



Genomics of gastroesophageal junction adenocarcinomas and the Siewert classification

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Cancers of the lower part of the esophagus, like gastric cancers, are of the adenocarcinoma histologic subtype, whereas upper esophageal cancers are most commonly squamous. Adenocarcinomas arising around the anatomic junction of the stomach and esophagus and spreading from 5 cm above to 5 cm below this junction are termed gastroesophageal junction (GEJ) adenocarcinomas. GEJ cancers have been sub-classified with the Siewert classification introduced 30 years ago into three anatomic categories (1). Siewert I cancers constitute most upper GEJ carcinomas with an epicenter located 1–5 cm above the anatomic junction. Siewert II cancers, also called true junctional cancers, extend from 1 cm above to 2 cm below the junction. Siewert III cancers are subcardial, extending 2–5 cm below the junction. The Siewert subtypes have been used to guide the surgical approach to GEJ adenocarcinomas, with Siewert I cancers often approached as esophageal carcinomas through a transthoracic esophagectomy and Siewert III cancers often approached as gastric cancers with gastrectomy and perigastric lymphadenectomy, while Siewert II cancers are treated

according to where the bulk of the disease is located (2). In addition, the Siewert anatomic location may portend prognostic significance, with type III cancers having the worst prognosis, type II cancers having an intermediate prognosis, and type I cancers having the best prognosis (3). The systemic treatment of GEJ adenocarcinomas has been less influenced by the exact location of the tumor and often these tumors have been included in landmark trials of gastric or esophageal adenocarcinomas (4).

In addition to sharing histological subtype, intestinal type gastric and esophageal adenocarcinomas share some pathogenic features, including a similar precursor lesion, which in the stomach is termed gastric intestinal metaplasia, and in the esophageal location is called Barrett's esophagus (5). Despite the similarity of these precursor lesions, other pathogenic features are divergent—most notably *Helicobacter pylori* infection, which is common in gastric cancers and is believed to be an inflammatory promoter of gastric carcinogenesis. However, it is not a common factor in esophageal adenocarcinomas, where gastroesophageal reflux and bile acids are pathogenic

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Table 1 Frequency of common alterations in esophageal, Siewert I gastroesophageal, Siewert II gastroesophageal, Siewert III gastroesophageal, and gastric adenocarcinomas (11)

Alteration	Esophageal adenocarcinoma	Siewert I gastroesophageal adenocarcinoma	Siewert II gastroesophageal adenocarcinoma	Siewert III gastroesophageal adenocarcinoma	Gastric adenocarcinoma
<i>TP53</i>	79%	77%	76%	64%	37%
<i>KRAS</i>	18%	21%	16%	17%	18%
<i>ERBB2</i>	28%	12%	20%	7%	13%
<i>CDKN2A</i>	28%	24%	20%	10%	4%
<i>ARID1A</i>	11%	14%	17%	27%	25%
<i>CDH1</i>	1%	2%	2%	12%	11%
<i>RHOA</i>	1%	0	0	2%	6%

instigators (6). Barrett's esophagus without dysplasia remains a polyclonal process. When dysplasia develops, it is taken over by monoclonal cell populations that may arise from diverse stem cell origins in the esophagus or the gastric cardia (7). It is noteworthy that both initiating factors, *Helicobacter pylori* infection and gastroesophageal reflux, induce chronic inflammation and repeated rounds of tissue injury and repair.

Gastric and esophageal adenocarcinomas also have notable genomic differences. Three subtypes are present in gastric adenocarcinoma, including an Epstein-Barr virus (EBV)-associated subtype, a genomically stable subtype enriched in diffuse histology, and a microsatellite instability (MSI) high subtype; however, these subtypes are absent or uncommonly observed in esophageal adenocarcinoma (8,9). The fourth gastric cancer subtype shows chromosomal instability (CIN). Esophageal adenocarcinomas are predominantly CIN-high tumors, although MSI-high and genomically stable tumors comprise up to 25% of these cancers in some series (10). The extent to which the genomic makeup of GEJ adenocarcinomas follows esophageal or gastric patterns and the influence of the anatomic location on genomic characteristics of these tumors had not been fully elucidated. However, Nakauchi *et al.* examined this in an extensive series of 350 GEJ adenocarcinomas (35% Siewert I, 49% Siewert II, and 17% Siewert III) using the Memorial Sloan Kettering Cancer Center Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) targeted genomic panel that included 341–468 genes in its different versions (11). The main conclusion of this analysis was that, when viewed as a whole, the genomic patterns of GEJ adenocarcinomas are intermediate

