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## **Is Radiation Therapy Needed in the Treatment of Gastroesophageal Junction Adenocarcinoma?**

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There is much confusion in the management of the spectrum of diseases that include esophageal cancer (both squamous and adenocarcinomas), gastroesophageal (GE) cancer, and gastric cancer. Unfortunately, GE junction adenocarcinomas are often lumped in therapeutic trials and analyses with either esophageal cancer or gastric cancer, for the simple reason that the incidence of both of the “classic” pure esophageal and gastric tumors is decreasing, while the incidence of GE junction tumors is increasing rapidly.

If one tries to determine whether GE junction cancers are the same as either gastric cancer or squamous cell cancer of the esophagus, the answer appears to be that they are not the same. The epidemiology of these three diseases is dramatically different. Esophageal squamous cancer is a disease of smokers and drinkers and is decreasing in incidence. Gastric cancer, the most common cancer in the United States a century ago, is now an unusual disease. It is strongly associated with *Helicobacter pylori* infection and decreased acid production. GE junction cancers share none of these attributes. It is rapidly increasing in incidence, and is associated with high acid production and Barrett’s changes in the esophagus. It is more similar to gastric cardia disease than the classic carcinomas of the esophagus or stomach.

The data for esophageal cancer do not strongly support the need for any one treatment modality: Surgery is roughly equivalent in outcome to combined radiation therapy and chemotherapy, and trimodality therapy may be somewhat superior to either surgery alone or radiochemotherapy alone, but not decisively so. Therefore, for tumors that have been treated in esophageal cancer studies, a reasonable question is whether there are data showing that any single modality is essential in patient management. It is important to realize that most of the recent esophageal cancer trials have included a strong majority of patients with GE junction cancers. Thus, data from these studies may be the most relevant to the outcome of a pure population of GE junction cancers.

Data supporting the use of adjuvant chemotherapy for gastric cancer hinges heavily on results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, reported by Cunningham et al in the *New England Journal of Medicine* in 2006. A substantial survival advantage was demonstrated in patients who received neoadjuvant ECF (epirubicin, cisplatin, 5-fluorouracil) chemotherapy. However, 75% of the patients had pure gastric cancer, 11% had GE junction tumors, and 14% had lower esophageal cancers. The authors' analysis did not demonstrate any obvious effect of tumor location on outcome, but the small patient numbers in some subsets (ie, 58 patients on both arms with GE junction cancers), raises the question of whether we really know the value of neoadjuvant ECF in patients with GE junction adenocarcinomas.

The role of radiation therapy is no better defined – but also no worse defined – than the role of chemotherapy. The Macdonald trial testing radiation therapy and chemotherapy as an adjuvant to surgical management of gastric cancer demonstrated a survival difference with trimodality therapy, similar in magnitude to that obtained with the addition of ECF alone. It is also clear from a number of trials that the incidence of local-regional failure is substantial in patients with esophageal and gastric cancers, and that radiation therapy can decrease the local-regional recurrence rate. Given that many believe that the chemotherapeutic intervention in the Macdonald trial was not likely to be effective by itself, and that the advantage in relapse was primarily related to fewer local-regional failures, there is a strong suggestion that the addition of radiation was the primary reason for the improved survival in the Macdonald trial. Thus, a reasonable

postulate is that the combination of radiation therapy plus improved chemotherapy, as is being studied in the present US GI Intergroup trial, may produce the best outcomes.

At present, we do not know how best to combine the various interventions in GE junction cancers. We are severely hampered by a lack of trials that have tested chemotherapy or radiation therapy in a well-defined population. We cannot treat heterogeneous groups of patients and pretend that we have defined the best, or even a good, management strategy. There is little question that current outcomes are still poor, regardless of which regimens are employed.