Mature Results from a Phase II Trial of Postoperative Concurrent Chemoradiotherapy for Poor Prognosis Cancer of the Esophagus and Gastroesophageal Junction

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Introduction: Mature results are presented from a phase II trial of postoperative concurrent chemoradiotherapy in patients with poor-prognosis cancer of the esophagus and gastroesophageal junction after primary surgical resection.

Methods: Resected patients with a pathologic stage of T3, N1, or M1a were eligible for this trial. Concurrent chemoradiotherapy was begun between 6 and 10 weeks after surgery and consisted of radiotherapy (1.8 Gy/d to a planned dose of 50.4–59.4 Gy), concurrent with two cycles of 5-fluorouracil (1000 mg/m^2/d) and cisplatin (20 mg/m^2/d), both given as 4-day continuous intravenous infusions during the first and fourth weeks of the radiation.

Results: Between 1995 and 2006, 50 patients were enrolled. The median age was 59 (range, 33–76) years, and most patients were male (86%), Caucasian (96%), and had undergone a transthoracic esophagogastrectomy (74%) for what proved to be a node positive (86%) adenocarcinoma (86%). Postoperative concurrent chemoradiotherapy was accompanied by neutropenia requiring hospitalization for fever in only four patients (8%) and no toxic deaths. With a median follow-up of 47 (range, 36–124) months, the Kaplan-Meier 4-year projected overall survival is 51%, freedom from recurrence 50%, distant metastatic control 56%, and locoregional control 86%. An earlier pathologic stage was the only predictor for a better outcome.

Conclusions: This schedule of postoperative concurrent chemoradiotherapy has acceptable toxicity for patients with poor-prognosis esophageal and gastroesophageal junction cancer after surgery. Outcomes are better than historical results after surgery alone and justify further investigation of this approach.

Key Words: Esophageal cancer, Gastroesophageal junction cancer, Chemoradiotherapy, Adjuvant therapy.

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Despite recent advances in our understanding and treatment, esophageal cancer continues to have a very poor overall prognosis.[1,2] Patients with this malignancy typically present late in their disease course, often with locoregionally advanced or distant metastatic involvement. As for most solid tumors, the single most important prognostic factor for survival has been the pathologic disease stage at diagnosis. Patients presenting with early carcinoma in situ or with T1 primary legions, with no nodal or distant metastatic involvement, have an excellent prognosis after surgical resection alone. However, those patients with metastatic disease at the time of presentation are considered incurable and are treated with palliative intent.[1–4]

Intermediate in prognosis between these two extremes are the patients with locally advanced (T2-4) or regional (N1, M1a) disease. Despite having technically resectable tumors, their prognosis is guarded after single modality surgery alone. Patients with T3 N0 disease, for example, have a 5-year survival below 30%, whereas those with nodal involvement, irrespective of the extent of their primary tumor, have an expected 5-year survival below 15%.[2,4,5] These are patients for whom the use of multimodality surgical adjuvant treatment seems most attractive.

Over the last two decades, such multimodality combinations of treatments have been extensively tested. Randomized phase III trials have explored induction chemotherapy followed by surgical resection,[6–9] induction concurrent chemoradiotherapy followed by surgical resection,[10–13] definitive concurrent chemoradiotherapy alone without surgery,[14–17] and adjuvant postoperative chemotherapy[18] or concurrent chemoradiotherapy.[19] Despite intensive investigation, the results have been mixed, and a true consensus defining the optimal approach has not emerged. Evidence has been generated supporting each of these treatment schedules, and the choice of a multimodality approach often reflects institutional preference or expertise, coupled with the specifics of individual patient staging and characteristics.

Complicating these treatment choices has been the recognized limitations of clinical staging. Endoscopic ultrasound, computerized tomography (CT), and positron emission tomography (PET) have been frequently performed in an attempt to accurately assign a clinical stage and define the

optimal treatment. Even when maximally used, the clinical stage is inaccurate in 20% or more of patients.[2,4,20] Indeed, most clinical trials testing multimodality approaches have failed to uniformly employ even these limited clinical staging tools.

