Molecular Pathology of Gastroesophageal Cancer

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KEYWORDS

• Esophageal squamous cell carcinoma • Esophageal adenocarcinoma • Gastric adenocarcinoma
• Molecular pathology

Key points

- Esophageal squamous cell carcinoma and esophageal adenocarcinoma are separate entities with differing molecular pathology.
- Gastric adenocarcinomas can be classified into 4 distinct molecular subtypes that may suggest treatments unique to the subtypes.
- Esophageal adenocarcinoma and chromosomal unstable–type gastric adenocarcinoma are very similar to each other and likely constitute a spectrum of the same disease.

ABSTRACT

Upper gastroesophageal carcinomas consist of cancers arising from the esophagus and stomach. Squamous cell carcinomas and adenocarcinomas are seen in the esophagus and despite arising from the same organ have different biology. Gastric adenocarcinomas are categorized into 4 molecular subtypes: high Epstein-Barr virus load, microsatellite unstable cancers, chromosomal unstable (CIN) cancers, and genomically stable cancers. Genomically stable gastric cancers correlate highly with histologically defined diffuse-type cancers. Esophageal carcinomas and CIN gastric cancers often are driven by high-level amplifications of oncogenes and contain a high degree of intratumoral heterogeneity. Targeted therapeutics is an active area of research for gastroesophageal cancers.

OVERVIEW

Upper gastrointestinal cancers comprise malignancies of the esophagus and stomach. Although most gastrointestinal cancers are adenocarcinomas, esophageal cancers come in both adenocarcinoma and squamous cell carcinoma. Despite being derived from the same organ, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) are quite different at both cellular and molecular levels and should be treated as separate entities.[1] Traditionally, adenocarcinomas of the esophagus and stomach were considered two separate types of cancer and treated as such. Recent evidence has suggested, however, that EAC is very similar to intestinal-type gastric adenocarcinomas of the proximal stomach.[1,2] Although they are discussed separately, they should be considered as a spectrum of the same disease.[3] In the United States, gastroesophageal cancers represent a significant source of cancer morbidity and mortality with more than 45,000 new cases resulting in more than 26,000 deaths estimated for 2021.[4] The lack of early endoscopic surveillance guidelines and the often subtle clinical symptoms have resulted in many patients presenting at time of diagnosis with advanced metastatic disease and 5-year survival rates under 20%.[5] As understanding of these

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Surgical Pathology 14 (2021) 443–453
https://doi.org/10.1016/j.path.2021.05.008

complex cancers continues to improve, new more efficacious and better tolerated targeted therapies are being developed.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

ESCC arises in the upper and middle esophagus and has a widely varying regional incidence, with highest rates in China, South Africa, and South America.[6] Risk factors also vary according to region, but common ones include tobacco, diet, and alcohol.[6] The molecular alterations present in ESCC have been well studied. As in other squamous cell carcinomas, ESCCs typically have a moderately high mutation burden and frequent copy number alterations. A recent The Cancer Genome Atlas (TCGA) article,[1] as well as others,[7,8] describe frequent activation of the RAS and PI(3)K pathways, loss of cell-cycle regulation, chromatin remodeling dysregulation, and alterations in transcription factors/cell differentiation pathways. RAS and PI(3)K pathway alterations include frequent amplifications of *EGFR* and *FGFR1* with *ERBB2*, *KRAS*, and *MET* less commonly amplified and common activating mutations in *PIK2CA*. *PTEN*, a negative regulator of *PIK3CA*, is inactivated through deletion or loss of function mutations in approximately 10% of cases. Commonly altered genes involved in cell-cycle regulation include very frequent deletions of *CDKN2A* (approximately 75% of ESCCs), deletions or mutations in *RB1*, and amplifications of *CCND1* and/or *CDK6*. Genes involved in chromatin remodeling are altered in approximately a third of cases with mutations or deletions of *SMARCA4*, *KDM6A*, and *KMT2D* the most common. Transcription factors or other genes involved in cell differentiation also commonly are altered. Amplifications involving genomic regions that contain *TP63*/*SOX2* are seen in approximately half of ESCCs with mutations in *NOTCH1* and *ZNF750* also somewhat common. Finally, a few other genes also commonly are altered. These include *TP53* mutations in more than 80% of cases, *MYC* amplifications, and less commonly *SMAD4* mutations or deletions.

