

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

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## ABSTRACT

There have been very few treatment-related studies specifically addressing adenocarcinomas of the gastroesophageal junction (GEJ). Studies addressing esophageal cancer have a larger percentage of patients with GEJ adenocarcinomas than do the primary gastric trials. Studies of surgery alone have shown high local failure rates for both esophageal and gastric cancers, and for both anatomic sites the addition of radiation therapy has been shown to decrease the local failure rate and improve survival. Chemotherapy as an adjuvant to surgery has also been shown to be of value in both anatomic sites. Combining all three treatment modalities, surgery, radiation therapy, and chemotherapy, is likely to produce the best overall outcomes for patients with this disease, which is rapidly increasing in incidence.

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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 cancer, and gastric cancer. Unfortunately, gastroesophageal junction (GEJ) 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 GEJ tumors is increasing rapidly.

If one tries to determine whether GEJ 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 epidemiology of these three diseases is dramatically different. Esophageal squamous cancer is a disease of smokers and drinkers and is decreasing in incidence. It is now a relatively rare disease. Esophageal cancer located high in the esophagus often requires a surgical resection of the larynx for appropriate management, so that patients with these high tumors are generally treated with radiation therapy and chemotherapy alone. Interestingly, the high esophageal cancers are usually treated with a substantially lower dose of radiation therapy than a pharyngeal wall tumor located only a few centime-

ters away and arising from similar mucosa.

Gastric cancer, the most common cancer in the United States a century ago, is now a relatively unusual disease. It is strongly associated with *Helicobacter pylori* infection, associated atrophic gastritis, and decreased acid production. GEJ cancers share none of these attributes. It is a disease of rapidly increasing incidence, and is associated with high acid production and Barrett’s changes in the esophagus. If anything, it is associated with a decreased incidence of *Helicobacter pylori* (as that decreases acid production). Patients with GEJ tumors tend to be obese and have a higher incidence of gastric reflux than the general population. The high rate of associated alcohol use and smoking in esophageal cancer is not seen in GEJ tumors. GEJ cancers are more similar to gastric cardia tumors than the classic carcinomas of the esophagus or stomach. Gastric cardia tumors are also increasing in incidence, although not as dramatically as GEJ cancers, and perhaps these two diseases should be lumped together.

## MANAGEMENT OF GEJ CANCERS: DERIVING DATA FROM ESOPHAGEAL AND GASTRIC CANCER STUDIES

In deciding the proper management of GEJ

cancers, clinical trials are needed that focus on this particular group of tumors. It is not clear that we can extrapolate from data derived from patients treated with classic gastric or esophageal cancers in determining the appropriate treatment for GEJ cancers. Most of the clinical trials of gastric cancer include about 20% to 25% of patients who have tumors of the GEJ or of the gastric cardia, and therefore, there is little reason to think that these data are especially relevant to GEJ cancers. In contrast, more recent trials of esophageal cancer in the United States and Europe have included a strong majority of patients with GEJ cancers (approximately 75% in the US studies), and therefore, may be more relevant to the question of how GEJ cancers should be treated. To make sense of the data, we should evaluate the results from studies of both gastric and esophageal cancers.

## Studies in Esophageal Cancer Patient Populations

Data from studies of esophageal cancer do

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not strongly support the need for any single treatment modality. Overall, it appears that each of the three primary treatment modalities adds to tumor control, although no single modality is unequivocally necessary. Radiation therapy combined with chemotherapy is clearly superior to radiation therapy alone, as shown by the Radiation Therapy Oncology Group (RTOG) trial that randomized patients to these two approaches.<sup>1</sup> Unfortunately, even though combined modality therapy was of value, local recurrence rates were quite high, in the range of 50% with nonsurgical therapy. These local recurrences tend to be symptomatic and have a major impact on quality of life. Surgery is roughly equivalent in survival outcome to combined radiation therapy and chemotherapy, especially for patients with squamous cell carcinomas.<sup>2,3</sup>

