Is intestinal metaplasia a necessary precursor lesion for adenocarcinomas of the distal esophagus, gastroesophageal junction and gastric cardia?

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SUMMARY. Adenocarcinoma of the distal esophagus and gastroesophageal junction are believed to arise in Barrett’s esophagus with intestinal metaplasia. Whether adenocarcinoma can arise in columnar lined esophagus without intestinal metaplasia is in doubt. Whether adenocarcinoma of the gastric cardia arises in intestinal metaplasia of the gastric cardia is also in doubt. We aim to evaluate the relationship of size and stage of adenocarcinoma of the distal esophagus, gastroesophageal junction and gastric cardia to intestinal metaplasia and other types of columnar epithelium. Seventy-four patients who had esophagogastrectomy for adenocarcinomas in this region were examined histologically to assess the frequency of residual intestinal metaplasia in the surrounding epithelium. Tumors without residual intestinal metaplasia were evaluated for the presence of other columnar epithelia and correlated with tumor size and stage. Cardiac mucosa was present around all tumors. Residual intestinal metaplasia was present in 48 (65%) tumors, including 33/38 (87%) distal esophageal, 10/25 (45%) junctional and 5/11 (45%) gastric cardia tumors. The prevalence of intestinal metaplasia was 100% in all tumors that were less than 1 cm in maximum diameter and all intramucosal tumors. The prevalence of residual intestinal metaplasia decreased with increasing tumor size and stage. These data strongly support the contention that adenocarcinomas of this region, including those in the gastric cardia, arise in intestinal metaplastic epithelium. The absence of residual intestinal metaplasia in larger tumors is the result of tumor overgrowing the intestinal metaplasia from which it arose.

KEY WORDS: adenocarcinoma, Barrett’s esophagus, gastric cardia, intestinal metaplasia.

INTRODUCTION

Columnar-lined esophagus is a reflux-induced metaplasia of the squamous epithelium of the esophagus. Paull et al. in 1976, recognized that several epithelial types were present in columnar-lined esophagus and developed an extremely accurate histologic classification.1 This divided columnar-lined esophagus into three types: junctional type, gastric-fundic type, and specialized type. The specialized columnar epithelium is characterized by the presence of goblet cells and is now more commonly called the intestinal metaplastic type of columnar-lined esophagus.2,3 Esophageal columnar epithelia that contain no goblet cells are divided into an epithelium composed only of mucous cells (Paull et al.’s junctional mucosa, now more commonly called cardiac mucosa) and an epithelium containing a mixture of mucous and parietal cells (Paull et al.’s gastric-fundic type epithelium, which we have suggested should be termed oxyntocardiac mucosa2,3).

By the late 1970s, it was recognized that adenocarcinoma complicated columnar-lined esophagus.4,5 In the mid-1980s Haggitt et al. showed that these tumors were surrounded by columnar-lined epithelium that frequently showed intestinal metaplasia6 and it became generally accepted that intestinal metaplasia was the precursor of reflux-induced adenocarcinoma. It was believed that the other types of esophageal columnar epithelia without goblet cells did not progress to malignancy without the development of intestinal metaplasia.7

The basis of definition of Barrett’s esophagus and the rationale for clinical management of patients depends on the recognition that intestinal metaplasia
is a necessary precursor for adenocarcinoma. Initially, based on Hayward’s assertion that 2 cm of columnar epithelium was normally present in the distal esophagus, the definition of Barrett’s esophagus required > 2 cm of columnar-lined esophagus with intestinal metaplasia. When Spechler et al. showed that intestinal metaplasia occurred in the distal 2 cm of the esophagus, the definition of Barrett’s esophagus was extended to include these patients with short-segment Barrett’s esophagus. The presently recommended definition of Barrett’s esophagus is the presence of intestinal metaplasia in a biopsy taken from any endoscopically visible columnar epithelium in the esophagus. Long-term surveillance is recommended only for patients who have intestinal metaplasia.

Despite the almost universal acceptance that intestinal metaplasia is a necessary change in the columnar-lined esophagus before adenocarcinoma develops, there is a background of unease about this. Spechler, in a review of the subject in 1997, states that the association of adenocarcinoma with columnar-lined esophagus without intestinal metaplasia is ‘unlikely’. In a 2004 consensus workshop in Chicago of 18 experts in the field of Barrett’s esophagus, there was even more doubt about the possibility of cardiac and fundic-type (oxyntocardiac) mucosa progressing to adenocarcinoma. In fact, two of the experts rejected the statement that ‘intestinal metaplasia documented by histology is a prerequisite criterion for the diagnosis of Barrett’s esophagus’ for this reason. Of even greater importance was the fact that a review of the available evidence for the point of view that intestinal metaplasia was a necessary precursor of adenocarcinoma was graded as IV (= evidence based on opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees). It appears from this review that the fact that intestinal metaplasia is a necessary precursor of esophageal adenocarcinoma is one that is based more on opinion than fact. This is surely an unsatisfactory state for such a fundamental fact on which we base the definition of Barrett’s esophagus and the management of patients diagnosed with columnar-lined esophagus.