ESCC arises from dysplastic (premalignant) lesions similar to other squamous cancers. Studies comparing ESCC and dysplasia adjacent to ESCC found remarkably similar aggregate mutational and copy number profiles, with areas of dysplasia having a similar frequency of events in genes commonly altered in ESCC.[9,10] Despite a similar frequency of alterations, when paired ESCC and dysplasia samples from the same patient were compared with each other, there still was a high degree of genomic heterogeneity as well as private, nonshared events. This suggests that fields of dysplasia may consist of an oligoclonal population, where 1 of these clones eventually develops an invasive phenotype to become ESCC. When dysplasia adjacent to ESCC was compared with dysplasia from patients without ESCC, 2 important differences were identified.[10] First, although *TP53* mutations still were identified in patients with only dysplastic tissue, a second event affecting the alternative allele was very rare. This is in contrast to ESCC and dysplasia adjacent to ESCC, where finding 2 alterations of *TP53* was extremely common. Second, the number of mutations and CNVs in patients with only dysplastic tissue was lower than both low-grade dysplasia and high-grade dysplasia taken adjacent to ESCC. These results raise the possibility of using molecular alterations to better stratify patients with esophageal squamous dysplasia into high and low risk.

ESOPHAGEAL ADENOCARCINOMA

EAC arises in the lower esophagus out of a field of columnar metaplasia that develops a varying degree of intestinal differentiation (called Barrett's esophagus [BE]). Although traditionally EAC was rare, with ESCC the predominate cancer type of the esophagus, there has been a dramatic rise in incidence of EAC within European and North American countries.[11–14] Combined with the low 5-year survival rate, this increase in incidence has driven an increased interest in understanding the molecular alterations that are present in this cancer. Several large studies have characterized the landscape of alterations present, including both by the TCGA[1] and the International Cancer Gene Consortium.[15] Like ESCC and many other cancers, pathways that commonly are altered in EAC include receptor tyrosine kinases (RTK) and their downstream signaling partners (Ras signaling), cell-cycle control, transcription factors/cell differentiation, chromatin remodeling, and transforming growth factor (TGF)-β signaling. Oncogenic activation through the RTK pathway typically occurs through amplification of *ERBB2*, *EGFR*, or *KRAS* which are present in approximately 25%, 15%, and 10% to 15% of cancers, respectively. Less commonly, amplifications can be seen in *IGFR1*, *FGFR1*, *FGFR2*, and *MET*. Additionally, amplifications in *VEGFA* are seen in 10% to 20% of EACs. Loss of cell-cycle regulation occurs through inactivation of *CDKN2A* in 75% of cases and amplifications of *CCNE1*, *CCND1*, and *CDK6*, all of which occur in 10% to 30% of EACs, with *CCND1* reported to be the most commonly amplified.[16] The majority of *CDKN2A*

inactivation in EAC occurs through promotor methylation and less commonly through deletions or mutations. The transcription factors *GATA4* and *GATA6*, which both have a role in cellular differentiation and development, are amplified in approximately 20% of EACs each and usually (but not always) are mutually exclusive. Although not as common as in ESCC, loss of function alterations in genes involved in chromatin remodeling can be seen in EAC. The most commonly altered genes include *SMARCA4* and *ARID1A*, both of which are altered in approximately 10% of cases. Deletions and loss of function mutations in *SMAD4* and *SMAD2*, which are mediators of TGF-β signaling, are seen in approximately 25% of EACs. *MYC* amplifications can be seen in 20% to 30% of these cancers. Loss of normal *TP53* function has been proposed to play a vital role in EAC progression and can be seen in approximately 75% of EACs with *MDM2* amplifications seen in some of the *TP53* wild-type cancers.[17]

EACs typically emerge from premalignant lesions within the lower esophagus, termed BE. BE, which is the replacement of the normally squamous lined esophagus with columnar epithelial cells that develop intestinal differentiation, is thought to form in response to injury induced by chronic bile and acid reflux and the resultant inflammation. The prevalence of BE is thought to be much higher than EAC and has been estimated to exist in 1% to 10% of adults in the United States.[18] The vast majority of those with BE never progresses to cancer, complicating the understanding of BE progression to EAC. In order to understand this process, several groups have either studied paired genomic profiles of EAC and adjacent BE or BE samples with known long-term follow-up to characterize the evolution of cancer from precursor lesions. These studies have identified that *TP53* inactivation is a common early event that can occur in nondysplastic BE. This is followed by the development of aneuploidy, often including development of genome doubling.[17,19–25] Transformation of dysplastic lesions to EAC is thought to occur via acquisition of high-level focal amplifications of oncogenes (as described previously), often in the context of complex genomic disruptions.[17,26,27]