At the Cleveland Clinic, our approach has included comprehensive pretreatment clinical staging in an effort to optimally define the overall treatment approach. Those patients with T1-2 N0 M0 disease proceed to surgical resection. Patients with T3-4, N1, or M1a tumors have, in general, been treated on one of a series of investigational protocols testing induction concurrent chemoradiotherapy followed by surgical resection.[21–24] Patients with M1b tumors are treated with palliative intent. Despite this algorithm, there remain patients with locoregionally advanced disease who first undergo surgical resection without induction therapy.[25] Many are clinically staged T1-2 N0 patients with unsuspected T3-4, N1, or M1a disease found at surgery. Other patients present with more advanced, but still technically resectable cancers and a strong preference for initial resection, or a compelling indication for early surgical intervention such as continued bleeding or perforation. The optimal treatment approach for such a patient after surgery is ill defined. Although similar patients with gastric (and gastroesophageal junction [GEJ]) cancers have a demonstrated benefit after postoperative chemoradiotherapy,[19] only limited data have been generated for the esophageal cancer patient.[26–28]

In an effort to address this relatively infrequent scenario, in 1995 we began a prospective phase II trial of postoperative concurrent chemoradiotherapy for patients with T3-4, N1, or M1a disease after surgery. We reported on 31 patients in 2003.[29] This report updates these initial results and adds data from 19 additional patients.

PATIENTS AND METHODS

Patients were eligible for this trial if, after undergoing primary surgical resection with curative intent for an esophageal or GEJ adenocarcinoma or squamous cell carcinoma, pathologic staging revealed T3-4, N1, or M1a disease. Eligible surgical procedures included either a transthoracic or transhiatal esophagogastrectomy or a total gastrectomy with Roux-en-Y esophagojejunostomy. An R0 or R1 resection was required. An extensive lymphadenectomy was routinely performed in all patients except in those undergoing transhiatal surgery. Surgery was performed at the Cleveland Clinic in all but two cases.

All patients required an Eastern Cooperative Oncology Group performance status of 0–1 and could not be entered on this study if they had received any previous systemic chemotherapy or radiation therapy for any other malignancy. Preexisting liver, kidney, or hematologic dysfunction also excluded patients from study entry.

Either before surgical resection or before entry on trial (or both), all patients underwent a full staging evaluation to exclude the possibility of distant metastases. A full medical history, physical examination, complete blood count, and serum chemistries including blood urea nitrogen, creatinine, calcium, phosphorus, alkaline phosphatase, aspartate aminotransferase, lactic dehydrogenase, albumin, total protein, bilirubin, and uric acid were performed before initiation of chemoradiotherapy. Fluorodeoxyglucose PET scanning was not obtained routinely before 2001 when it became readily available at our institution. However, all patients underwent presurgical CT, and esophagogastroduodenoscopy, with endoscopic ultrasound (in the 48 patients undergoing surgery at the Cleveland Clinic) to define their clinical stage. Staging definitions were based on the American Joint Committee on Cancer staging manual being used at the time of original diagnosis.[30] For esophagus cancer, these definitions have changed little over this time period (editions 4–6).

The study was approved and reviewed yearly by the Cleveland Clinic Foundation Institutional Review Board and written informed consent was obtained from all patients before beginning the treatment.

Between 6 and 10 weeks after surgery, concurrent chemoradiotherapy was begun. Figure 1 details the treatment schema. Radiotherapy (1.8 Gy/d to a dose of 50.4–59.4 Gy) was administered concurrent with two cycles of 5-fluorouracil (1000 mg/m^2/d) and cisplatin (20 mg/m^2/d) both given as 4-day continuous intravenous infusions during the first and fourth weeks of the radiation therapy. Chemotherapy administration required hospitalization for appropriate hydration and antiemetic therapy. Peripheral venous access was used for the 5-fluorouracil administration.