Adenocarcinoma of the distal esophagus and gastroesophageal junction has increased in incidence exponentially in the past three decades in the US and Western Europe. A similar increase has been seen in the incidence of adenocarcinoma of the gastric cardia. Although unproven, there is suspicion that these gastric cardiac tumors may arise in intestinal metaplasia. When Spechler et al. showed that intestinal metaplasia occurred in the distal 2 cm of the esophagus, the definition of Barrett’s esophagus was extended to include these patients with short-segment Barrett’s esophagus. The presently recommended definition of Barrett’s esophagus is the presence of intestinal metaplasia in a biopsy taken from any endoscopically visible columnar epithelium in the esophagus. Long-term surveillance is recommended only for patients who have intestinal metaplasia.

MATERIALS AND METHODS

Seventy-four patients who underwent esophagogastrectomy for adenocarcinoma of the distal esophagus, gastro-esophageal junction and gastric cardia during the years 1997–2000 were selected for study. These tumors had their epicenter ranging from 5 cm proximal and 3 cm distal to the gastroesophageal junction. The relationship of the epicenter of the tumor to the grossly defined gastro-esophageal junction was used to classify these tumors as: distal esophageal (proximal to the junction); junctional (at the junction); and gastric cardiac (distal to the junction). The gastro-esophageal junction was defined as a line drawn between the end of the tubular esophagus and the saccular stomach as recommended by the Association of Directors of Anatomic and Surgical Pathology. The tumor was measured for maximum mucosal diameter and depth of gross invasion. The microscopic characteristics of the tumor, its depth of invasion, pathologic stage, presence of lymphovascular invasion and spread, and lymph node involvement were assessed in the standard manner for these tumors.

In addition, the specimen was sectioned extensively in a manner that permitted complete evaluation of the mucosal types present immediately surrounding the tumor on all sides. In 10 cases where the tumor involved the full circumference of the esophagus, only the proximal and distal edges of the tumor abutted non-neoplastic epithelium. The epithelial types were classified into squamous, cardiac (epithelia composed only of mucous cells without any parietal cells; Paull et al.’s junctional type), oxynto-cardiac (containing glands composed of a mixture of parietal and mucous cells; Paull et al.’s gastric-fundic-type), intestinal (defined by the presence of goblet cells), oxyntic (containing glands composed of parietal and chief cells without mucous cells). The types of epithelia around each tumor were recorded.

This study was performed after obtaining approval from the Institutional Review Board of the Keck School of Medicine at the University of Southern California. Slides from all cases were reviewed initially by two pathologists (KW, YM) and reviewed by a third (PC).

RESULTS

There were 58 men and 16 women in this series for a M : F ratio of 3.6 : 1. The tumors were classified as 38 (51.4%) distal esophageal, 25 (33.8%) junctional, and 11 (14.8%) gastric cardiac based on the
relationship of the epicenter of the tumor on gross examination to the end of the tubular esophagus, as recommended. Of the 38 distal esophageal cancers, 30 were men and eight (21%) were women. Four (16%) of the 25 patients with junctional tumors and four (36%) of the 11 patients with gastric cardiac tumors were women. The mean age was 64.1 years (median: 66 years; range: 31–86 years).

The tumor size ranged from grossly invisible intramucosal carcinomas to large tumors exceeding 15 cm in greatest dimension. Histologically, they were all pure adenocarcinomas and ranged from well differentiated to poorly differentiated and showed many different histologic subtypes including tubular, mucinous, papillary, signet ring cell, solid, microcystic and clear cell types of adenocarcinoma. The depth of invasion of the tumor was intramucosal in 14 cases (18.9%), submucosal in eight cases (10.8%), intramural in four cases (5.4%) and transmural in 48 cases (64.9%).

Lymph node involvement correlated with depth of tumor invasion. There was one patient among the 14 intramucosal tumors that was node-negative; this patient had a poorly differentiated intramucosal carcinoma that measured 3 cm with one positive node out of 45 nodes. Two (25%) of eight patients with submucosal tumors, three (75%) of four patients with intramural tumors, and 43 (90%) of 48 patients with transmural tumors had positive lymph nodes.