GASTRIC ADENOCARCINOMA

Gastric cancer is one of the world's leading causes of cancer mortality, with an estimated 783,000 deaths in 2018.[28,29] Similar to esophageal cancer, the incidence is highly variable according to geographic region. Most cases of gastric cancer are associated with *Helicobacter pylori* or Epstein-Barr virus (EBV) infection and a small subset are associated with germline mutations in *CDH1* (E-cadherin) or mismatch repair genes (Lynch syndrome).[30,31] Gastric adenocarcinomas traditionally are classified by histology. The Lauren classification divides gastric cancer into diffuse and intestinal types whereas the World Health Organization uses papillary, tubular, mucinous, and poorly cohesive.[32,33] Recent comprehensive molecular characterization has suggested, however, a classification system based on genomic and methylation differences. TCGA Research Network gastric cancer study, suggests gastric cancers should be categorized in 4 molecular subtypes (**Table 1**).[2] Although more work needs to be done to better correlate the molecular findings with clinical parameters, these molecular subtypes provide more insight into the biology of the tumor and give some suggestions for targeted therapies. The first molecular subtype includes gastric cancers that are EBV positive. These tumors tend to have extensive DNA methylation of gene promotors and low overall mutation and copy number alteration rates and often are found in the gastric body or fundus. EBV-positive gastric adenocarcinomas almost always have *CDKN2A* promotor methylation and have high rates of *PIK3CA* and *ARID1A* mutations and low rates of *TP53* mutations. Amplifications involving *CD274* (programmed death ligand [PD-L] 1 protein), *JAK2*, and *ERBB2* can be seen in approximately 15%, 12%, and 12% of EBV-positive gastric cancers, respectively. The second molecular subtype of gastric cancers are the microsatellite instability (MSI) gastric cancers. These cancers are characterized by hypermethylation with methylation of (and thus inactivation of) the *MLH1* gene promotor. This leads to defective mismatch repair and highly elevated mutation rates. Prominent alterations in MSI gastric cancers include mutations in *PIK3CA*, *ERBB3*, *KRAS*, *NRAS*, *PTEN*, and *RASA1*. High-level amplifications are rare in MSI gastric cancers but occasionally are found involving *PIK3CA*. The third molecular subtype of gastric cancer is the genomically stable subgroup. These gastric cancers are EBV-negative and microsatellite stable with a low level of copy number alterations. This subgroup is enriched for the diffuse-type gastric cancers in the Lauren classification. As such, frequent alterations in *CDH1* can be found. Other commonly altered genes include *ARID1A* and *RHOA*. Although copy number alterations are rare, activating amplifications or mutations in *FGFR2*, *ERBB2*, *KRAS*, *NRAS*, and *PIK3CA* can be seen in 5% to 10% of cancers for each gene. The fourth molecular subtype is the chromosomal instability (CIN) subtype that is characterized by a

Table 1
Molecular classification of gastric adenocarcinomas

Subgroup	Defining Characteristic	Methylation Status	Mutation Rates	Copy Number Variant Rates	Associations
EBV positive	High EBV burden	Extensive DNA promotor methylation (CIMP)	Low to moderate	Low to moderate	Enriched in gastric fundus and body
MSI	Microsatellite unstable	Hypermethylation with methylation of *MLH1* promotor	High	Low to moderate	Loss of mismatch repair through mutation (Lynch syndrome) or MLH1 promotor methylation
Genomically stable	Low degree of genomic complexity	Variable (moderate)	Low	Low	Enriched for diffuse-type cancers
CIN	High degree of genomic complexity	Variable (moderate)	Moderate	High	Enriched in proximal stomach

Abbreviations: CIMP, CpG island methylator phenotype.

high degree of copy number changes. This subtype is found more commonly in the proximal stomach and is very similar to EACs. Like EAC, the CIN gastric cancers have frequent *TP53* mutations, amplifications in the RTK/RAS pathway (*ERBB2*, *EGFR*, *FGFR2*, *ERBB3*, *MET*, *KRAS*, and *NRAS*) and in cell-cycle mediators (*CCNE1*, *CCND1*, and *CDK6*). Loss-of-function mutations in the β-catenin pathway (*APC* and *CTNNB1*) also can be seen.