between esophageal adenocarcinoma and gastric cancer patterns, but when divided according to anatomic location, the two upper Siewert types follow the patterns of esophageal adenocarcinomas while the Siewert III subtype aligns with gastric adenocarcinomas. Clinicopathologic characteristics of esophageal adenocarcinomas, such as association with Barrett's esophagus, male sex, and white race, were more common in Siewert I and II GEJ cancers, while female sex, poor differentiation, and signet ring histology were more prevalent in Siewert III tumors. This pinpoints the zone at 2 cm below the anatomic cardia as the boundary where the genomics of resident cancers diverge, with tumors above this point mirroring esophageal adenocarcinoma genomics and tumors centered below this point aligning most with the genomics of gastric cancers. One has to bear in mind, however, that the boundary is not abrupt and a continuum is evident in the transition of genomic characteristics, including the copy number alterations (CNAs) and the tumor mutation burden (TMB, mutations/Mb).

Nakauchi *et al.* found that the most prevalent mutations in GEJ adenocarcinomas affect the tumor suppressor *TP53* and were observed in 74% of cases (11). This rate is similar to the rate in esophageal cancers (79%) and much higher than the prevalence of *TP53* mutations observed in gastric cancers (37%). Interestingly, when GEJ adenocarcinomas were viewed according to Siewert location, the prevalence of *TP53* mutations in Siewert III cancers remained much higher (64%) than in gastric cancers and closer to the prevalence in Siewert I and II GEJ cancers (76%) and esophageal adenocarcinomas (Table 1). This observation corroborates the fact that Siewert III cancers, despite their similarity in some genomic aspects with gastric adenocarcinomas,

present a higher prevalence of the CIN-high phenotype than gastric cancers, and the high CIN subtype is the most prevalent in Siewert III carcinomas. *TP53* mutations are a hallmark of CIN and are required for CIN tolerance in cooperation with additional alterations (12). Therefore, *TP53* mutations in the subset of Siewert III GEJ cancers with high CIN would contribute to cancer cell survival and evasion of apoptosis, similar to other CIN-high cancers.

The second and third most prevalent mutations in GEJ adenocarcinomas are those in *ARID1A* and *CDH1* aligned in Siewert I/II and Siewert III tumors, with prevalence in esophageal and gastric adenocarcinomas, respectively (Table 1) (11). In addition, the prevalence of MSI in Siewert I/II GEJ cancers (4.1%, 7.1%, respectively) mirrored the prevalence in esophageal adenocarcinomas and the prevalence of MSI in Siewert III GEJ cancers (15%) mirrored the prevalence in gastric adenocarcinomas. Also aligning with gastric cancers, the prevalence of the genomically stable phenotype in Siewert III GEJ adenocarcinomas is higher than in other Siewert types.

As a result of the similarities with gastric cancers, Siewert III GEJ cancers are more heterogeneous genomically than Siewert I and II cancers with the three subtypes, CIN-high, MSI-high, and genomically stable, well represented. The therapeutic implications of the genomic subtypes are currently restricted to the MSI-high subtype, with cancers of this subtype being candidates for immunotherapy treatment with immune checkpoint inhibitors (13). EBV-associated cancers tend to also respond well to immune checkpoint inhibitors, potentially due to their high expression of programmed death ligand 1 (PD-L1) (14). Other alterations with available targeted therapies do not strictly align with genomic groups but are enriched in some of those groups. For example, HER2 amplifications are enriched in CIN cancers and are therefore more prevalent in esophageal and Siewert I and II GEJ adenocarcinomas. Regarding Claudin 18.2 positivity, a study in gastric cancers based on immunohistochemistry showed that it may be observed in both cases with *TP53* mutated and wild type staining patterns and in cases with preserved or lost E-cadherin expression (15).

Based on the high prevalence of CIN in Siewert I and II GEJ cancers, novel therapies targeting cancers with high CIN are particularly relevant for this patient population. Such targeted treatments, which include MPS1 inhibitors, kinesin inhibitors, and DNA damage response inhibitors, have been investigated in preclinical models but have yet

to fulfill their clinical promise (16-18). These therapies seek to promote the demise of cancer cells with high CIN by increasing their aneuploidy beyond a level that is compatible with survival. CIN-high cancers may also be particularly sensitive to DNA damage response inhibitors, such as CHK1/2 inhibitors and Wee1 kinase inhibitors, in combination with chemotherapy (18). Accurate and reliable quantification of CIN and the underlying failure of DNA damage repair mechanisms leading to CIN in clinical samples will be instrumental as biomarkers to advance CIN-targeting therapy development.

