 in 0, 6 (27%), 9 (41%), or 7 (32%) cases,
respectively (Table 1)(\textbf{Figures 1, 2, and 3}). Patholo-
gists 1 and 2 agreed in distinguishing noninvasive neo-
plasia from invasive neoplasia in 68% of cases (\( \kappa = 0.36 \)),
pathologists 1 and 3 agreed in 64% of cases (\( \kappa = 0.35 \)),
and pathologists 2 and 3 agreed in 68% of cases (\( \kappa = 0.36 \)).

Three patients underwent gastrectomy soon after the
initial detection of HGD or severe dysplasia. The remain-
ing 19 patients had endoscopic surveillance for a me-
dian follow-up period of 15 months (range, 1-89 months).
Each patient had a minimum of 2 surveillance endo-
copies. Two patients (9.0%) had apparent regression of dys-
plasia to normal by endoscopic surveillance on at least 2
consecutive occasions. Neither patient had any endo-
coscopic procedure performed other than biopsies. Both pa-
tients were alive at 13 or 89 months and free of invasive
carcinoma (\textbf{Figure 4}). Ten patients (45.5%) had per-
sistent HGD but no invasive carcinoma on endoscopic
surveillance for a median period of 25 months (range,
1-61 months). Of these, 3 patients were alive at 26, 28,
or 61 months. The remaining 7 patients died of causes
unrelated to gastric cancer at a median interval of 19
months (range, 1-38 months). One patient had a post-
Invasive adenocarcinoma was detected in 10 patients (45.5%). In 5 cases, invasive carcinoma was detected within 3 months of the initial diagnosis of HGD or severe dysplasia. These included all 3 patients who underwent immediate gastrectomy, with detection of early gastric cancer (pT1 pN0) in 2 cases and advanced gastric cancer (pT2 pN0) in 1 case. Another 2 patients had detection of invasive carcinoma on surveillance endoscopy within 3 months. Both had endoscopic mucosal resection of early gastric cancer (pT1 pNX). In the remaining 3 patients, invasive cancer was detected after 1 year at a median follow-up interval of 15 months (range, 13-34 months). One patient had peritoneal metastasis from gastric adenocarcinoma at laparotomy with intent to perform gastrectomy for a nonhealing gastric ulcer with HGD only on endoscopic biopsy specimens. In the other 4 cases, invasive carcinoma was diagnosed at surveillance endoscopy. Two patients underwent gastrectomy, and both had early gastric cancer (pT1 pN0). Pathological stage could not be determined for the other 2 patients who did not have resection because of extraordinarily high perioperative risk factors.

Analysis of correlation between the majority diagnosis and final detection of invasive carcinoma was limited to the 15 patients who did not die of unrelated causes. Seven patients had a majority diagnosis of invasive neoplasia, and 8 patients had a majority diagnosis of noninvasive neoplasia (Table 1). Invasive adenocarcinoma was finally detected in a significantly greater proportion of patients with a majority diagnosis of invasive neoplasia (6 patients [86%]) as compared with those with noninvasive neoplasia (4 patients [50%]; P<.001).

**COMMENT**

This study examined pathological or clinical outcomes for 22 patients with an initial diagnosis of HGD or severe dysplasia of the gastric epithelium in endoscopic biopsy specimens. For the present study, all specimens were separately reviewed by 3 experienced gastrointestinal pathologists and the diagnosis was revised to IMC in 14% to 32%, suspicious for invasive carcinoma in 23% to 41%, or LGD in 0% to 18% of patients. Variation between the initial diagnosis and subsequent reclassification was not statistically measured because of small sample size. Overall, the low proportion of LGD at reclassification was consistent with a previous report of high specificity (low false-positive rate) in the distinction of HGD from LGD and implies little variation in the minimal diagnostic criteria for HGD. In contrast, a substantial number of cases was reclassified as suspicious for invasive carcinoma or IMC, and this was indicative of the difficulty in distinguishing between HGD and invasive carcinoma.

The strength of agreement among the pathologists for distinguishing LGD or HGD from suspicious for invasive carcinoma or IMC was only fair. Suspicous for invasive carcinoma was grouped with IMC because both were likely to invoke a similar threshold for therapeutic intervention. Also, LGD was grouped with HGD because both categories represent noninvasive neoplasia and it was important to examine the precision in distinction from invasive carcinoma. A similar approach of category grouping has been used by the authors of the Padova classification of gastric dysplasia. To our knowledge, interpathologist agreement in reclassification of gastric HGD has not been reported previously and the present data are novel. Pertinent comparison may be made with a similar study of HGD and superficial adenocarcinoma in Barrett esophagus. Even with esophagectomy specimens, where more material was available for diagnosis, the strength of interpathologist agreement on distinguishing HGD from IMC remained moderate.

It has been previously suggested that the endoscopic diagnosis of gastric HGD should be confirmed by a second experienced pathologist. The extent of disagreement within pairs of expert pathologists in the present study implies that a single additional opinion may guide clinical decision making to only a limited extent. How-
ever, a diagnosis of suspicious for invasive carcinoma or IMC by any 2 of 3 pathologists correlated strongly with subsequent definitive detection of invasive carcinoma. A third expert opinion may therefore be valuable in cases of disagreement between the initial 2 pathologists.

Three patients underwent gastrectomy soon after the diagnosis of HGD. Invasive carcinoma was detected in all 3 gastrectomy specimens. Other investigators have also reported a high incidence (83%-92%) of “missed” invasive carcinoma. A similar concern about missed cancer drives recommendation for esophagectomy in patients with HGD in Barrett esophagus. A rigorous system of endoscopic examination, including 4-quadrant biopsies at 2-cm intervals using jumbo forceps, has been reported to improve malignancy detection in Barrett esophagus. Such a topographic system is difficult to apply to the stomach and may partly explain the high incidence of missed cancer.

