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Response to Neoadjuvant Chemotherapy Best Predicts Survival After Curative Resection of Gastric Cancer

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Objective
In Western populations, long-term survival rates after curative resection of gastric cancer remain extremely poor. The lack of effective adjuvant therapy has prompted the evaluation of neoadjuvant approaches. Since 1988, we have conducted three separate phase II trials using neoadjuvant chemotherapy to treat patients with potentially resectable gastric cancer. The present study was conducted to evaluate whether response to neoadjuvant chemotherapy is predictive of survival in patients with resectable gastric cancer.

Methods
Eighty-three patients with pathologically confirmed gastric adenocarcinoma were treated with neoadjuvant chemotherapy before planned surgical resection. Response was assessed by upper gastrointestinal series, endoscopy, computed tomography scan, and pathologic examination.

Results
For the three phase II trials, clinical response rates ranged from 24% to 38%. Three patients (4%) had a complete pathologic response. Sixty-one patients (73%) underwent a curative resection. Median follow-up was 26 months. Univariate analysis revealed T stage, number of positive nodes, and response to chemotherapy to be significant predictors of overall survival. However, on multivariate analysis, response to chemotherapy was found to be the only independent prognostic factor.

Conclusions
Response to neoadjuvant chemotherapy is the single most important predictor of overall survival after neoadjuvant chemotherapy for gastric cancer. These findings support further evaluation of neoadjuvant approaches in the treatment of this disease.

Despite its declining incidence during this century, gastric cancer remains a leading cause of cancer death in the United States.[1] The 5-year survival rate after apparently curative surgical resection remains only 20% to 30% in Western populations.[2,3] Numerous studies have examined the utility of adjuvant chemotherapy after surgical resection.[4–8] With few exceptions, these studies have failed to demonstrate any improvement in overall or relapse-free survival.[9,10] Neoadjuvant chemotherapy for gastric cancer was first studied in the context of locally advanced "unresectable" disease.[11] There are numerous theoretical benefits to a neoadjuvant strategy, including:

- Chemotherapy-induced tumor downstaging may enhance resectability.
- Patients receive systemic therapy without delay, and virtually all patients can receive the prescribed therapy.
- Treatment is administered while there is measurable disease present to assess response, thus allowing therapy to be continued only in patients more likely to benefit.
- During preoperative chemotherapy, patients with rapidly progressive disease can often be identified and spared a nontherapeutic gastrectomy.

With such benefits in mind, we have treated a total of 83 patients with potentially resectable gastric cancer on three consecutive phase II neoadjuvant chemotherapy protocols: etoposide, 5-fluorouracil (5-FU), and cisplatin (EFP); etoposide, doxorubicin (Adriamycin), and cisplatin (EAP); and 5-FU, α-interferon, and cisplatin (FIP).[12–14] An analysis of the known prognostic factors was performed to determine

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Table 1. NEOADJUVANT CHEMOTHERAPY TRIALS FOR GASTRIC CANCER

Protocol	Preop Doses	Postop Doses	Clinical Response Rate (%)
EFP (n = 25)	2	3	24
EAP (n = 34)	3	2	31
FIP (n = 24)	5	0	38

their value in predicting overall survival after completion of these regimens.

METHODS

Patient Demographics and Staging

Between 1988 and 1994, 83 patients with histologically proven gastric adenocarcinoma underwent neoadjuvant chemotherapy before planned surgical resection. There were 51 men and 33 women, with a mean age of 54.8 years (range 30 to 74). The pretreatment staging workup included chest x-ray, upper gastrointestinal (GI) series, and a computed tomography (CT) scan of the abdomen. Diagnostic laparoscopy was added to the staging evaluation during the EAP study and performed thereafter. During diagnostic laparoscopy, a feeding jejunostomy catheter was placed for nutritional support. When technically feasible, endoscopic ultrasound was also performed.

Chemotherapy

Patients were treated during one of three consecutive phase II trials conducted at the M. D. Anderson Cancer Center (Table 1). Eligibility for all three trials included a Zubrod performance status of 2 or less, a measurable tumor mass on upper GI series that was at least a T2 lesion by endoscopic ultrasound, and no evidence of metastatic (M1) disease as defined by American Joint Committee on Cancer (AJCC) staging criteria. The initial trial consisted of two courses of preoperative etoposide (90 mg/m^2, days 1, 3, 5), 5-FU (900 mg/m^2, continuous infusion days 1 to 5), and cisplatin (20 mg/m^2, days 1 to 5). If there was objective clinical evidence of response, three additional courses were given after gastric resection. The second trial used etoposide (120 mg/m^2, days 4–6), doxorubicin (20 mg/m^2, days 1 and 7), and cisplatin (40 mg/m^2, days 2 and 8), given as three preoperative courses. Responders received two additional postoperative courses of chemotherapy. The most recently completed trial used 5-FU (500 mg/m^2, continuous infusion days 1 to 5), α-interferon (3 milU subcutaneously three times per week for 3 weeks), and cisplatin (15 mg/m^2, days 1 to 5), given entirely in the preoperative period. Patients received up to five courses of chemotherapy. Response was evaluated after the first and third courses of therapy. If there was progression of disease at any point or no response after three courses, chemotherapy was discontinued and the patient was taken to surgery.

