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Guest Editorial

Crescendos and Decrescendos: Gastric and Esophageal Cancers

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Jaffer A. Ajani, MD, an internationally recognized expert on gastrointestinal cancers, is Professor of Gastrointestinal Medical Oncology at MD Anderson Cancer Center and Chair of the NCCN Clinical Practice Guidelines in Oncology for Esophageal and Gastric Cancers. He has participated over the past 20 years in numerous trials using innovative combined modality therapies for localized gastric and esophageal cancers, and some of his work has led to the development of strategies of preoperative therapy for resectable upper gastrointestinal cancers.

His current research focus is on developing programs to research the molecular markers for progression of Barrett's metaplasia to adenocarcinoma. These research efforts involve multi-institutional collaboration with investigators at the University of Chicago, University of Pennsylvania, Mayo Clinic, and Yonsei University, in Seoul, Korea.

In addition to his work with NCCN, Dr. Ajani participates actively in the International Society of Gastrointestinal Oncology is the editor of the Society's journal, *Gastrointestinal Oncology Research*.

The worldwide burden of gastric and esophageal cancers is bewildering,[1] and yet the progress against these cancers has been noticeably slow. We are witnessing an alarming increase in the incidence of adenocarcinoma of the proximal stomach, gastroesophageal junction, and lower esophagus in the West.[2] Although the exact reasons for the increase in the incidence of adenocarcinoma remain elusive, its association with high body mass index (BMI), gastroesophageal reflux disease (GERD), and Barrett's metaplasia is inescapable.[3–5] BMI has disturbingly doubled in all societies around the globe in the past decades.[6] Visceral adipose tissue (VAT) is known to elaborate adiponectin, leptin, and many other cytokines,[7,8] and these contribute to the inflammatory milieu in which Barrett's esophagus arises and consequently progresses to adenocarcinoma in some patients. VAT has been linked directly to an increased risk of GERD and gastroesophageal adenocarcinoma.[9–12]

Although prognosis of patients with these cancers has improved over time,[13] the extent of progress remains very unsatisfactory. Most patients and their relatives are deeply devastated to learn that the chance of cure is so slim despite our claims of how modern our multidisciplinary approaches are and all other sophistications we proudly portray in our institutions. It is disappointing that once we group patients by the baseline clinical cancer stage, we treat each patient, with similar stage of the cancer, alike because we have not invested enough resources to learn how to customize therapy. The empiric strategy seems reasonable for early cancers, in which inherent tumor heterogeneity is understandably low. For example, we can anticipate predictably high survival rates from a uniform but appropriate therapy of patients with stage I cancer. It is when cancer is in stage II or higher that the outcomes are uncertain and often frustrating for everyone involved.

Not all efforts in the past decade have been futile; some areas of progress have been reported. In the realm of identifying subsets of patients with gastric cancer, the biomarker *ERBB2* has emerged as useful. A pivotal study in which 3803 patients were screened for the overexpression of the *ERBB2* protein and 594 patients were randomized to a combination of cytotoxic agents plus trastuzumab or placebo, the overall survival of patients who received trastuzumab was significantly longer than those who received placebo.[14] However, the benefit was limited to patients whose tumors expressed high levels (3+ or 2+ when fluorescence in situ hybridization showed increased copy number of the *ERBB2* gene) of *ERBB2* protein by immunohistochemistry. The *ERBB2* biology in gastroesophageal cancer seems to differ considerably from its biology in breast cancer. It will be important to explore the role of trastuzumab in the adjuvant setting, and also to address the *ERBB2*-overexpressing cancers that become refractory to trastuzumab. Two randomized phase III trials are investigating lapatinib in this patient population, and more drugs are in the queue.

For patients with localized esophageal cancer, we can point to what appears to be level 1 evidence from a long-debated strategy of preoperative chemoradiation therapy. In a Dutch trial[15] that randomly assigned 363 patients to receive either chemoradiation (paclitaxel plus carboplatin with 40 Gy of radiation) and surgery (n = 175) or surgery alone (n = 188), patients who received preoperative chemoradiation had significantly longer overall survival. The combined modality therapy was well tolerated. The benefit to patients with squamous cell carcinoma was considerable (hazard ratio [HR], 0.34; 95% CI, 0.17–0.68), whereas it was borderline to none in patients with adenocarcinoma (HR, 0.82; 95% CI, 0.58–1.16). Detailed results have not yet been published.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.

One major decrescendo is the seventh AJCC staging classification (7th edition) of esophageal cancer.[16] The new gastric cancer classification has a few deficiencies, but the esophageal cancer classification is plagued with problems. First, the classification is based on patients treated with primary surgery in various regions of the world (also meaning an uneven quality of surgery). Second, the survival does not seem to be esophageal cancer–specific. For example, it is difficult to explain a greater than 40% rate of death from stage 0 squamous cell carcinoma and an approximately 25% rate of death from stage 0 adenocarcinoma. Third, the proximal 5 cm of the stomach is included in the esophageal classification, but the therapeutic approach for esophageal cancer and gastric cancer are diverse, and these 2 entities are often treated by different multidisciplinary groups. Fourth, classification based on surgical stage cannot be effectively applied to baseline clinical stage or stage determined after preoperative therapy. Fifth, size of the nodes is not addressed. And finally, among others, the numeric nodal classification is less helpful in practice because it does not discriminate important implications of the anatomic locations of the nodes (e.g., the current classification does not discriminate the clinical importance of paraesophageal nodes from others, such as para-aortic nodes, supraclavicular nodes, retroperitoneal, or nodes both above and below the diaphragm; it simply counts nodes). The new classification provides limited guidance in establishing a therapeutic strategy compared with the old classification. An early revision of this classification would be very helpful.

Finally, we are witnessing a crescendo in esophageal-preserving endoscopic approaches to Barrett's esophagus with high-grade dysplasia, Tis, and T1a carcinoma.

Many areas remain unresolved, including 1) optimum therapy of gastroesophageal junction cancer (preoperative chemotherapy vs. preoperative chemoradiation), 2) clinical T2N0M0 cancers (surgery alone or multimodality therapy), 3) therapeutic approach by histology (squamous cell carcinoma vs. adenocarcinoa), 4) therapeutic approach by location in the thorax (low vs. high in the thorax), 5) endoscopic eradication of Barrett's metaplasia and/or low-grade dysplasia, and 6) treatment of Barrett's high-grade dysplasia after definitive chemoradiation. In this issue of *JNCCN*, many experts provide their considerable insight into these and other aspects of gastroesophageal cancer and its premalignant condition. The hope is that readers will find these discussions useful and, ultimately, that patients will be the beneficiaries of this new-found knowledge.

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