Effect of Helicobacter pylori infection on outcomes in resected gastric and gastroesophageal junction cancer

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Contributions: (I) Conception and design: JM Kolb, C Ang; (II) Administrative support: None; (III) Provision of study materials or patients: C Ang; (IV) Collection and assembly of data: JM Kolb; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Helicobacter pylori (H pylori) infection is a known risk factor for gastric cancer (GC) and has been linked with gastroesophageal junction (GEJ) cancer. Studies examining the relationship between H. pylori infection, GC characteristics and prognosis are limited and have yielded conflicting results. We report on the clinicopathologic characteristics and oncologic outcomes of gastric and GEJ cancer patients with and without a history of H. pylori treated at our institution.

Methods: We retrospectively reviewed the medical records of patients over the age of 18 years who underwent curative resection for GEJ and GC at Mount Sinai Hospital between 2007 and 2012 who had histopathologic documentation of the presence or absence of H pylori infection. Demographic, clinical, pathologic, treatment characteristics and outcomes including recurrence-free survival (RFS) and overall survival (OS) were compared.

Results: Ninety-five patients were identified. The majority of patients were male (61%), white (36%) or Asian (34%), with median age at diagnosis 64. Tumors were stage I (51%), stage II (23%), stage III (25%), and stage IV (1%). H pylori infection status was documented at the time of cancer diagnosis in 89 (94%) patients, and following cancer diagnosis and treatment in 6 (6%) patients. Younger age at diagnosis, Asian race and Lauren histologic classification were associated with H Pylori infection. H pylori positive patients exhibited higher 5-year OS and 5-year RFS compared to H pylori negative patients, though the difference was not statistically significant in either univariate or multivariate analyses.

Conclusions: In this retrospective series of predominantly early stage GC and GEJ cancers, H. pylori positive patients were significantly younger at cancer diagnosis and were more frequently Asian compared to H. pylori negative patients. Other demographic and histologic classifications except for Lauren histologic classification were similar between the two groups. H pylori positive patients appeared to have improved outcomes compared to H. pylori negative patients.

Keywords: Gastric adenocarcinoma; gastric cancer; helicobacter pylori (H pylori); gastroesophageal junction adenocarcinoma

Submitted Nov 15, 2016. Accepted for publication Dec 22, 2016.
doi: 10.21037/jgo.2017.01.22

View this article at: http://dx.doi.org/10.21037/jgo.2017.01.22
Introduction

Gastric cancer is the 5th most common cancer worldwide and kills approximately 723,000 people every year (1). Helicobacter pylori (H pylori) infection has been associated with an up to six-fold increase in risk of developing gastric cancer (GC), but its relationship with gastroesophageal junction (GEJ) cancer is less well defined (2-5). H pylori causes chronic active inflammation of the gastric mucosa leading to loss of gastric glands (atrophy gastritis), which progresses to intestinal metaplasia and dysplasia, and adenocarcinoma (6,7). H pylori is typically seen in developing countries and has been associated with poorer socioeconomic status (8,9). Eradication therapy for H pylori has been tied to lower rates of lower rates of GC (10,11), however its role may be more limited once histologic intestinal metaplasia or severe atrophy develops (12).

Studies evaluating the impact of H pylori infection on outcomes in early stage GC are limited. The purpose of this study was to evaluate the differences in clinical-pathologic features and outcomes of patients with GC and GEJ cancer based on H pylori status.

Methods

We retrospectively reviewed the medical records of patients over the age of 18 years who underwent curative resection for GC and GEJ cancer at Mount Sinai Hospital between 2007 and 2012. All patients had histopathologic documentation of the presence or absence of H pylori infection. Eligible patients were identified via an institutional database and tumor registry using ICD diagnosis codes. Study data was collected from patients’ medical records.

Patients with a prior curatively treated non gastric, non gastroesophageal junction malignancy were included, but those who developed a secondary malignancy post GC/GEJ cancer diagnosis were excluded.

Demographic, clinical, pathologic, treatment and outcomes information was collected. Histologic evaluation was performed according to the Lauren classification (intestinal, diffuse, mixed) and histologic type (well, moderately, or poorly differentiated, signet ring cell) (13). The standard surgical treatment was radical total or subtotal gastrectomy with lymph node dissection (mostly D2) (14). H pylori was evaluated based on Giemsa stain of endoscopic biopsies or resected gastric tissue. Survival time was measured from date of tissue diagnosis to date of most recent follow up visit or date of death.