Radiation therapy was delivered on linear accelerators using ≥6-MV photon beams. Either a two-dimensional (2DP) or a three-dimensional treatment (3DP) planning approach was used for delivery of therapy based on the preference of the treating radiation oncologist. Radiation treatment planning was performed using Plato Sunrise 2.6.3 (Nucletron, Veenendaal, The Netherlands) or Pinnacle versions 6.2–7.6 (Phillips, Amsterdam, The Netherlands). 2DP and 3DP field borders were based on pretreatment investigations and imaging, correlated with the patient's postoperative anatomy. In 2D, bony landmarks helped define tumor and nodal regions at risk and fluoroscopy localized the anastomosis. Fixed 5 cm craniocaudal, and 2 to 2.5 cm radial, margins were then set to map out tumor limits to set the field borders. 2DP dosimetry was generated at the central axis of the fields, the center of the field, and at planes 1.0 to 1.5 cm inside the superior and inferior margins of the treatment volume to ensure dose uniformity. 3DP involved target volume delineation using soft tissue anatomy as defined by axial CT slices. Presurgical images (CT, PET) were fused to planning CT simulation images. Involved esophagus and lymph nodes with American Joint Committee on Cancer-defined regional nodes at risk were included in the postoperative clinical target volume.

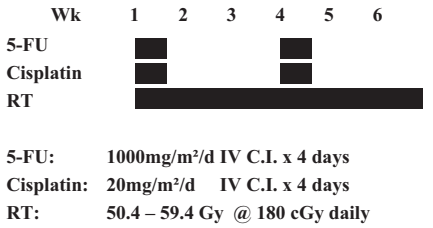

FIGURE 1. Treatment schema.

Normal structures were contoured for each case. 3DP dose was designed to provide coverage of the target accounting for daily variations (planning target volume), and prescriptions were never to less than the 95% isodose line. Dose-volume histograms were used to verify that radiation plans optimized target coverage and normal tissue sparing. Dose-volume histograms were *de facto* not obtainable with 2DP. Representative treatment fields used in a patient with M1a disease and close surgical margins are portrayed in Figures 2*A*, *B*.

Patients were seen at least weekly during their postoperative chemoradiotherapy to monitor and treat side effects, particularly esophagitis and myelosupression. Hospitalization with antibiotic therapy was required for neutropenia if associated with fever. Hospitalization was also required if mucositis or dysphagia precluded an adequate oral intake; however, most patients had a feeding jejunostomy tube placed at the time of their surgery and could be alimented adequately without the need for intravenous support or hospitalization.

After the completion of all treatment, patients were evaluated every 3 months for evidence of disease recurrence. Radiographic and endoscopic procedures were repeated as clinically indicated. Disease progression was characterized as either locoregional or metastatic, and sites of recurrence were recorded.

Statistical Considerations

The primary end point for this trial was overall survival. Additional outcomes were defined for this analysis including locoregional control, distant metastatic control, and freedom from recurrence. The event corresponding to locoregional control is any local or regional failure. The event corresponding to distant metastatic control is any distant failure. The events corresponding to freedom from recurrence are local, regional, or distant failure, and the event corresponding to overall survival is all-cause mortality. All outcomes were calculated from the date of surgery. When this study was designed, the historical median survival after surgery was approximately 12 months. With a 5% level of significance, 46 patients would be required to have 90% power to detect an improvement in this median survival to 24 months.[31] Allowing for a 10% ineligibility/unevaluability rate, the targeted accrual would increase to 50 patients. Outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Analyses were done using SAS software (SAS Institute, Inc., Cary, NC).

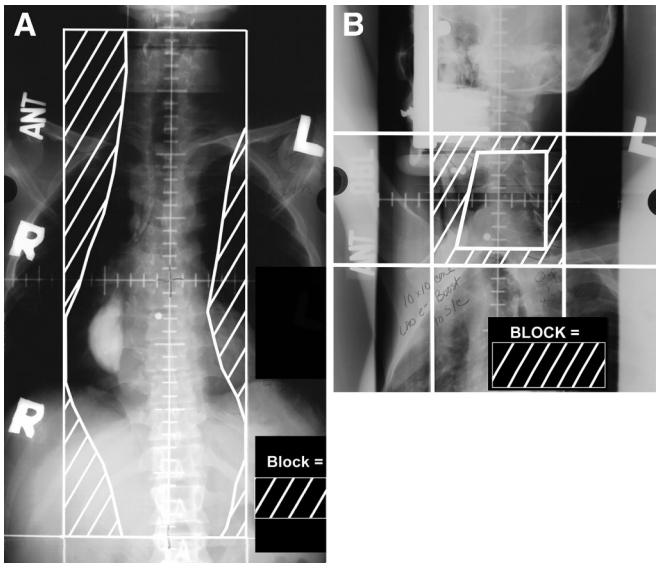

FIGURE 2. Representative treatment fields for delivery of postoperative radiotherapy in a patient with M1a distal esophageal cancer and close surgical margins. *A,* Anterior field (from a three-field technique) with blocks. *B,* Boost field to anastomosis.