Residual intestinal metaplasia, characterized by the presence of goblet cells was found in 48 (65%) of the 74 patients. Intestinal metaplasia was seen in 33 (87%) of 38 patients with distal esophageal tumors, 10 (40%) of 25 patients with junctional tumors, and five (45%) of the 11 patients with gastric cardiac tumors. Cardiac and oxyntocardiac types of mucosa were present around the tumor in all cases. Cardiac and oxyntocardiac epithelial types were the only epithelial types found in the 26 patients who did not have residual intestinal metaplasia. Gastric oxyntic mucosa was frequently present, but only at the distal edge of the tumors, representing extension of the tumor into the part of the stomach lined by oxyntic mucosa.

The prevalence of residual intestinal metaplasia was greatest in the tumors that did not infiltrate through the muscle wall of the esophagus. All 14 (100%) patients with intramucosal adenocarcinoma, 7/8 (88%) patients with submucosal tumors, and 3/4 (75%) patients with intramural tumors (i.e. a total of 24/26 or 92% of patients with tumors restricted to the wall of the esophagus) had residual intestinal metaplasia, compared with 24/48 (50%) patients who had transmural tumors ($P \leq 0.01$). All intramucosal and submucosal tumors were either in the distal esophagus or gastroesophageal junction; all gastric cardiac tumors were at least intramural.

The likelihood of finding residual intestinal metaplasia decreased with increasing tumor size. All eight tumors with a size of 1 cm or less had intestinal metaplasia; the locations of these tumors were distal oesophageal (5 cases) and junctional (3 cases). There were no tumors 1 cm or less that were classified as gastric cardiac carcinomas. A total of 31/41 (76%) tumors with a size of 4 cm or less had intestinal metaplasia. This contrasted with 17/33 (52%) patients with tumors greater than 4 cm in size with residual intestinal metaplasia. The smallest lesion that did not have residual intestinal metaplasia was 1.4 cm in greatest diameter.

**DISCUSSION**

This study attempts to answer two questions: (a) Does adenocarcinoma of the distal esophagus and gastroesophageal junction always arise in intestinal metaplasia or can it arise in non-intestinalized columnar lined esophagus?; and (b) Does adenocarcinoma of the gastric cardia arise in intestinal metaplasia of the gastric cardia?

The data in this study show that residual intestinal metaplasia was found in 48/74 (65%) of patients. The thoroughness of the histologic study makes it unlikely that the absence of intestinal metaplasia can be explained by sampling error. Lagergren et al. reported that 118/189 (62%) of patients with esophageal adenocarcinoma had residual Barrett's

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**Table 1** Clinical and pathological features of the 74 patients with adenocarcinoma that comprise the study group

<table>
<thead>
<tr>
<th>Location of tumor</th>
<th>Distal esophagus</th>
<th>GEJ†</th>
<th>Gastric cardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Epicenter above the GEJ</td>
<td>Epicer at GEJ</td>
<td>Epicenter &lt; 3 cm below GEJ</td>
</tr>
<tr>
<td>Number (total = 74)</td>
<td>38 (51.4%)</td>
<td>25 (33.8%)</td>
<td>11 (14.8%)</td>
</tr>
<tr>
<td>M : F</td>
<td>30 : 8</td>
<td>21 : 4</td>
<td>7 : 4</td>
</tr>
<tr>
<td>Percentage females</td>
<td>21%</td>
<td>16%</td>
<td>36%</td>
</tr>
<tr>
<td>Early : Late stage‡</td>
<td>13 : 25</td>
<td>9 : 16</td>
<td>0 : 11</td>
</tr>
<tr>
<td>Size &lt; 1 cm (total = 8)</td>
<td>5/38 (13%)</td>
<td>3/25 (12%)</td>
<td>0/11 (0%)</td>
</tr>
<tr>
<td>Residual intestinal metaplasia (total = 48)</td>
<td>10/25 (40%)</td>
<td>5/11 (45%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac mucosa around tumor (total = 74)</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

†The gastroesophageal junction is defined as a line drawn across the distal limit of the tubular esophagus. ‡Early stage includes intramucosal and submucosal tumors without invasion of the muscularis externa. Late stage tumors are at minimum into the muscle wall (intramural) and frequently through the muscle wall (transmural). GEJ, gastroesophageal junction.
esophagus. Hamilton et al. reported finding residual Barrett’s esophagus in 39/61 (64%) of their series of adenocarcinoma of the esophagus and gastroesophageal junction. Based on our data and this literature, it is possible to conclude that approximately one-third of patients with adenocarcinoma of the distal esophagus have no evidence of residual intestinal metaplasia.