Nineteen patients underwent endoscopic surveillance following the diagnosis of HGD. Seven patients (32%) died of unrelated causes during the follow-up period. Invasive carcinoma had not been detected at endoscopic surveillance in any of these patients. Similarly, 33% of patients with early gastric cancer (invasive carcinoma limited to the mucosa or submucosa) and no resection have been reported to die because of other reasons. High-grade dysplasia or early gastric cancer are often discovered incidentally during investigation of unrelated symptoms. Some authors have argued that such incidental detection results in overdiagnosis of a “pseudo-disease” that does not influence mortality. Such arguments may be contentious but do emphasize that a substantial proportion of patients with HGD or early gastric cancer are elderly or infirm with a limited life span because of coexisting illness.

Invasive carcinoma was found in 7 patients who underwent endoscopic surveillance. Together with the 3 cases of invasive carcinoma in gastrectomies for HGD, the overall incidence of invasive carcinoma in patients who did not die of unrelated causes was 67%. The majority of previous series of HGD report cancer incidence of 80% to 85% (Table 2); surprisingly, none of these earlier series report any deaths due to unrelated causes and it is unclear whether such cases were excluded. The single series that reports a low incidence of 31% is questionable, particularly because regression of HGD is reported in almost one half of the cases. The incidence of cancer was analyzed according to a threshold interval of 12 months from diagnosis of HGD, in attempt to differentiate cancer prevalence at diagnosis from subsequent neoplastic progression. There are no consistent proportions for prevalent or incident cases in different series (Table 2). In view of the preceding discussion that endoscopic diagnosis of HGD is associated with invasive carcinoma from inception in the majority of cases, such temporal division of cancer incidence may be irrelevant. In fact, 2 patients (9%) in the present series had advanced gastric cancer at final staging. Previous series of gastric HGD have also reported advanced cancer in 16% to 23% of patients. Notably, in large series of early gastric cancer, there is invasive carcinoma within or beyond the submucosa in 15% of cases. Careful endoscopic evaluation, including mucosal staining by local application of indigocarmine or intravenous fluorescein, and use of endoscopic ultrasound are useful to clarify the depth of neoplastic invasion.

Three patients had persistent HGD at endoscopic surveillance; 1 patient had been followed up for 5 years and is highly unlikely to have harbored undetected invasive carcinoma. Two patients had apparently complete regression of HGD to normal mucosa. One case had been reclassified as LGD by 2 pathologists, and it is possible that there was true regression. Complete removal of a small, single focus of HGD by the biopsy forceps was an alternative possibility. Although sampling errors cannot be entirely excluded, such patients focus attention on the small but unique population that survives without invasive cancer after a diagnosis of gastric HGD.

Clinical management of the patient with a new diagnosis of gastric epithelial dysplasia often poses a dilemma. Rugge et al recommend systematic endoscopic surveillance of gastric dysplasia of any grade but do not report the incidence of endoscopically missed cancer in cases of HGD. Other investigators recommend gastric resection because of the high prevalence of invasive carcinoma and the small risk of advanced disease. The present data support resection in carefully evaluated cases with a diagnosis of suspicious for invasive carcinoma or IMC by at least 2 pathologists. Endoscopic surveillance may have a role in selected cases with a diagnosis of HGD.

Table 2. Pathological Outcomes in Series of High-Grade or Severe Dysplasia of the Gastric Epithelium

<table>
<thead>
<tr>
<th>Source (Study Period)</th>
<th>No. of Patients</th>
<th>Regression</th>
<th>Persistent HGD</th>
<th>Invasive Carcinoma at &lt;12 mo</th>
<th>Invasive Carcinoma at ≥12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saraga et al, Switzerland (1974-1981)</td>
<td>21</td>
<td>4 (19)</td>
<td>0</td>
<td>14 (67)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Coma del Corral et al, Spain (1978-1983)</td>
<td>26</td>
<td>12 (46)</td>
<td>6 (23)</td>
<td>5 (19)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Lansdown et al, England (1983-1987)</td>
<td>13</td>
<td>0</td>
<td>2 (15)</td>
<td>9 (70)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Farinati et al, Italy (1985-1991)</td>
<td>31</td>
<td>2 (6)</td>
<td>4 (13)</td>
<td>22 (71)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Rugge et al, Italy (1987-2001)</td>
<td>25</td>
<td>1 (4)</td>
<td>4 (16)</td>
<td>9 (36)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Present (1996-2003)</td>
<td>22</td>
<td>2 (8)</td>
<td>10 (46)*</td>
<td>5 (23) (33)†</td>
<td>5 (23) (33)†</td>
</tr>
</tbody>
</table>

Abbreviation: HGD, high-grade dysplasia.

*Seven of these 10 patients died of causes unrelated to gastric cancer.
†Percentage of the total number of patients (n = 15) who did not die of unrelated causes.
only (without any invasive component) by 2 pathologists. A significant minority of patients died of unrelated causes prior to the onset of any complication of gastric cancer, and gastrectomy is not a trivial operation. Some patients may therefore be best served by a policy of nonintervention. Increasingly available expertise in endoscopic mucosal resection in Western centers will provide an effective alternative to surgery in some cases. Endoscopic mucosal resection also makes available a large quantity of tissue for more definitive pathological evaluation and serves as an intermediate staging strategy. Alternatively, endoscopic argon plasma coagulation therapy may be considered in selected cases. Effective anti–H pylori treatment has been reported to promote regression of gastric atrophy and intestinal metaplasia, but the role of such therapy for dysplasia is presently unknown.

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REFERENCES