

16.1. Esophagus and Esophagogastric Junction: Squamous Cell Carcinoma

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Emerging Prognostic Factors for Clinical Care

There is significant controversy regarding where the esophagus ends and the stomach begins. Cardialization of the esophagus due to metaplasia and effacement of the esophagus is a theory forwarded to describe the rapid increase in EGJ cancers related to reflux.¹ The designation of Siewert type II/III tumors encompassing the distal esophagus and proximal 5 cm of the stomach (cardia) is an area of contention for staging.² Cancers arising in this segment have been staged variably as esophageal or gastric tumors, often depending on the treating physician. In this edition, as a compromise to the treatment algorithms surrounding stomach cancers, which differ substantially from esophageal protocols, and to maintain harmony with an international delegation of gastric surgeons treating lower EGJ cancers, tumors of the cardia with an epicenter greater than 2 cm from the EGJ will be staged using the stomach cancer staging system (see Chapter 17). It is well recognized that the prognosis of all EGJ tumors depends on cancer categories (T, N, M, G) and not on EGJ location or Siewert type.³ It is our hope that data from major genomic studies eventually will be integrated into the staging system and remove the need to assign either esophageal or stomach cancer staging based solely on an assessment of tumor epicenter in relation to the distal end of the EGJ .

Presently, there are no validated biomarkers (in blood or somatic tumor specimens) that are part of the staging system. Although FDG PET/CT is part of the clinical evaluation for extent of disease, and is being studied as a measure of response to treatment, the intensity of FDG avidity (measured as subtraction uptake value) has not yet been validated as a surrogate for outcome so as to affect the staging system.

Data are emerging from extensive genomic analyses of squamous cell carcinoma and adenocarcinoma of the esophagus. It is anticipated that these data will be developed and that molecular analysis to evaluate specific somatic genomic alterations and expression of distinct genes will increasingly guide therapy for esophageal cancer, especially in relation to the use of emerging biologic or targeted therapies. Several studies documented that esophageal adenocarcinoma versus squamous cell carcinoma have distinct patterns of recurrent somatic alterations.^{4,5} Although there currently are no targeted therapies used routinely in esophageal squamous cell carcinoma, there are recurrent genomic alterations at the loci of potentially targetable oncogenes, including amplification of genes encoding cyclin D1 and epidermal growth factor receptor and mutations of the gene encoding key PI3-kinase subunits.⁶ Additional recurrent alterations, such as frequent amplification of chromosome 3q, are

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shared across squamous cell cancers of multiple histologies,⁷ demonstrating molecular features that link tumors of this histologic type.

Recurrent somatic alterations in esophageal adenocarcinoma resemble many of the features described for gastric adenocarcinoma,⁸ as they share similar patterns of structural genomic alterations. These structural alterations frequently lead to massive amplification of genes encoding key growth-promoting proteins, many of which may be targeted by existing or emerging therapeutics. Among these, metastatic esophageal adenocarcinoma patients with amplification of the gene encoding receptor tyrosine kinase ERBB2 (HER2) are commonly treated with a combination of the therapeutic antibody trastuzumab and cytotoxic therapy, based on results from the ToGa (Trastuzumab for Gastric Cancer) trial in gastric/gastroesophageal junction cancer.⁹ At this time, evaluation for ERBB2 amplification in metastatic esophageal adenocarcinoma is the only standard genomic assay in the care of esophageal cancer. Beyond ERBB2, there are frequent amplifications at the loci of other receptor tyrosine kinases and cell cycle mediators,^{8,10} which may become targets for future therapies. AJCC Level of Evidence: III

Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.¹¹ Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

Recommendations for Clinical Trial Stratification

Clinical trials should either stratify cancers by histology (squamous cell cancer vs. adenocarcinomas) or be limited to either squamous cell cancer or to adenocarcinoma of the esophagus. Epidemiologic and genomic data currently available strongly support the idea that squamous cell cancers and adenocarcinomas of the esophagus are totally different cancers arising in the same organ. Trials including patients of intermediate stage (lymph node negative vs. lymph node positive) should be powered to allow analysis of outcome by stage.

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