Recurrence-free survival (RFS) and overall survival (OS) were calculated from the date of diagnosis to the date of first radiographically documented recurrence, and date of last follow-up or death, respectively. The baseline characteristics and clinical and pathological outcomes were compared between two groups using chi-square, Fisher’s exact or Mann-Whitney U test. Multiple comparisons were carried out with Bonferroni corrections. Kaplan-Meier method and log-rank tests were used for survival analyses. All tests were two-sided with alpha level of 0.05. All analyses were performed in SAS v9.4 statistical software (SAS Institute, Cary, NC, USA)

Results

Ninety-five patients were identified. Demographic, disease characteristics, pathology, treatment and outcomes are summarized in Table 1. The majority of patients were male (n=58, 61%), white (36%) or Asian (34%), with median age at diagnosis 63–68. Tumors were stage I (51%), stage II (23%), stage III (25%), and stage IV (1%). H pylori infection status was documented at the time of cancer diagnosis in 89 (94%) patients, and following cancer diagnosis and treatment in 6 (6%) patients. All 6 of these patients were H pylori negative and had no documented history of prior treatment for H pylori.

Younger age at diagnosis and Asian race were associated with H pylori positive GC based on univariate analysis. There was a higher proportion of Caucasians in the H pylori negative group (45% vs. 24%). There were a total of four GEJ cancers, which were all H pylori negative.

Lauren histologic classification was associated with H pylori infection, though pair-wise comparisons of the different subtypes (intestinal, diffuse, indeterminate, unknown) were not significantly different. There was no difference in cancer therapies (chemotherapy/radiation) according to H pylori status. None of these cancers were considered Barrett related since there was no documented Barrett metaplasia in pathology reports.

There was a trend towards better outcomes in H pylori positive patients. H pylori positive patients exhibited increased 5-year OS [79% (95% CI: 60–90%) vs. 60% (95% CI: 42–73%), P=NS] and 5-year RFS [67% (95% CI: 39–84%) vs. 58% (95% CI: 39–74%), P=NS] compared to H pylori negative patients. Outcomes remained improved in H pylori positive patients after controlling for prognostic factors including stage, treatment, lymphovascular invasion and perineural invasion [OS HR =1.56 (95% CI: 0.57–4.23),
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>H pylori positive (N=35)</th>
<th>H pylori negative (N=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (min-max)</td>
<td>63 [42–89]</td>
<td>68 [32–92]</td>
<td>0.027</td>
</tr>
<tr>
<td>Male/female</td>
<td>24 (69%)/11 (31%)</td>
<td>34 (57%)/26 (43%)</td>
<td>0.251</td>
</tr>
<tr>
<td>Race (white/black/Asian/Hispanic/other)</td>
<td>8 (24%)/5 (15%)/18 (55%)/0 (0%)/2 (6%)</td>
<td>26 (45%)/9 (16%)/14 (24%)/2 (3%)/7 (12%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Location: GEJ or gastric</td>
<td>0 (0%)/35 (100%)</td>
<td>4 (7%)/56 (93%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Gastric tumors: cardia/non cardia</td>
<td>5 (14%)/30 (86%)</td>
<td>3 (5%)/53 (95%)</td>
<td>0.252</td>
</tr>
<tr>
<td>Stage: I/II/III/IV</td>
<td>20 (57%)/4 (11%)/11 (31%)/0 (0%)</td>
<td>28 (47%)/18 (30%)/13 (22%)/1 (1%)</td>
<td>0.123</td>
</tr>
<tr>
<td>Lymphovascular invasion (yes/no/unknown)</td>
<td>11 (31%)/13 (37%)/11 (31%)</td>
<td>23 (38%)/23 (38%)/14 (62%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Perineural invasion (yes/no/unknown)</td>
<td>9 (26%)/9 (26%)/17 (48%)</td>
<td>11 (18%)/15 (25%)/34 (57%)</td>
<td>0.655</td>
</tr>
<tr>
<td>Lauren classification: intestinal/diffuse/indeterminate/unknown</td>
<td>7 (20%)/10 (29%)/7 (20%)/11 (31%)</td>
<td>18 (30%)/8 (13%)/4 (7%)/30 (50%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Margin status (positive/negative)</td>
<td>4 (12%)/30 (88%)</td>
<td>3 (5%)/57 (95%)</td>
<td>0.249</td>
</tr>
<tr>
<td>Lymph node positive (yes/no)</td>
<td>18 (51%)/17 (49%)</td>
<td>21 (35%)/39 (65%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Lymph node ratio</td>
<td></td>
<td></td>
<td>0.168*</td>
</tr>
<tr>
<td>≤0.3</td>
<td>27</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>0.31–0.6</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>≥0.6</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td>0.793</td>
</tr>
<tr>
<td>No chemo +/- RT</td>
<td>17 (48%)</td>
<td>30 (50%)</td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>7 (20%)</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>Chemo + RT</td>
<td>10 (29%)</td>
<td>14 (23%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3%)</td>
<td>5 (8%)</td>
<td></td>
</tr>
<tr>
<td>Recurrence (yes/no/unknown)</td>
<td>7 (20%)/28 (80%)/0 (0%)</td>
<td>17 (28%)/39 (65%)/4 (7%)</td>
<td>0.167*</td>
</tr>
<tr>
<td>5-year OS</td>
<td>79% (95% CI: 60–90%)</td>
<td>60% (95% CI: 42–73%)</td>
<td>0.340</td>
</tr>
<tr>
<td>5-year RFS</td>
<td>67% (95% CI: 39–84%)</td>
<td>58% (95% CI: 39–74%)</td>
<td>0.798</td>
</tr>
</tbody>
</table>

