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 of the oesophagus which 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/BEC have emerged in recent years from both deep analysis of human samples and from mouse models. From both deep analysis of human samples and mouse models, the description of BE, it seems timely to reconsider. 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. 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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develop EAC or GEJ cancer are never first diagnosed with BE.\(^2\) 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 \textit{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 with genomic instability12 leading to oncogene activation13 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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