RESULTS

Between February 1995 and January 2006, all eligible patients seen at the Cleveland Clinic were offered participation in this trial. Fifty such patients were identified and enrolled. The patient and tumor characteristics are detailed in Table 1. The median age was 59 (range, 33–76) years. A total of 43 patients (86%) had a pathologic diagnosis of adenocarcinoma and 19 of the adenocarcinoma patients (44%) had histologic evidence of Barrett esophagus. A transthoracic

TABLE 1. Patient and Tumor Characteristics

	Number (%)
Gender	
Male	43 (86)
Female	7 (14)
Race	
White	48 (96)
African American	2 (4)
Tumor location	
Mid esophagus	4 (8)
Lower esophagus	10 (20)
Gastroesophageal junction	36 (72)
Histopathology	
Adenocarcinoma	43 (86)
Squamous cell carcinoma	7 (14)
Tumor differentiation	
Well differentiated	1 (2)
Moderately well differentiated	16 (32)
Poorly differentiated	33 (66)
Pathologic stage	
T3 N0	7 (14)
T1 N1	6 (12)
T2 N1	2 (4)
T3 N1	31 (62)
T4 N1	1 (2)
T3 N1 M1a	3 (6)
Surgical procedures	
Transhiatal esophagogastrectomy	5 (10)
Transthoracic esophagogastrectomy	37 (74)
Total gastrectomy	8 (16)
Surgical margins	
Positive	9 (18)
Negative	41 (82)

esophagogastrectomy had been performed in 37 patients (74%), transhiatal esophagogastrectomy in five patients (10%), and a total gastrectomy in eight patients (16%). Pathologic staging is detailed and proved greater than the clinical staging in 28 patients (56%). The median number of nodes sampled at surgery was 18 (range, 4–50). The 43 N1 patients had a median of 3 (range, 1–18) positive nodes identified. Nine patients (18%) had an R1 resection with positive surgical margins. The likelihood of a positive surgical margin was not increased in those patients undergoing total gastrectomy.

Toxicity from the postoperative concurrent chemoradiotherapy, graded using Common Toxicity Criteria, is detailed in Table 2. Of note are modest nausea, vomiting, mucositis, and dysphagia. Renal dysfunction, with a transient rise in serum creatinine to 1.8 mg/dl, was noted in only one patient. Although 16 patients (32%) experienced grade 3–4 neutropenia ($<1000/mm^3$), hospitalization for neutropenia with fever was required in only 4 patients (8%). Thirteen other patients required an unplanned hospitalization for a variety of different reasons. (Table 3) There were no toxic deaths. The median administered radiation therapy dose was 50.4 (range, 10.8–60) Gy. All but three patients completed all of their planned chemotherapy and radiation. Treatment was halted after the first course of chemotherapy and only limited radiation in one patient because of the development of (presumably unrelated) ischemic colitis and in another after an acute myocardial infarction that was not temporally related to the fluorouracil infusion. The third patient completed chemotherapy but discontinued radiation after 40 Gy due to nausea.

With a median follow-up of 47 (range, 36–124) months, the Kaplan-Meier 4-year projected overall survival is 51% (Figure 3), 4-year freedom from recurrence 50%, distant metastatic control 56%, and locoregional control 86%. The median survival is 53 months. These results seem better than the 4-year projected survival of 44%, with a median survival of 28 months as we first reported in 2003.[29] An updated analysis of the 31 patients included in this 2003 report has not changed. However, the 19 additional patients added to our series have, as a group experienced considerably improved outcomes, with a projected 4-year survival of 58.5%, thus improving the overall results. Although these 19 patients are statistically similar in their pathologic stage, their clinical staging was statistically earlier than the original 31 patients first reported ($p = 0.007$).

