Aetiology and classification of adenocarcinoma of the gastro-oesophageal junction/cardia

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Gut 2010 59: 282-284
doi: 10.1136/gut.2009.186825

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The gastro-oesophageal junction (including the proximal cardia region of the stomach) is an anatomical site with a remarkably high and rapidly rising incidence of adenocarcinoma.[1] Understanding the aetiology of cancer at this site and its relationship to adenocarcinoma of the oesophagus and of the stomach poses a challenge to surgeons, gastroenterologists and pathologists. Determining the origin of these cancers is of more than academic interest as their surgical management depends upon whether they are derived from the oesophagus or the stomach.[2–4]

In 1996, Siewert *et al* proposed a classification of gastro-oesophageal junction adenocarcinomas based upon their location relative to the gastro-oesophageal junction identified by the proximal margin of the gastric folds.[4 5] Gastro-oesophageal junction cancers were considered to be those whose centre lay between 5 cm proximal to and 5 cm distal to the gastro-oesophageal junction. Siewert *et al* subdivided these gastro-oesophageal junction cancers into type I if the tumour centre lay 1–5 cm proximal to the gastro-oesophageal junction, type II if between 1 cm proximal and 1 cm distal to the junction and type III if 1–5 cm distal to the junction. This classification has been internationally recognised and is used by surgeons to plan management of the tumour.[2 3]

Siewert type 1 adenocarinomas have epidemiological and histological characteristics similar to oesophageal adenocarcinomas, including a marked male predominance, an association with a history of reflux symptoms and predominance of intestinal type Lauren histology.[2 5] In contrast, Siewert type III adenocarcinomas resemble distal (non-cardia) gastric cancers with less marked male dominance, a similar proportion of intestinal and diffuse histological types and no association with reflux.[5] Type I junctional adenocarcinomas are therefore considered to be oesophageal cancers which happen to be located in the distal oesophagus and type III junctional cancers to be gastric cancers which happen to be in the cardia. Siewert type II adenocarcinomas (centred within 1 cm of the gastro-oesophageal junction) have epidemiological and histological characteristics intermediate between those of type I and type III cancers. The Siewert classification does not advance our understanding of the aetiology of this particular subset of adenocarcinomas.

Adenocarcinomas arising within 1 cm of the gastro-oesophageal junction occur commonly, so their aetiology and classification are important. Are they of heterogeneous aetiology? Do some of them arise in short or ultrashort Barrett's segments, making them true oesophageal adenocarcinomas? Do others arise from the most proximal stomach, making them true gastric cancers? Alternatively, do junctional cancers have an aetiology distinct from both oesophageal adenocarcinoma and more distal (non-cardia) gastric cancer?

The fact that junctional cancers have epidemiological and histological characteristics between those of oesophageal and non-cardia gastric adenocarcinoma would be consistent with heterogeneous aetiologies, with some being oesophageal adenocarcinoma and others gastric carcinomas.[6 7] If so, the challenge is to differentiate junctional cancers into those of gastric and those of oesophageal origin. If this could be done, it would be possible to simplify the classification of adenocarcinoma of the upper gastrointestinal tract into two types—oesophageal adenocarcinomas and gastric adenocarcinomas.

Our improved understanding of the aetiology and pathogenesis of oesophageal adenocarcinoma and non-cardia gastric cancer over recent decades may be the key to classifying junctional adenocarcinomas. Non-cardia gastric adenocarcinomas, which may be of intestinal, diffuse or mixed Lauren type,[8] are associated with *Helicobacter pylori*-induced atrophic gastritis and intestinal metaplasia, and the intestinal subtype is thought to arise from the latter.[9] Oesophageal adenocarcinomas nearly always have an intestinal histological type, having arisen from Barrett's intestinal metaplasia, secondary to gastro-oesophageal reflux.[10] While oesophageal adenocarcinoma and the intestinal subtype of non-cardia gastric adenocarcinoma are themselves histologically indistinguishable, gastric mucosa well clear of the carcinoma is strikingly different between the two. In patients with non-cardia gastric adenocarcinoma of the intestinal subtype the mucosa of the rest of the stomach usually shows a body-predominant or pangastritis, with atrophy, intestinal metaplasia and low or absent acid secretion.[9 11–17] In contrast, in patients with oesophageal adenocarcinoma, the gastric mucosa is usually healthy, without any *H. pylori* gastritis and able to secrete normal or high amounts of acid.[18 19]

We have investigated whether the state of the gastric mucosa well clear of the tumour might indicate whether junctional adenocarcinomas are of two distinct aetiologies, with some resembling oesophageal adenocarcinomas and others resembling non-cardia gastric adenocarcinomas.[9] In a nested case–control study, we examined serological evidence of *H pylori* infection and atrophic gastritis (pepsinogen I/II) in patients with adenocarcinoma within 2 cm of the gastro-oesophageal junction and patients with non-cardia gastric cancers.[9] Patients with non-cardia gastric cancer had lower pepsinogen I/II ratios than controls, consistent with this cancer being strongly associated with gastric atrophy. Pepsinogen I/II values were normally distributed in controls and patients with non-cardia gastric cancers, in keeping with the latter being a homogeneous group.

