Adenocarcinoma of the oesophagus: is it gastric cancer?

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The incidence of gastro-oesophageal junction (GEJ) cancer, comprising both oesophageal (EAC) and junctional gastric adenocarcinomas, has increased dramatically in Western countries, correlating with a decrease in non-cardia gastric cancer (GC). A better understanding of the origin and pathogenesis of these cancers may allow for improved cancer prevention, detection and treatment. GEJ adenocarcinomas include tumours classified in the past as either oesophageal or gastric in origin. Adenocarcinoma located just above the GEJ (ie, EAC) was for many years viewed as a distinct entity from GC. This view followed the strong association of EAC with Barrett's Oesophagus (BE), a metaplastic condition of the lower oesophagus which was viewed as a transdifferentiation of normal squamous epithelium to an intestinalised mucosa in the setting of gastric acid reflux. This assumption of a squamous origin of EAC led to (1) an extensive programme of surveillance of BE patients, (2) the inclusion of oesophageal squamous (ESCC) and adenocarcinoma (EAC) together in some clinical trials and (3) a clear distinction of EAC from GC. We propose here to rethink this approach based on novel insights on the origins and pathogenesis of GEJ cancer.

New data supporting a gastric origin of EAC/BE have emerged in recent years from both deep analysis of human samples and with experimental results from human derived cells and mouse models. The hypothesis that BE originates in the gastric cardia was proposed in 2012, based on findings in lineage tracing studies in a BE (L2-IL-1b) mouse model, which recapitulates the histologic progression from oesophagitis to dysplasia.[1] Lineage tracing allows for the genetic definition and tracking of stem cells and their progeny and can help determine the cellular origin of neoplasms. Subsequently, The Cancer Genome Atlas Research Network (TCGA) in 2017 demonstrated in comprehensive molecular genomic profiling of both oesophageal and GCs the distinct features of the two histological subtypes of oesophageal cancer, EAC and ESCC, with ESCC showing much greater similarity to head and neck SCC. Furthermore, joint analysis of EAC and GC could not identify features clearly demarcating EAC from the chromosomal instability (CIN) class of GC, suggesting a shared origin.[2] By contrast, variants of GC that are more common in the non-cardia regions of the stomach including tumours with microsatellite instability, Epstein-Barr virus infection or the diffuse histologic type are less common in GCs localised to the cardia and in EAC. Genetic results from TCGA are consistent with recent epigenetic studies of BE relative to normal gastric and oesophageal tissues, which also demonstrated evidence for a gastric origin to BE.[3] Furthermore, a recent study utilising comprehensive single-cell transcriptomic profiling, in silico lineage tracing, mutation analyses from human tissues spanning the proximal stomach to squamous oesophagus healthy and diseased donors, showed that BE originates from gastric cardia progenitors through distinct transcriptional programmes.[4] This latter study also experimentally determined the capacity of organoid cultures of human gastric tissue to differentiate into BE. Indeed, this emerging view of BE/EAC as originating from gastric tissue is consistent with key pathologic findings that BE always begins at the very distal oesophagus, contiguous with the gastric cardia, and that BE comprises a mosaic of gastric and intestinal cell types which is largely indistinguishable from intestinal metaplasia in the stomach.[5]

This new thinking regarding the relationship of EAC echoes the original descriptions of metaplasia of the distal oesophagus by Norman Barrett, who assumed at the time that BE resulted from proximal migration of stomach epithelium.[6] So, more than 70 years following the description of BE, it seems timely to recognise BE's gastric origin and view EAC and GEJ cancer as an extension of GC or 'gastro-EAC' (GEAC), reflecting their common aetiology (inflammation) and common genomic features, and explore the clinical consequences, both in terms of cancer screening and cancer therapy. The initial recognition of BE metaplasia of the distal oesophagus was followed in later decades by marked increases in EAC rates in the Western world. However, whereas metaplasia at the GEJ appears to be promoted by inflammation-induced injury from refluxed gastric acid and bile due to diet or obesity, in the distal stomach this is mostly induced by *H. pylori*, an established precipitant to gastric intestinal metaplasia. *B*oth stimuli lead to stem cell expansion and thus metaplasia or a risk of progression to cancer. To what extent the predilection to non-CIN forms of GC in regions distal to the GEJ are due to distinct effects of *Helicobacter pylori* and acid reflux or due to distinctions in the intrinsic stem cell biology or microenvironment along the anatomic gradient of the stomach remains unclear. Nevertheless, *H. pylori* infection has been declining while GERD has been increasing, thus leading to the changed distribution and more proximal location of GEAC tumours. Prior to the recent studies, when the dominant thinking was thought that BE emerged from differentiated squamous epithelial cells and while rates of EAC (and junctional or cardia GC) were steadily rising, the primary focus was instead on understanding BE metaplasia and prevention efforts limited to the detection and risk stratification of BE.