There are two possible explanations for the absence of residual intestinal metaplasia around the tumor. The first possibility is that the adenocarcinoma in the patients who did not have intestinal metaplasia arose in cardiac and oxyntocardiac mucosa without goblet cells. The second possibility is that the adenocarcinoma arose in intestinal metaplasia but destroyed the precursor epithelium by its growth.

The correct interpretation between these two possibilities has considerable practical significance. The definition of Barrett’s esophagus and the decision to place patients under long-term surveillance when Barrett’s esophagus is diagnosed is based on the premise that intestinal metaplasia is a necessary precursor stage of adenocarcinoma. If adenocarcinoma arose in columnar-lined esophagus without intestinal metaplasia, the very definition of Barrett’s esophagus will need revision and the criteria for surveillance re-evaluated.

The data in this study provide strong evidence that these adenocarcinomas arose from intestinal metaplastic epithelium. If adenocarcinomas developed in columnar epithelia without intestinal metaplasia with any significant frequency, there would be no difference in the prevalence of residual intestinal metaplasia in small and large tumors. If, on the other hand, adenocarcinomas developed in intestinal metaplasia and destroyed the precursor lesion as it grew, the prevalence of residual intestinal metaplasia would bear a strong relationship with tumor size and stage. This is dictated by the reasonable assumption that destruction of the precursor lesion becomes more common as the size of the tumor increases.

The data in the study show a clear and significant relationship between the prevalence of intestinal metaplasia and the size of the tumor. Tumors that were < 1 cm in size invariably showed residual intestinal metaplasia. The smallest tumor without intestinal metaplasia was 1.4 cm in diameter. The likelihood of not finding intestinal metaplasia progressively increased with increasing size of tumor. Absence of intestinal metaplasia was common only in tumors > 4 cm in size that showed transmural invasion. In a previous study by Cameron et al., intestinal metaplasia was found in 19/22 (86%) of cases of adenocarcinomas of the esophagus and esophagogastric junction that measured less than 2 cm.

There was a similar relationship between the prevalence of intestinal metaplasia and the pathologic stage of the tumor. All 14 (100%) patients with intramucosal adenocarcinoma had residual intestinal metaplasia. The likelihood of finding residual intestinal metaplasia progressively decreased with increasing tumor stage; 7/8 (88%) patients with submucosal tumors, 3/4 (75%) patients with intramural tumors, and 24/48 (50%) patients with transmural tumors had residual intestinal metaplasia. Van Sandick et al. similarly reported that all 32 cases of pathologic stage T1 adenocarcinomas of the esophagus and esophagogastric junction had residual intestinal metaplasia.

The positive relationship between finding residual intestinal metaplasia and the size and stage of the tumor provides strong support for the widely held belief that intestinal metaplasia is a necessary precursor lesion for adenocarcinoma of the esophagus. The present definition of Barrett’s esophagus as requiring the presence of intestinal metaplasia and the present practice of restricting long-term surveillance only to those patients with intestinal metaplasia is justified.

The second question is more difficult to answer, both from our study and from the literature. There are very few studies of adenocarcinoma of the gastric cardia, largely because of difficulties with accurate and standardized definition of this entity. At one extreme, Lagergren et al. defined adenocarcinoma of the gastric cardia as ‘a tumor (that had) … its center within 2 cm proximal, or 3 cm distal, to the gastroesophageal junction.’ At the other extreme, Odze defines the true gastric cardia as ‘the area of mucosa located distal to the anatomic gastroesophageal junction (defined as the proximal limit of the gastric folds) and proximal to the portion of stomach (corpus) that is composed entirely of oxyntic glands.’ According to Odze, this is normally < 0.4 cm. Most of Lagergren et al.’s gastric cardia adenocarcinomas arise in a region that would not fall within Odze’s definition of the true gastric cardia. In the present study, we used the most common definition that is used to define adenocarcinoma of the gastric cardia: that it is a tumor with its epicenter within 3 cm distal to the gastroesophageal junction. The fact that tumors so classified as gastric cardia adenocarcinomas had cardiac mucosa with and without intestinal metaplasia appears to justify this definition.