The mean pepsinogen I/II value in the junctional cancers was similar to that of their controls but, whereas values in the control group were normally distributed, the junctional cancers had a non-normal distribution with a wide range of values. When the *H pylori*-positive junctional cancers were compared with *H pylori*-positive controls, the junctional cancers showed a significant association with gastric atrophy. This finding supported the concept of junctional cancers being of heterogeneous aetiology, with some resembling non-cardia gastric cancer in being associated with *H pylori*-induced atrophic gastritis and others having no association, or even a negative association, with gastric atrophy.

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In a further study, we examined the association of junctional adenocarcinoma with serological evidence of atrophy as well as with reflux symptoms, comparing it with that seen in patients with oesophageal adenocarcinoma and with non-cardia gastric cancer.[20] In keeping with previous observations, oesophageal adenocarcinomas showed a strong association with reflux symptoms but not with gastric atrophy, while non-cardia gastric cancers showed a strong association with atrophy but not with reflux symptoms. In contrast, junctional adenocarcinomas were positively associated with severe gastric atrophy and severe reflux symptoms, but importantly the association with reflux symptoms was confined to those without evidence of gastric atrophy. We believe this observation is again indicative of junctional adenocarcinomas having two distinct aetiologies, with some resembling oesophageal adenocarcinoma and others resembling non-cardia gastric cancer.

A third study performed by Ren *et al* further supports junctional adenocarcinomas being of two distinct aetiologies.[21] This study examined the association of gastric atrophy with junctional versus non-cardia gastric cancers The study was performed in China where Barrett's oesophagus and oesophageal adenocarcinomas are extremely rare. If cancers of the gastro-oesophageal junction are either oesophageal adenocarcinomas or gastric adenocarcinomas aetiologically similar to non-cardia gastric cancer then in a part of the world where oesophageal adenocarcinoma is extremely rare, all junctional cancers should show the same positive association with atrophy as non-cardia gastric cancers. This was indeed the case, with junctional cancers having an association with atrophy similar to more distal gastric cancers.

If junctional cancers are either oesophageal adenocarcinomas which are negatively associated with *H pylori*[18 19] or cancers of similar aetiology to non-cardia gastric cancers, which we know are positively associated with *H pylori*,[22] then there should be different associations between junctional adenocarcinomas and *H pylori* in different parts of the world. In the developed world where the ratio of oesophageal adenocarcinoma to non-cardia gastric cancer is relatively high, a substantial proportion of junctional cancers lead to a relatively weak association between junctional cancer and *H pylori* infection. In contrast, in the developing world where the ratio of oesophageal to non-cardia gastric adenocarcinoma is low, there should be a strong relationship between junctional cancers and *H pylori*. In the meta-analysis by the Eurogast Study Group, it was indeed observed that though there was no global association between junctional cancers and *H pylori*, there was a strong tendency for a negative association in studies from the Western world but a positive association in studies from the East.[23]

There is therefore now substantial evidence indicating that adenocarcinomas at the gastro-oesophageal junction are of two distinct aetiologies, with some being oesophageal adenocarcinomas probably arising from short or ultrashort Barrett's oesophagus and the others being gastric adenocarcinomas caused by *H pylori* infection and atrophic gastritis, as with cardia gastric cancers.

The challenge now is to determine whether an adenocarcinoma arising at the gastro-oesophageal junction is oesophageal or gastric. As recognised by Siewert *et al*, when the cancer is close to the gastro-oesophageal junction it is usually impossible to determine from inspection of the cancer and the surrounding mucosa whether it has arisen from the proximal stomach or a short Barrett's segment.[3–5] The key to correct classification is likely to be the differences which exist between oesophageal and gastric cancer with respect to epidemiology, pathogenesis and sometimes tumour histology (figure 1).