Two different forms of metaplasia have been described in the stomach. The first, gastric intestinal metaplasia, is histologically similar to BE. In one study, genomic and methylation–based profiling of gastric intestinal metaplasia showed that it harbored several recurrent genomic alterations and methylation patterns different than normal gastric epithelium.[34] This study, which looked at a mix of metaplasia from patients with regressive/stable disease and a lower number of patients in which the metaplasia progressed to high-grade dysplasia or cancer, found an overall lower mutational and copy number burden compared with gastric adenocarcinomas. Despite this, recurrent hot spot mutations in *FBXW7* and rarer mutations in *TP53* and *ARID1A* still were identified. In addition, copy number gains of 8q involving the oncogene *MYC* were seen. When metaplasia from patients who progressed were compared with those who did not progress, a trend for increased numbers of mutations, copy number alterations, and shorter telomeres was seen in the intestinal metaplasia from progressors.

The second type of metaplasia is termed, spasmolytic polypeptide–expressing metaplasia (SPEM) or pseudopyloric metaplasia. The exact relationship of gastric intestinal metaplasia and SPEM to each other and to gastric cancers is controversial and an area of ongoing research. Few studies have looked at the genomic landscape of SPEM; however, Srivastava and colleagues performed paired targeted sequencing on a small number of gastric cancer patients who had concurrent intestinal metaplasia and SPEM.[35] In this study, they found SPEM to have a much lower number of mutations compared with the paired intestinal-type gastric adenocarcinomas whereas the regions of intestinal metaplasia had similar numbers of mutations as the cancers. Further studies are needed to better delineate the genomic progression of gastric precancerous lesions to the different subtypes of gastric cancer.

INTRATUMORAL GENOMIC HETEROGENEITY IN ESOPHAGEAL AND GASTRIC ADENOCARCINOMA

As described previously, both esophageal and CIN-type gastric adenocarcinoma develop from preneoplastic lesions where early *TP53* mutations are common. This is followed by the development of aneuploidy and significant disruption of normal chromosomes. It is through this process that most of these cancers get their source of oncogenic signaling, namely development of high-level

amplifications of oncogenes late in the progression process. This is in contrast to gastrointestinal adenocarcinomas of other sites where activating mutations in important oncogenes occur relatively early in the progression process. For example, *KRAS* mutations in colon or pancreatic adenocarcinoma. This highly unstable state seen in esophageal and CIN-type gastric adenocarcinoma can lead to significant heterogeneity within the late preneoplastic lesion and the invasive cancer. Several recent studies have looked at multiregion primary and metastatic tumor sequencing and found a high degree of heterogeneity.[24,36] This heterogeneity potentially includes targetable oncogenic drivers. Pectasides and colleagues[24] found that between paired primary and metastatic samples nearly half of patients had discrepant pathogenic alterations. When they looked at samples with activating alterations in RTKs, a major focus of targeted therapy, more than half of patients had discrepant results between samples depending on the cohort utilized. This heterogeneity in important driver genes may be a major source for failure of precision medicine/targeted therapy in these diseases and points toward the need of careful sample selection for clinical testing. There is some suggestion that sequencing of plasma circulating tumor DNA may be a better predictor of response to targeted therapy.[24,37]

PRECISION MEDICINE IN UPPER GASTROINTESTINAL CANCERS

As understanding of the molecular mechanisms underpinning upper gastrointestinal cancers has improved, new more efficacious and better tolerated targeted therapies, including immunotherapeutics have advanced the landscape of treatment beyond cytotoxic chemotherapy, summarized in **Table 2**. To date, however, many of these therapies have shown only modest success. Therefore, improved understanding of the genomic heterogeneity and other mechanisms of resistance will be vitally important to further improve treatment strategies. These novel treatments and how they are tailored based on patient histology, anatomic location, and pathologic biomarkers are discussed.