The prevalence of residual intestinal metaplasia in adenocarcinoma of the gastroesophageal junction (10/25 or 40%) and gastric cardia (5/11 or 45%) were similar and significantly less than that in the upper esophagus (33/38 or 87%). It is difficult to elucidate the significance of the difference between the prevalence of residual intestinal metaplasia in the distal esophagus and adenocarcinomas in the more distal locations. Patients who develop distal esophageal adenocarcinoma are more likely to have longer segments of Barrett’s esophagus than those that have
tumors of the gastroesophageal junction and gastric cardia. Longer segments of Barrett’s esophagus are likely to have a greater amount of intestinal metaplasia, making it more likely that residual intestinal metaplasia will be found in distal esophageal tumors than those in the junction and gastric cardia. The difference in prevalence of residual intestinal metaplasia in the different locations may therefore relate to the amount of intestinal metaplasia present rather than to any difference in the risk of adenocarcinoma.

It is unfortunate that there were no tumors < 1 cm or intramucosal tumors among the gastric cardiac adenocarcinoma. The most likely explanation for this is that the setting for very early cancers is in patients who are under long-term surveillance for Barrett’s esophagus and this does not include intestinal metaplasia of the gastric cardia. Ruol et al. reported the presence of intestinal metaplasia in 11/16 (69%) early-stage adenocarcinomas of the gastric cardia, compared with 25/26 (96%) similar tumors in the esophagus, and suggested that gastric cardiac cancers most likely arise in intestinal metaplasia of the gastric cardia.

There is also a paucity of data in the literature on the natural history of intestinal metaplasia of the gastric cardia. This is largely the result of two common practices of gastroenterologists. First is that endoscopically normal patients are not biopsied. Because intestinal metaplasia of the gastric cardia is found in patients without an endoscopic abnormality, this ensures that there is under-diagnosis of intestinal metaplasia of the gastric cardia. Second, even when diagnosed, these patients are not placed under surveillance, which effectively prevents the lack of accumulation of data on the natural history of this entity.

The study by Hirota et al. of patients presenting for upper endoscopy, indicates that there is a risk of cancer in intestinal metaplasia of the gastric cardia. They reported a prevalence of 5.6% (47/833) of intestinal metaplasia in a biopsy taken immediately distal to a normal endoscopic squamocolumnar junction; this was four times greater than the prevalence of long segment Barrett’s esophagus (1.6%) and similar to that of short segment Barrett’s esophagus (6.0%). In the patients with intestinal metaplasia in the biopsy taken distal to the gastroesophageal junction, dysplasia or cancer was noted in 6.4% patients; this was four times less than the incidence of dysplasia and cancer in patients with long segment Barrett’s esophagus (31%) and about half that in short segment disease (10%). This suggests that intestinal metaplasia of the gastric cardia is much more prevalent (four times) in the population than long-segment Barrett’s esophagus, but has a risk of cancer that is much less (four times) than that of long-segment Barrett’s esophagus. This would explain Lagergren et al.’s finding of 189 adenocarcinomas of the distal esophagus compared with 262 adenocarcinomas of the gastric cardia in his study of adenocarcinomas of this region.

In a recent study, Rex et al. reported that the prevalence Barrett’s esophagus was 65/961 patients (6.8%), with 12 (1.2%) of these being long-segment Barrett’s esophagus. In contrast, 122/940 (12.9%) patients had intestinal metaplasia of the gastric cardia. This study was different than Hirota et al. in that the population was a purely screening population who were offered upper endoscopy with biopsy at the time of presentation for screening colonoscopy. The prevalence of long- and short-segment Barrett’s esophagus, 1.2% (12/961) and 5.5% (53/961), respectively, were similar to Hirota et al. However, the prevalence of intestinal metaplasia of the gastric cardia was nearly double that of Hirota et al. (12.9% vs. 5.6%). This suggests that the prevalence of intestinal metaplasia of the gastric cardia in the population is very high. Even with a low incidence of adenocarcinoma, the total number of cancers that arise in this low-risk lesion has the potential to be large.

Adenocarcinoma of the gastric cardia is increasing in incidence in a manner that is parallel to adenocarcinoma of the esophagus and the total number of cases is at least equal to esophageal adenocarcinoma. Adenocarcinoma of the gastric cardia is epidemiologically associated with symptomatic reflux, albeit to a lesser extent than adenocarcinoma of the esophagus. Case control studies show that infection with Helicobacter pylori is not associated with a higher incidence of adenocarcinoma of the gastric cardia. Based on the available evidence, it appears likely that intestinal metaplasia of the gastric cardia is the likely precursor lesion for adenocarcinoma of the cardia. The only alternative to this is that there is no precursor lesion for adenocarcinoma of the gastric cardia, because no specific pathology exists in the cardia except inflammation and intestinal metaplasia. The finding in this study that 5/11 (45%) of patients with adenocarcinoma of the cardia had residual intestinal metaplasia despite the fact that these tumors were all large and high-stage, supports the concept that the latter is a highly significant precursor lesion for the former.

References


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