The effectiveness of preoperative radiation therapy and concurrent chemotherapy compared with surgery alone has been evaluated in multiple clinical trials, with most of them showing no clear advantage to trimodality therapy. A number of meta-analyses have been performed to evaluate this question in more detail, most recently by GebSKI et al.<sup>4</sup> They analyzed 10 studies of trimodality therapy vs. surgery alone, including 1,209 patients, and found that the hazard ratio for all-cause survival favored trimodality therapy with a value of 0.81 ( $P=.002$ ). What is of interest is that virtually all 10 studies demonstrated some advantage to trimodality therapy, even if the differences were small for many of the trials. They also analyzed 8 studies of neoadjuvant chemotherapy vs. surgery alone that included 1,724 patients. The hazard ratio for all-cause survival with neoadjuvant chemotherapy was 0.9 ( $P=.05$ ), with a larger effect seen for adenocarcinomas than squamous cell tumors. There was a greater spread in the results from individual studies for neoadjuvant chemotherapy, and several of the studies demonstrated poorer survival for neoadjuvant therapy compared with surgery alone. The large US GI Intergroup trial by Kelsen et al showed virtually identical outcomes with the use of preoperative and postoperative chemotherapy (5-FU and cisplatin) compared with surgery alone.<sup>5</sup>

Another important issue is the rate of local failure with various therapeutic

approaches. Even if local recurrence did not translate into decreased tumor control and survival, it still produces substantial morbidity and decreases quality of life for the patient. The data overall suggest that local-regional recurrence occurs in approximately 50% of patients with primary radiation therapy and surgery, 35% with primary surgical resection, and 15% with trimodality therapy.<sup>1,3,5</sup> Thus, there appears to be an advantage for the use of trimodality therapy on this basis, even if survival were not different.

### Studies in Gastric Cancer Populations

The information related to gastric cancer is distinctly different from that for esophageal cancer. First, surgery is clearly essential in the management of gastric tumors. Cures without surgical resection are anecdotal. The limited normal tissue tolerance of the stomach to irradiation prevents high-dose radiation therapy from being used, and chemotherapy alone is not truly curative. Typically, radiation doses of approximately 5,000 cGy are thought to represent the maximum that can be delivered to large volumes of the stomach.

Multiple clinical trials have evaluated adjuvant chemotherapy, with older meta-analyses demonstrating only a small advantage with this approach. The present data supporting the use of adjuvant chemotherapy for gastric cancer hinge 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.<sup>6</sup> A substantial survival advantage was demonstrated in patients who received neoadjuvant and postoperative ECF (epirubicin 50 mg/m<sup>2</sup>, day 1; cisplatin 60 mg/m<sup>2</sup>, day 1; 5-fluorouracil [5-FU] 200 mg/m<sup>2</sup>, days 1–21) chemotherapy. However, 75% of these patients had pure gastric cancer, 11% had GEJ 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 GEJ cancers) raises the question of whether we really know the value of neoadjuvant ECF in patients with GEJ adenocarcinomas. Although ECF provided some improvement

in local control, local-regional recurrence remained a problem. Most investigators have taken these data as strong support for the role of chemotherapy added to surgery in the management of gastric cancer, but have not necessarily accepted that neoadjuvant therapy is superior to other delivery schedules.

The role of radiation therapy is no better defined—but also no worse defined—than the role of chemotherapy for gastric cancers. A number of studies have evaluated recurrence patterns in patients undergoing surgery alone: the most recent large study, conducted by D'Angelica et al at Memorial Sloan-Kettering Cancer Center, showed that 55% of patients with tumor recurrence had a local recurrence as a portion of their failure pattern and approximately 25% had local-regional failure alone.<sup>7</sup> The sites of failure were primarily in regional lymph nodes, at anastomotic sites, and in the gastric bed. Similar numbers of patients had local-regional failure as had distant failure. These results demonstrate that even with contemporary surgical approaches at an institution known for aggressive surgical management, local recurrence remains a problem—and a problem not likely to be corrected by present-day chemotherapy. Initial studies evaluating postoperative radiation therapy typically showed no survival advantage compared with surgery alone, although perhaps, some advantage in terms of local control.<sup>8</sup> Very few trials tested the combination of radiation therapy and chemotherapy delivered postoperatively, although there has been a suggestion of benefit from the combination.<sup>9</sup>

The primary trial testing radiation therapy and chemotherapy as an adjuvant to surgical management of gastric cancer was run by the Southwest Oncology Group and the GI Intergroup (SWOG 9008/INT-0116) and demonstrated a survival benefit with trimodality therapy.<sup>10</sup> Patients had standard surgical resection followed by 5-FU and leucovorin before, during, and after radiation therapy. The survival difference obtained with trimodality therapy vs. surgery alone was similar in magnitude to that obtained with the addition of ECF alone in the MAGIC trial. Many believe that the chemotherapeutic intervention of 5-FU and leucovorin in the SWOG trial was not likely to be effective by itself.