The emergence of genomics and its clinical accessibility has changed the way cancer treatment is approached. Molecular characteristics of the cancer now are just as important in clinical oncology decision making as cancer anatomic location and histology. Specifically, for gastroesophageal cancers, detailed sequencing studies have revealed shared subtypes with common molecular pathogenesis.[1,2] Growth factor signaling pathway activation is a shared trait for the most prevalent CIN subtype of gastroesophageal cancer. Thus, targeting these signaling cascades has translated well clinically. The human epidermal growth factor receptor 2 (HER2/*ERBB2*) is overexpressed or amplified in 10% to 30% of gastroesophageal cancers.[47] The landmark ToGA trial examined the efficacy of targeting this pathway using trastuzumab, a monoclonal antibody against HER2, for HER2-positive (ie, 3+ staining on immunohistochemistry [IHC] or [fluorescence in situ hybridization positive]) gastroesophageal junction and stomach adenocarcinomas.[38] Although no esophageal cancer patients were included in this study, these results are applied to advanced esophageal cancer patients due to molecular similarities between gastric adenocarcinoma and EAC, and similar rates of HER2 positivity.[48] Addition of trastuzumab to chemotherapy in the first-line treatment setting significantly improved survival metrics and has now become standard-of-care treatment of HER2-positive patients.

In the second-line treatment setting, targeting the vascular endothelial growth factor (VEGF) signaling pathway has proved clinically efficacious. In particular, ramucirumab, a monoclonal antibody blocking human VEGF receptor 2 (*VEGFR2*) has been shown superior to single-agent chemotherapy in two large phase III clinical trials.[40,41] The first trial, REGARD, showed that monotherapy with ramucirumab was superior to placebo in the second-line setting for gastric or gastroesophageal junction adenocarcinomas.[40] The RAINBOW trial also showed clinical improvements with the addition of ramucirumab to single-agent paclitaxel chemotherapy in the second-line setting for gastric or gastroesophageal junction adenocarcinomas.[41] Again, as discussed previously, these results have been extrapolated to EACs given their similarities to gastric and gastroesophageal junction adenocarcinomas. Unlike trastuzumab, ramucirumab is approved to be used in gastroesophageal adenocarcinoma patient without an *a priori* biomarker test.

Currently, these 2 agents are the only targeted agents approved for advanced gastroesophageal cancers. Multiple other pathways have been examined but have not proved clinically efficacious.[49] Much work remains to not only develop better pathway targeting agents but also elucidate new ways to predict and select patients that most likely would benefit from these treatments. One new agent that recently has gained Food and Drug Administration (FDA) breakthrough therapy

Table 2
Approved targeted therapies for gastroesophageal cancer

Targeted Agent	Mechanism of Action	Biomarker	Clinical Trial	Histology	Line of Therapy	Anatomic Location	Efficacy
Trastuzumab (Herceptin)	Monoclonal antibody against human epidermal growth factor receptor 2 (HER2/ERBB2)	HER2-positive tumors (3+ staining on IHC or FISH positive)	ToGA[38]	Adenocarcinoma	First	Gastroesophageal junction and stomach	Improved survival
Fam-trastuzumab Deruxtecan (Enhertu)	Antibody drug conjugate targeting human epidermal growth factor receptor 2 (HER2/ERBB2)	HER2-positive tumors (3+ staining on IHC or 2+ staining on IHC and FISH positive)	DESTINY-Gastric01[39]	Adenocarcinoma	Third	Gastroesophageal junction and stomach	Improved survival
Ramucirumab (Cyramza)	Monoclonal antibody against human VEGFR2	None	REGARD[40]	Adenocarcinoma	Second	Gastroesophageal junction and stomach	Improved survival
			RAINBOW[41]	Adenocarcinoma	Second	Gastroesophageal junction and stomach	Improved survival

Pembrolizumab (Keytruda)	Monoclonal antibody against PD-1 receptor	PD-L1 positive tumors (CPS 1 or higher)	KEYNOTE-061[42]	Adenocarcinoma (79%), tubular adenocarcinoma (10%), signet ring cell carcinoma (4%)	Third	Gastroesophageal junction and stomach	Did not improve survival in the second-line setting but better adverse event profile compared with paclitaxel monotherapy
		PD-L1 positive tumors (CPS 10 or higher)	KEYNOTE-181[43]	Squamous cell carcinoma and adenocarcinoma	Second (FDA approved only for squamous cell carcinoma histology in the second-line setting)	Esophagus and Siewert type 1 gastroesophageal junction	Improved survival
		MSI-HIGH tumors	KEYNOTE-061[42]	Adenocarcinoma (79%), tubular adenocarcinoma (10%), signet ring cell carcinoma (4%)	Second	Gastroesophageal junction and stomach	Improved survival
			KEYNOTE-158[44]	Any solid tumor	Second	Any solid tumor	Improved survival
		Tumor mutational burden (at least 10 mutations per megabase)	KEYNOTE-158[45]	Any solid tumor	Second	Any solid tumor	Improved survival
Nivolumab (Optivo)	Monoclonal antibody against PD-1 receptor	None	ATTRACTION-3[46]	Squamous cell carcinoma	Second	Esophagus	Improved survival

designation is Fam-trastuzumab deruxtecan, a HER2 antibody-drug conjugate that was shown to have clinical activity in a cohort of heavily pretreated HER2-positive gastric/gastroesophageal junction adenocarcinoma patients.[39] This promising new agent demonstrates the potential of targeted agents to not only improve survival but also incur fewer treatment related toxicities compared with cytotoxic chemotherapies.