The first thing to consider is the histology of the cancer itself. If it is of pure Lauren diffuse histological subtype, then it is almost certainly a gastric cancer as this histology is rarely, if ever, seen in true oesophageal adenocarcinomas.[10] The greater challenge is determining the origin of the adenocarcinomas of the intestinal histological subtype. Oesophageal and gastric adenocarcinomas of intestinal subtype are histologically indistinguishable, having arisen on a background of intestinal metaplasia. Hopes that cytokeratin 7 and 20 immunophenotypes might differentiate between intestinal metaplasia or indeed between adenocarcinoma of gastric versus oesophageal origin have unfortunately not been realised.[24–30] Other groups have investigated whether Barrett's and gastric adenocarcinomas can be differentiated by comparative genomic hybridisation. Deletion of 14q31–32.1 as a marker of Barrett's adenocarcinoma has not been confirmed.[31–34]

We suggest the key to whether an intestinal type adenocarcinoma of the gastro-oesophageal junction is oesophageal or gastric in origin is not the histology

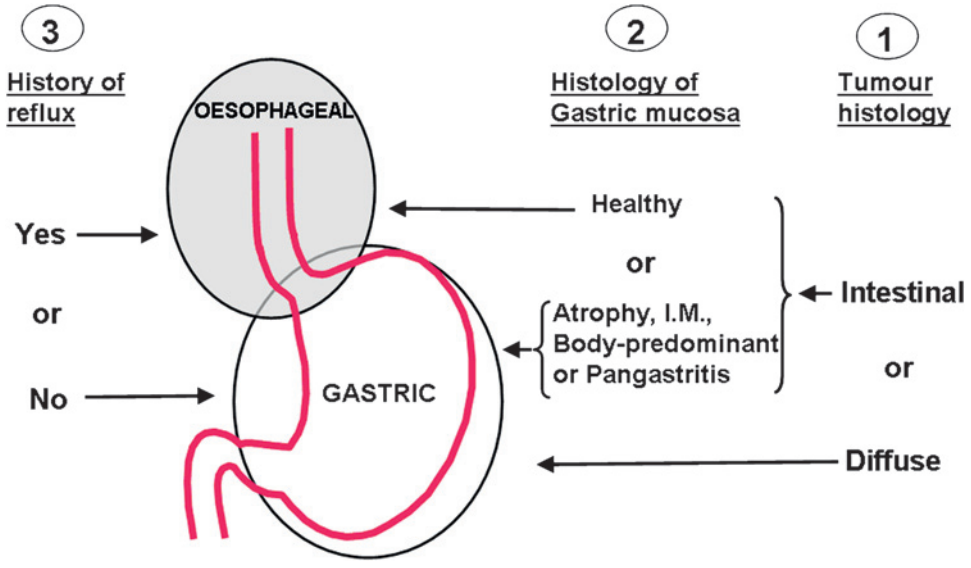

Figure 1 Tumour histology, gastric mucosal histology and history of reflux are three key pointers to whether adenocarcinoma at the gastro-oesophageal junction is oesophageal or gastric in origin.

of the cancer itself but the histology of the stomach well clear of the cancer. Gastric cancers are strongly associated with mucosal atrophy, intestinal metaplasia and body-predominant *H pylori* gastritis.[9 11–17] In contrast, oesophageal adenocarcinomas occur in subjects with healthy non-atrophic gastric mucosa.[18 19] It is important not only to biopsy a junctional carcinoma itself but, whenever possible, also to biopsy the gastric antrum and corpus for atrophy, intestinal metaplasia and body-predominant gastritis, the presence of which will strongly suggest that an adenocarcinoma is of gastric origin.

The other readily available information which may further help determine whether an intestinal-type adenocarcinoma at the gastro-oesophageal junction is gastric or oesophageal in origin is the history of reflux symptoms. A significant reflux history points to oesophageal adenocarcinoma, for which reflux symptoms are a risk factor,[35] whereas patients with gastric cancer associated with *H pylori* atrophic gastritis are protected from acid reflux.[36 37] Unfortunately, the gender of the patient is unlikely to be helpful as recent studies indicate a similar male predominance of intestinal-type adenocarcinoma of the stomach and oesophagus, in both due to a 15–20 year lag in cancer development in females.[10]

In summary, recent evidence indicates that adenocarcinomas of the gastro-oesophageal junction have two distinct aetiologies, one shared with oesophageal adenocarcinoma and the other with non-cardia gastric adenocarcinoma. Despite morphological and histological similarities, these two cancers arising at the gastro-oesophageal junction differ profoundly in their aetiology and origin, one being oesophageal and one gastric. It is important to separate oesophageal from gastric junctional cancers to allow meaningful epidemiological analysis and to guide surgical management. The two cancers may also respond differently to other treatment modalities such as chemotherapy and endoscopic mucosal resection, and studies of such treatments should be analysed by the likely origin of the lesion treated. Appropriate classification of most junctional cancers can be achieved by examining key indicators (figure 1). The terms "gastro-oesophageal junction", "junctional" and "cardia" adenocarcinoma should be discarded, with all adenocarcinomas arising around the oesophogastric junction being classified as "oesophageal" or "gastric" and their location in the relevant organ given.

Competing interests None.

Provenance and peer review Commissioned; not externally peer reviewed.

Revised 18 November 2009
Accepted 24 November 2009

Gut 2010;**59**:282–284. doi:10.1136/gut.2009.186825

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