Pathologic stage, nonetheless, proved the most important predictor for outcome. When comparing patients with pathologic stage T3 N0, N1 M0, and M1a disease, the overall survival ($p = 0.015$, Figure 4), freedom from recurrence ($p = 0.034$), and distant metastatic control ($p = 0.05$) were better in patients with earlier pathologic stage. It is of note that the pathologic stage did not impact the probability of locoregional control, which was excellent in all patient subgroups.

TABLE 2. Chemoradiotherapy Toxicity ($n = 50$)

	Number (%)
Nausea, vomiting (≥grade 3)	4 (8)
Mucositis, dysphagia (≥grade 3)	6 (12)
Neutropenia ($<1000/mm^3$)	16 (32)
Neutropenia with hospitalization for fever	4 (8)
Thrombocytopenia ($<20{,}000/mm^3$)	2 (4)
Toxic death	0

TABLE 3. Unplanned Hospitalization ($n = 50$)

	Number (%)
Neutropenic fever	4 (8)
Nonneutropenic fever/infection	2 (4)
Nausea/anorexia/dehydration	3 (6)
Diarrhea	2 (4)
Venous thromboembolism	2 (4)
Ischemic colitis	1 (2)
Cholecystitis	1 (2)
Myocardial infarction	1 (2)
Cardiac dysrhythmia	1 (2)

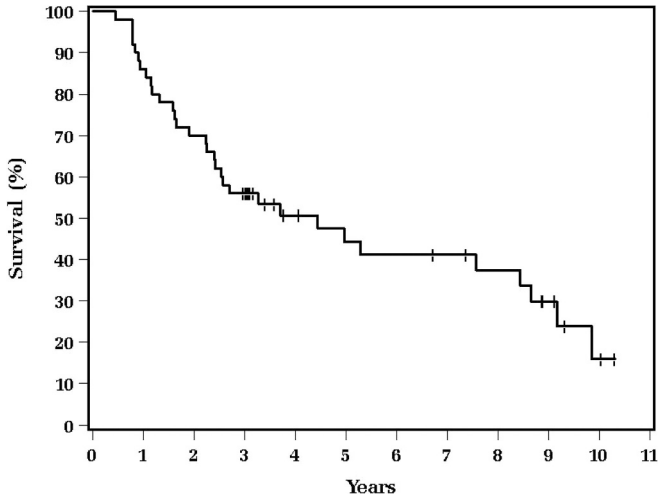

FIGURE 3. Overall survival ($n = 50$ patients).

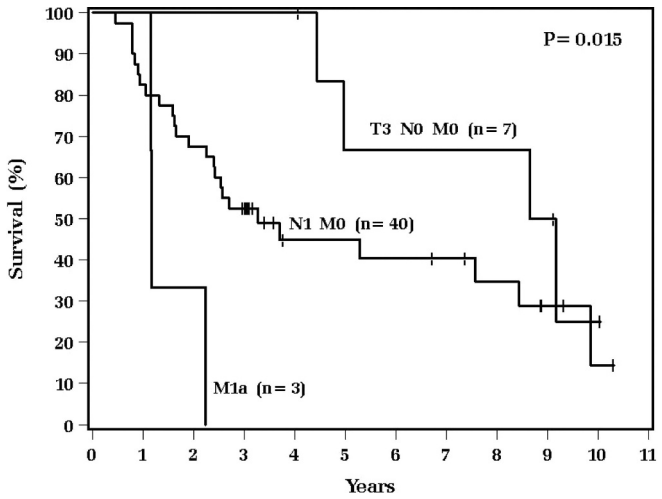

FIGURE 4. Overall survival by pathologic stage.

Tumor differentiation, margin positivity, and tumor location (in patients with adenocarcinoma) did not impact outcome. Although univariate analysis suggested that patients with squamous cell carcinoma had a better freedom from recurrence ($p = 0.05$) and distant metastatic control rate ($p = 0.07$) than those with adenocarcinoma, in a multivariable model only stage proved predictive of outcome.