Given the chronic injurious nature that spurs formation of gastroesophageal cancers[50,51] (ie, smoking for ESCCs, acid reflux for EACs, and *Helicobacter pylori* infection for gastric adenocarcinomas), it is not surprising that these entities have been found to accumulate somatic mutations.[52] These genomic changes likely result in neoantigens, which ultimately are targeted by the immune system through cancer immunosurveillence.[53] Thus, immunotherapy and specifically targeting programmed death-1 (PD-1) receptor to block immunosuppressing ligands (PD-L1 and PDL-2) have resulted in new approved therapies for gastroesophageal cancer patients. The first agent, pembrolizumab, is approved in the United States to be used in concert with a combined positive score (CPS)[54] designed to preferentially select patients with higher PD-L1 levels and a higher probability of response. Specifically, for gastroesophageal adenocarcinomas, pembrolizumab is approved to be used for CPS score of 1 or higher in the third-line treatment setting based on results from KEYNOTE-061 study[42] showing no significant clinical efficacy for these patients as second-line therapy. Pembrolizumab also is approved to be used after progression on one or more prior treatments (ie, second-line treatment) for ESCCs that expresses high PD-L1 levels (CPS $\geq$10) based on the KEYNOTE-181 study.[43] In addition, pembrolizumab is approved to be used for tumor histology agnostic treatment of any solid tumor with defective mismatch repair (MSI-high) or high tumor mutation burden ($\geq$10 mut/Mb).[42,44,45] A second immunotherapy with a similar mechanism of action, nivolumab, is approved in the United States in the second line to treat ESCCs regardless of PD-L1 levels based on results of the ATTRACTION-3 trial.[46] These immunotherapy treatments have not only provided new safer avenues to treat gastroesophageal cancer patients but also have changed the basic approaches to cancer treatment. Multiple trials have recently completed or are ongoing to investigate the efficacy of these agents as part of combination systemic therapy. The promise of immunotherapy is evidenced by multiple recent FDA approvals. In the metastatic setting, immunotherapy is now approved for use in combination with frontline chemotherapy based on results of the CheckMate 649 [PMID: 34102137], ATTRACTION-4 [PMID: 30566590], and KEYNOTE-590 [PMID: 30735435] trials. In fact, the use of immunotherapy is now also favored in HER-2 positive patients [PMID: 33167735]. Furthermore, in the adjuvant setting after curative intent tri-modality therapy, immunotherapy has been approved based on the CheckMate 577 data [PMID: 33789008].

This article details examples of how understanding the molecular pathology of gastroesophageal cancers can have a direct impact on patient care. The complexity and heterogeneity of all cancers, including gastroesophageal cancers, mandate personalization of oncologic treatment. One-size-fits-all chemotherapy no longer is the ideal treatment of many of these patients. Elucidating the underlying pathogenesis of these diseases has resulted in and will continue to lead to important advancements in cancer diagnosis, prognosis, and individualized treatments.

CLINICS CARE POINTS

- ESCC and EAC are separate entities with differing molecular pathology.
- Gastric adenocarcinomas can be classified into 4 distinct molecular subtypes that may suggest treatments unique to the subtypes.
- EAC and CIN-type gastric adenocarcinoma are driven by a high degree of CIN and high-level amplifications of oncogenes, which leads to significant intratumor heterogeneity. This heterogeneity can lead to the wrong treatment being assigned if not testing the lesion that is wanted to treat.
- Targeted therapy in upper gastroesophageal cancers is an active area of research and is evolving rapidly.

DISCLOSURE

Dr. Stachler: NIH National Institute of Diabetes and Digestive and Kidney Diseases (K08 K08DK109209) and Doris Duke Charitable Foundation. Dr. Jin: NIH National Heart, Lung, and Blood Institute (T32HL007088), and the Barrett's Esophagus Translational Research Network (NCI U54CA163060).

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