In light of this new view of GEACs (figure 1), including EAC, proximal and non-cardia GC, as a singular group of diseases wherein the most common form is a group of CIN GEAs that cross classic anatomic boundaries, screening and early diagnosis should also be reconsidered. There is a disconnect between a growing clinical problem which includes cancers in the proximal stomach, cancers emerging directly from the GEJ and cancers emerging in the setting of BE in the distal oesophagus, and a surveillance system that is focused solely on detecting and evaluating BE. In patients with BE, the risk of progression to cancer is low, estimated at 0.1%–0.3% per year.[7] Nevertheless, BE patients are frequently enrolled in endoscopic surveillance programmes aiming to detect oesophageal dysplasia or early stage EAC, and while such programmes may reduce cancer mortality for those rare tumours emerging in the setting of BE, the vast majority of patients that will

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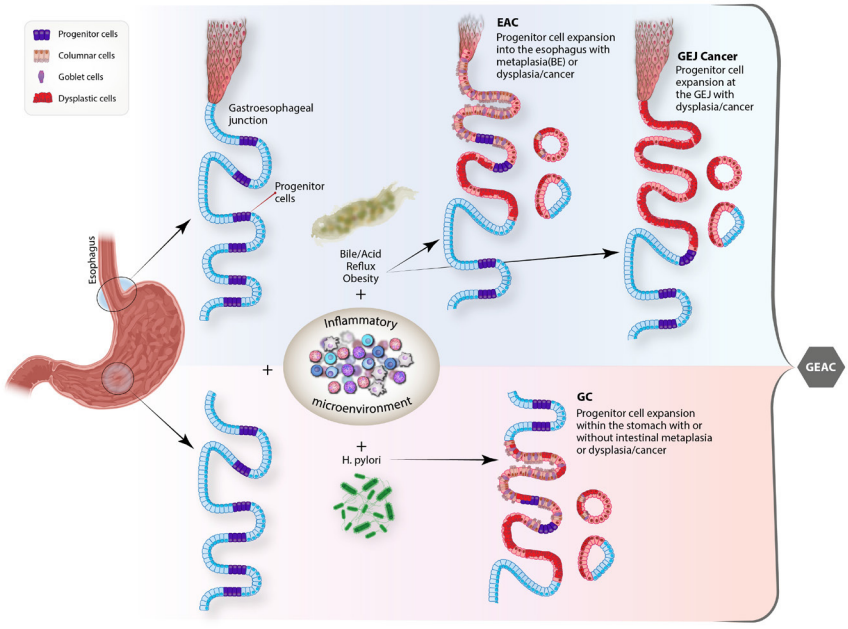

Figure 1 Illustration of a novel view on the origin and definition of gastro-oesophageal adenocarcinoma (GEAC) grouping gastro-oesophageal junction (GEJ) oesophageal adenocarcinoma (EAC) and non-junctional gastric cancer (GC) as one common entity, due to their common origin from gastric progenitor cells (purple) which expand due to distinct couses of inflammation (reflux, bile, *Helicobacter pylori*) giving rise to metaplasia (with or without goblet cells) or dysplasia at the junctional are or non-junctional stomach.

develop EAC or GEJ cancer are never first diagnosed with BE.[8] Rather, given the likely origins of GEAC from undifferentiated gastric cells, we need to look more closely at the response of cardia progenitors to chronic inflammatory conditions (such as GERD and *H. pylori* gastritis), and how they might progress along the path to either histopathological types of differentiated metaplasia or dysplasia and cancer.

Accumulating evidence suggests that BE and EAC pathogenesis involves the aberrant differentiation of stem or progenitor cells at the GEJ. The proximal expansion of cardia progenitors most likely occurs as a last resort, due to deficiencies in squamous healing and the greater resistance of columnar epithelial progenitors to acid/bile injury. The high mutation rate and clonal complexity of BE is evidence of the ongoing evolutionary process that begins long before the development of a detectable malignancy or even metaplasia.[9] GERD induces chronic inflammation that fuels genomic evolution, selecting for clones harbouring cancer-associated mutations in a distinct sequence[10 11] or genomic instability[12] leading to oncogene activation[13] which increase the chance of cancer development with or without metaplastic development. The stem cell niche represents a clonal mosaic, where genetically distinct clones compete, leading to a dynamic equilibrium of subclone expansion and retraction. In this setting, visible metaplasia may be simply a biomarker of epigenetic reprogramming of epithelial cells at the GEJ, as opposed to a necessary precursor lesion during a process of reprogramming of cardia progenitor cells toward a distinct precancerous state. Molecular alterations that promote these changes, such as CIN, an established hallmark of cancer, may in combination with other risk factors help guide future surveillance and detection strategies.

Finally, the understanding that EAC and GC originate from similar gastric stem or progenitor cell populations has important implications for medical treatment. The distinct genetic and epigenetic profiles of GEAC (EAC and GC) in comparison to ESCC strongly argue against any combining of EAC and ESCC patients in clinical trials, as has occurred commonly in past and in some ongoing phase III drug approval studies. EAC and ESCC are distinct in their lineage, epigenetics and key molecular drivers, thus necessitating separate clinical trials. The FDA has already allowed the grouping of GEJ EAC and GC as a common entity in recent immunotherapy approval, but has still approved combined EAC and ESCC trials. Moreover, although there are distinct molecular subtypes in EAC and GC[14 15] as there are within colorectal adenocarcinoma, these cancers in the future should be viewed as the single entity: GEAC, with non-surgical therapeutic approaches guided less by location and more by their distinct molecular profiles and associated histopathological phenotypes (intestinal vs diffuse type).

Moving forward this new view has the potential to accelerate our understanding of this disease and enhance our tools for prevention, screening and therapy.

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