DISCUSSION

This is mature data from a prospective phase II trial exploring the role of concurrent chemoradiotherapy in poor prognosis esophageal and GEJ cancer patients after primary surgical resection. Treatment toxicity was acceptable and the median overall survival was 53 months with a projected 4-year overall survival of 51%. These figures are promising, particularly when compared with the historical results after surgery alone[1,2,4–7,29] or even to the data generated from trials exploring preoperative induction chemoradiotherapy.[10–13,21–24] A recent series from the Cleveland Clinic, for example, reports a 3-year projected overall survival of only 28% with a freedom from recurrence of 31% for patients with similar (although clinically) staged T3, N1, or M1a disease.[23] It is important to stress, however, that these are not comparable patient populations. Most of the patients entered on the current study were clinically felt to have earlier tumors, defining a patient cohort with less advanced disease and therefore a better prognosis. Despite its inherent inaccuracy, the importance of clinical staging is underscored by our observation of an improved outcome in the 19 patients we added to our original cohort of 31 patients reported in 2003.[29] The improved outcome we observed can likely be attributed to an earlier clinical stage in the more recent patients, despite similarity in their pathologic stage.

Additionally, only those patients who had tolerated and recovered from surgical resection were eligible for this trial. Patients with significant perioperative morbidity impact the results of induction chemoradiotherapy trials but were not entered on this study. Thus, direct comparison of the results from this postoperative experience with the reported results after induction chemoradiation therapy is not appropriate.

There is very little high-level evidence to support a postoperative concurrent chemoradiotherapeutic approach in esophageal cancer.[26,27] The only large phase III randomized study was an Intergroup trial reported by Macdonald et al.[19] for patients with gastric cancer. Although "approximately 20%" of these patients had a gastroesophageal malignancy, the outcome of the GEJ patients was not specifically detailed. Extrapolation of these results to patients with distal or midesophageal primary tumors, or to those with squamous cell carcinoma, is somewhat speculative but is a common clinical practice. Similarly, data supporting a role for postoperative single modality radiation or chemotherapy, although of interest, is limited.[18,28,32]

Nonetheless, adjuvant concurrent chemoradiotherapy is an attractive approach for several reasons. First, treatment in a postoperative setting allows a treatment decision to be based on the true pathologic stage rather than on the relatively inaccurate clinical stage, thus avoiding the use of chemoradiotherapy in those patients who might otherwise not require this intervention.[25] Similarly, a more accurate assessment of disease extent for the radiotherapist is possible after surgical resection and delineation of disease involvement. Second, the use of chemoradiotherapy postoperatively addresses the ongoing concern about the increase in perioperative morbidity and mortality seen after preoperative induction. Although recent multimodality series have suggested an improvement in this perioperative morbidity with careful attention to radiotherapeutic, anesthetic, and surgical technique,[23] any added complications from preoperative chemoradiotherapy can be avoided altogether with a postoperative treatment approach. Third, preoperative dysphagia and issues of nutritional support often compromise a patient's tolerance of induction chemoradiotherapy. In postoperative patients, dysphagia has been relieved and postoperative alimentation can be supported by a surgically placed feeding tube, thus allowing for better tolerance of the intervention.

Potential disadvantages exist as well. Recovery after esophagogastric resection is difficult and may preclude the use of postoperative chemoradiotherapy in a significant number of patients. Despite better nutritional support, overall functional status is often reduced after surgery, potentially interfering with overall treatment tolerance. Furthermore, the impact of the altered postoperative blood supply on the delivery of chemotherapy and oxygenation of the tumor bed must be considered, at least in theory, potentially detrimental, and the difficulties of treatment planning after surgical resection and reconstruction cannot be underestimated.

Perhaps the greatest concern is that the use of a postoperative adjuvant chemoradiotherapeutic approach eliminates the potential benefit of induction treatment on the success of surgery. This benefit, however, remains ill defined, and it is unclear whether induction chemoradiotherapy actually improves resectability or the ultimate outcome after treatment.

CONCLUSION

Although the use of multiple treatment modalities in patients with locoregionally advanced esophageal cancer seems better than single modality surgery alone, the optimal order in which these treatments should be used is unknown. Meta-analysis data suggests a significant benefit from induction chemoradiotherapy before surgical resection, and this has become a standard of care.[33] We suggest that postoperative concurrent chemoradiotherapy can be successful and may have significant advantages for the clinically understaged patient or for the patient with locoregionally more advanced but resectable disease who undergoes initial surgical resection for another reason. Further study of this approach, particularly in comparison with preoperative chemoradiotherapy, is justified.

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