*not significant among 3 ratio groups; **P value for all categories (including unknown).
RFS HR =1.57 (95% CI: 0.53–4.63), P=NS]. The trend persisted after the exclusion of patients with a history of prior malignancy (N=10, one each of papillary thyroid, hepatocellular carcinoma, lung, follicular lymphoma, renal cell carcinoma, colon, uterine, prostate, and two breast cancers) [OS HR =2.73 (95% CI: 0.81–9.06), RFS HR =2.47 (95% CI: 0.70–8.71), P=NS] and patients whose H pylori status was not documented at time of GC or GEJ cancer diagnosis [OS HR =1.31 (95% CI: 0.46–3.78), RFS HR =1.21 (95% CI: 0.31–4.71), P=NS].

Discussion

The importance of H pylori status on outcomes in GC after curative resection has been studied with mixed results. Multiple studies have not been able to show a meaningful relationship between H pylori infection and prognosis. In a group of 157 patients with GC who underwent curative surgery in China, H pylori positivity and quantitative PCR were related to N staging, but were not associated with a difference in OS or RFS (15). These findings have been replicated in similar populations (16), as well as in distal gastric cancer (17), stage IV noncardiac gastric cancer (18) and proximal gastric cancer crossing the GEJ (19). There are however some studies that report negative outcomes with H pylori infection. Li and colleagues showed that H pylori positive status was associated with poorer disease specific survival (DSS) and RFS and that H pylori infection could be an independent predictor of prognosis in GC (20).

There is some data to support a protective benefit of H pylori infection. A German study of 166 GC patients undergoing curative resection between 1992–2002, showed higher RFS (56.7 vs. 19.2 months, HR =2.16; P<0.05) and OS (61.9 vs. 19.2 months, HR =2; P<0.05) in H pylori infected cancers compared to uninfected patients (21). Similarly, an Italian study showed that H pylori positivity independently predicted long term survival [HR =2.47, (1.40–4.35), P=0.002] (22). Another study of 559 patients showed increased OS (84.3 vs. 44.2 months, P=0.008) for H pylori positive compared to negative patients, though there was no difference in RFS or disease specific survival (23).

In the current series, H pylori positive patients tended to have better survival outcomes compared to H pylori negative patients but the differences were not significant, likely owing to the small sample size. Nevertheless, the trend remained consistent after adjusting for poor prognostic factors such as lymphatic and/or blood vessel invasion (24-26), perineural invasion (27), stage and treatment.

Several hypotheses might explain the improved outcomes seen in H pylori positive versus negative patients. There is some evidence that tumor specific immune responses may be enhanced in H pylori positive patients. In one study, H pylori positive gastric tumors had fewer regulatory T cells than negative tumors (21). Autoantibodies generated against H pylori components may also demonstrate cross-reactivity against GC cells which express H pylori antigens or mimic molecules (28). Furthermore, a higher frequency of microsatellite instability (MSI) has been observed in H pylori positive than negative GCs (29,30) which may also confer a more favorable prognosis, similar to what is observed in colorectal cancer. Given recent data showing MSI to be a strong predictor of response to immune checkpoint inhibitors (31), it would be interesting to explore whether responses to these agents differ by H pylori status.

We observed that H pylori infected patients were younger and were more frequently Asian compared to H pylori uninfected patients. The low frequency of GEJ cancers encountered is consistent with the literature that H pylori is primarily a risk factor for GC and less for GEJ cancer. H pylori infection can cause atrophic gastritis and induce specific cytokines that result in decreased acid production. Reduction in acid production and resultant decreased risk of gastroesophageal reflux may explain why GEJ cancer is less commonly associated with H pylori (32). Our results showed that H pylori positive tumors were more frequently diffuse/mixed histology rather than intestinal type. Although H pylori is more commonly associated with intestinal type, it can be seen with diffuse type too (33,34). The lymph node (LN) ratio and number of metastatic LN have been shown to impact survival in GC (25). To our knowledge, there are no studies that comment on the extent of lymph node involvement based on H pylori status. Our results show no difference in the lymph node ratio according to H pylori status.

This study is limited by its retrospective design and small sample size providing insufficient power to discern differences between the groups. Only a limited number of patients had documented H pylori status, and we were unable to determine if H pylori negative patients had previously been positive and treated. There is also some potential for case misclassification since H pylori status was discerned by histopathology alone, and patient use of anti-secretory therapy was unknown.

In conclusion, this retrospective series adds to the body of literature reporting a trend towards improved
GC outcomes among H pylori infected compared to uninfected patients. Further studies are needed to explore the molecular underpinnings and possible therapeutic implications of these differences.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the institutional review board of the Mount Sinai Hospital (No. FWA00005656).

References