Concern has been raised because of the difficulty in delivering appropriate radiation fields (a large problem with quality control in INT-0116), likely because gastric radiation therapy has not been commonly used, and therefore not commonly taught, during residency programs. Better guidelines have been promulgated to help correct this problem. An analysis of patterns of failure in this study showed that the advantage in relapse with trimodality therapy was primarily related to fewer local-regional failures, without any substantial change in distant metastases. This strongly suggests that the addition of radiation and the improvement in local control was the primary reason for the improved survival in the SWOG study.

This result is not surprising. It is clear from a number of trials that the incidence of local-regional failure is substantial in patients with gastric cancers, and that radiation therapy can decrease the local-regional recurrence rate.<sup>8,9</sup> Thus, a reasonable postulate is that the combination of radiation therapy plus improved chemotherapy, as is being studied in an ongoing US GI Intergroup trial, may produce the best outcomes.

The SWOG trial has been heavily criticized because most of the patients had operations that would be considered inadequate by good surgical oncologists. There is substantial interest in the use of D2 dissections, which is essentially resection of the second echelon of lymph nodes along with the primary site, a technique popularized by the Japanese. However, the data do not support the necessity of D2 dissections for most patients. Two randomized trials conducted in Europe, one by the Medical Research Council and one by a Dutch group, both randomized patients to undergo D1 or D2 dissection<sup>11,12</sup>; neither study demonstrated an advantage for D2 dissection in terms of tumor control or survival. Thus, because no advantage of D2 resection has been shown in randomized trials, it is difficult to argue that the reason radiation therapy was of value in the SWOG trial was because D2 surgery was not performed.

A second criticism is that overall survival results with surgery alone in the European studies were similar to those in the adjuvant group in the SWOG study. However, in the SWOG trial, patients had

more advanced stages of disease and more patients had nodal involvement than those in the European studies. This occurred despite the fact that the European patients had more lymph nodes removed (so one would expect to find more nodal positivity) and had improved pathologic evaluation (which would also tend to produce higher, not lower, stage disease). Finally, the 5-year survival rates in the treated arms are similar between the ECF neoadjuvant trial and the SWOG trial, suggesting that US patients were not doing more poorly than would be expected.

### CURRENT APPROACHES AND FUTURE PERSPECTIVES FOR GEJ CANCERS

At present, we do not know how best to combine the various interventions in the treatment of GEJ cancers. We are severely hampered by a lack of trials that have tested chemotherapy or radiation therapy in a well-defined population. Based on the gastric cancer trials, ECF or combined radiation therapy and chemotherapy with surgery improve survival. However, a demonstrated value of adjuvant chemotherapy in no way diminishes the value of radiation therapy in improving local-regional control and long-term outcome, including survival. Based on the gastric cancer data, one would consider the use of both ECF and radiation therapy. This regimen is, in fact, currently being tested in a GI Intergroup trial being run by the Cancer and Leukemia Group B (CALGB): patients in one arm are receiving the treatment administered in the trimodality arm of the SWOG study, and those in the other arm are receiving ECF before and after radiation therapy with concurrent continuous infusion 5-FU during radiotherapy. All patients are being treated in the postoperative setting.

If one were to design an appropriate regimen based on the esophageal cancer studies (which, as mentioned, included large numbers of patients with GEJ cancers), one would also postulate that both radiation therapy and chemotherapy have a role in disease management. Local recurrence rates are decreased and survival is increased with this strategy. In contrast to the gastric cancer approach, the esophageal cancer studies have primarily used preoperative therapy.

A major problem is that minimal data are available that truly focus on the management of GEJ adenocarcinomas. Both esophageal and gastric cancer trials included both the "classic" tumors of those sites as well as GEJ cancers, so the results are muddled. 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.

What is a reasonable strategy for the future? First, patients should be entered on trials specifically designed for GEJ cancers, which could include cardia tumors as well as pure GEJ adenocarcinomas most commonly associated with Barrett's esophagus. They should not be lumped with the classic gastric cancers or with squamous carcinomas of the esophagus. Second, given the esophageal cancer results, an emphasis should be placed on neoadjuvant therapy with careful attention being paid to both local-regional control and long-term survival. A careful analysis of recurrence patterns is extremely helpful in understanding the manner in which our present therapies are inadequate and will help us define new approaches more likely to be successful.

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### Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.