On the other hand, Siewert type III GEJ adenocarcinomas, similar to gastric cancers, contain a sizeable minority of genomically stable cases, which are enriched for the diffuse histologic type. Consistently, *CDH1* mutations are also enriched in Siewert III GEJ cancers. Adenocarcinomas with diffuse histology arising in the stomach or the GEJ are clinically aggressive and therapies targeted specifically for these tumors do not exist. Notoriously, direct targeting of the loss of function of tumor suppressors such as E-cadherin is not an easy task, as it would require the recovery of the altered mutated protein structure and function. In addition, E-cadherin expression is frequently suppressed in diffuse cancers due to methylation of the gene promoter (19). As an alternative to the recovery of E-cadherin protein and function, a synthetic lethality approach was proposed based on the discovery that E-cadherin loss endows breast and gastric cancer cells with a vulnerability to inhibition of kinase ROS1 (20). In these cells, ROS1 inhibitors, such as foretinib and crizotinib, caused mitotic defects and multiple nuclei induction, resulting in cell death. Diffuse type gastric cancer cell lines were more sensitive to ROS1 inhibitors than intestinal-type cancers. Despite these preclinical results, a clinical trial with the ROS1 inhibitor entrectinib in lobular breast cancers in the neoadjuvant setting in combination with letrozole produced no pathologic complete responses (21). However, about half of the patients (49%) achieved radiologic responses (complete in 10%, partial in 39%). No trials of ROS1 inhibitors in diffuse gastric cancers have been reported and the value of this synthetic lethality approach remains untested in gastric cancer clinical trials. The concept of synthetic lethality is nevertheless enticing as a therapeutic strategy. In patients with hereditary diffuse gastric carcinomas, tumors arise by inactivation of the normal *CDH1* allele through various mechanisms, including promoter methylation, loss of heterozygosity, and point mutations. These mechanisms are also observed in sporadic diffuse gastric cancers,

where promoter methylation appears to be dominant (22). Therefore, therapeutic opportunities for E-cadherin reactivation, for example with demethylating agents, can be considered in gastric and Siewert III GEJ adenocarcinomas. The other frequent mutation in Siewert III cancers concerns the epigenetic modulator and member of the Switch/Sucrose Non-fermentable (SWI/SNF) complex ARID1A. *ARID1A* mutations have also been observed, in addition to Siewert III and gastric adenocarcinomas, in smaller subsets of Siewert I and II and esophageal adenocarcinomas, and have been associated with alterations of the tumor immune microenvironment, providing a rationale for immunotherapies (23,24). Beyond PD-L1/programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) inhibitors, novel immune therapies, including bispecific antibodies, have been recently introduced in these cancers and represent the new frontier for immune-based therapies (25). In addition, *ARID1A* mutations display an association with the CpG island methylation phenotype (CIMP) across gastrointestinal cancers, which may create therapeutic opportunities for epigenetic therapies (26,27). For example, reversing hypermethylation at the MLH1 and CDH1 promoters could be particularly relevant for MSI-high and diffuse GEJ and gastric cancers. Gastric cancer cells with *ARID1A* mutations display activation of the PI3K/AKT pathway and have shown sensitivity to PI3K or AKT inhibitors in preclinical models (28,29). Translating these findings into the clinic could benefit patients with GEJ adenocarcinomas with *ARID1A* mutations.

In conclusion, the detailed genomic evaluation of GEJ adenocarcinomas according to their location along the junction provides a useful overview of these cancers and confirms their relationships with adenocarcinomas of neighboring locations in the esophagus and stomach. Although different molecular subtypes of gastric cancer display unique biological features, CIN type gastric cancers are quite similar to esophageal adenocarcinomas, as esophageal adenocarcinomas are almost always CIN. In addition, CIN type gastric cancers increase in frequency in more proximal locations and in the GEJ. It is noteworthy that no separate genomic subtypes arise in this analysis and all GEJ adenocarcinomas can be classified in one of the genomic categories observed in esophageal or gastric adenocarcinomas. As noted by the authors of the report, the anatomic location may eventually be less important than the presence of genomic alterations in determining the prognosis and treatment of these cancers (11). The

genomic subtypes arise as potential prognostic and predictive biomarkers of response to chemotherapy and immunotherapies (10). Additional research is warranted to confirm the predictive value of genomic subtypes and determine how best to integrate genomic profiling into clinical practice for patients with GEJ adenocarcinomas.

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