Biology is king and continues to rule

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Central Message

The TCGA Oesophageal Study provided concrete evidence of a genomic difference between EAC and squamous cell carcinoma.

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In their Feature Editorial, Lagisetty and colleagues,¹ with many years of expertise in esophageal cancer, concisely outline the clinical implications of the The Cancer Genome Atlas Oesophageal Study. They highlight the mainly nonoverlapping genomic taxonomy and histology in esophagogastric cancers. They note greater genomic similarities between esophageal squamous cell carcinoma and head/neck squamous cell carcinoma and between esophageal adenocarcinoma (EAC) and gastric adenocarcinoma than between the 2 esophageal histologies.² They discuss the landmark Chemoradiotherapy for Oesophageal Cancer Followed by Surgery (CROSS) and Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trials, which enrolled patients on the basis of anatomy with combined histologies. Both trials acknowledged this limitation but used the combination to meet accrual goals.

Lagisetty and colleagues¹ note the importance of histology in trial design histology rather than anatomy for upper gastrointestinal malignancies. Currently, the Perioperative Chemotherapy Compared to Neoadjuvant Chemoradiation in Patients With Adenocarcinoma of the Esophagus (ESOPEC) Trial has begun to probe this issue by limiting enrollment to patients with EAC and gastroesophageal junction adenocarcinoma.³ This multicenter, prospective, randomized trial will compare the efficacy of neoadjuvant chemoradiation and surgery (CROSS protocol) with perioperative chemotherapy (similar to MAGIC) but with 5-fluorouracil, leucovorin, oxaliplatin, docetaxel, which is a gastroesophageal junction cancer regimen reportedly better tolerated than epirubicin, cisplatin, 5-fluorouracil.⁴

Histologic classifications are increasingly subdivided into molecular classifications. In the TCGA gastric adenocarcinoma project, gastric cancers were divided into 4 subtypes: Epstein-Barr virus positive, microsatellite unstable, genomically stable, and chromosomal instability.⁵ Other subtypes behave as isolated entities secondary to germline alterations. For example, patients with CHD1 germline mutations present with early-onset, diffuse, and aggressive gastric adenocarcinoma.⁶ These patients often are managed

by prophylactic gastrectomy. EAC resembled the chromosomal unstable variant of gastric adenocarcinoma. One weakness of the TCGA Study was the lack of commentary on such germline variants within their cohort. In addition, despite the strong parallel between histology and genomic profile, genetic alterations existed on a craniocaudal spectrum and unique genomic subsets existed within each histology.

Although histologic stratification in therapeutic studies is an appropriate starting point, genomic testing will become important to direct future personalized treatment algorithms ruled by both somatic and germline cancer biology. Given that molecular characterization and targeted therapies are evolving so rapidly, trials with traditional end points such as overall survival or disease-free survival that take years to complete may be too slow to keep pace with these developments. In contrast, neoadjuvant trials with pathologic complete response as the primary outcome and as a surrogate for long-term outcomes may be a more appropriate design for this rapidly changing landscape. But as we already know, biology remains the king, and we are unable to usurp the throne.

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