Surgery

Four to six weeks after the completion of preoperative chemotherapy, all patients were restaged with a chest x-ray, upper GI series, and CT scan of the abdomen. If there was no evidence of metastatic disease, a gastrectomy with D2 lymphadenectomy and splenic preservation was performed. At surgery, a feeding jejunostomy was inserted in all patients for postoperative nutritional support. Distant disease was classified as peritoneal or visceral metastases or evidence of distant nodal involvement (beyond N2), as defined by AJCC staging criteria. Proximal and distal margins of resection were examined during surgery by frozen-section pathologic examination. Curative resection was defined as removal of all gross disease and negative pathologic margins on permanent pathologic section.

Assessment of Response

For the purposes of this study, response was defined both clinically and pathologically. Patients were considered responders if they had either a clinical or a pathologic response. Clinical response was assessed by upper GI series, upper endoscopy, and CT scan of the abdomen. Responses were scored as complete response, partial response, stable disease, or progressive disease. A reduction in bidimensional tumor diameter of >50% on upper GI series and CT scan was considered a partial response. Response to therapy was judged and agreed on by at least two observers who reviewed the data for each case. If progression of disease was clearly demonstrated by a single modality but not others, this was scored as progression of disease. All surgical specimens underwent gross and microscopic examination for evidence of response to chemotherapy. A complete pathologic response was defined as the absence of histopathologic evidence of malignancy. A pathologic partial response was defined as <10% viable tumor cells seen on serial hematoxylin-and-eosin–stained sections, as previously described.[15] Tumors with 10% to 50% viable tumor cells were scored as having a minor response, and those with >50% viable cells were scored as no response. Again, for the purposes of the present study, patients with either a clinical or a pathologic response (partial or complete) were scored as responders.

Statistical Analysis

To eliminate statistical bias associated with analyzing survival in terms of tumor response and duration of preoperative therapy, all results were calculated from the date of surgical resection.[16] Comparisons of preoperative characteristics, including tumor grade and tumor location, for

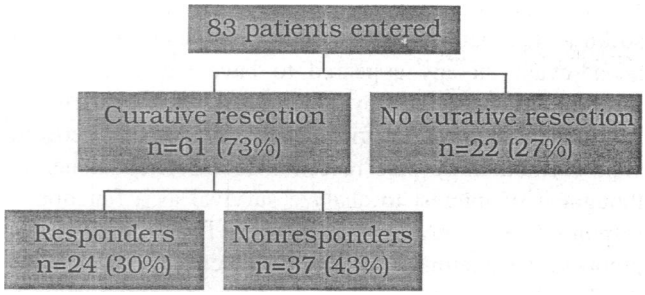

Figure 1. Neoadjuvant chemotherapy in 83 patients with potentially resectable gastric cancer.

responders *versus* nonresponders were performed using Fisher's exact test. Actuarial survival was calculated using the method of Kaplan–Meier. Univariate analyses were performed using the log-rank test; multivariate analysis was conducted using the Cox proportional hazards model. For all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Resectability and Margins

Of the 83 patients entered in the three phase II trials, 61 (73%) ultimately underwent a potentially curative resection. Of the 22 patients who were unable to undergo a potentially curative resection, 20 had developed evidence of disease progression, whereas 2 patients underwent resection and were found to have positive microscopic margins. Of the patients who developed progressive disease, 12 had disease progression documented by radiographic imaging alone and thereby avoided a nontherapeutic laparotomy. No patients with progressive disease required resection for palliation.

Response Rates

Of the 61 patients who underwent curative resection, there were 24 responders (39%) and 37 nonresponders (61%) (Fig. 1). Twenty-two patients had clinical evidence of response. Pathologic response to treatment was evident in 16 patients, 3 of whom had complete responses. Partial pathologic response was observed in ten patients, and minor responses were evident in three patients. Two patients had evidence of a major pathologic response without a demonstrable clinical response, whereas six patients had a clinical response without a definitive pathologic response. Thus, in 14 of the 24 responders (58%), there was both clinical and pathologic evidence of treatment effect.

Analysis of Pretreatment Prognostic Factors

To determine whether responders differed from nonresponders with regard to pretreatment tumor characteristics, known prognostic factors including tumor grade and tumor location, were analyzed for the two groups. No significant differences were identified.

Table 2. PATHOLOGIC CHARACTERISTICS AFTER NEOADJUVANT CHEMOTHERAPY AND CURATIVE RESECTION

Prognostic Factor		N	%
T stage*	T1–T2	18	30
	T3–T4	43	70
# positive nodes	0	20	33
	1–3	17	28
	>3	24	39
Differentiation	Well-mod.	14	23
	Poor	47	77
Location	Proximal	24	39
	Body/distal	34	56
	Linitis	3	5

* In three patients with pathologic complete responses, T stage shown is based on preoperative EUS staging (T2–1, T3–2).

Prognostic Factors and Survival

Table 2 depicts the tumor characteristics for the 61 patients who underwent curative resections. Most had advanced disease, as demonstrated by the 71% rate of serosal penetration (T3 + T4) and 67% incidence of nodal positivity; 39% of patients had more than three positive nodes despite neoadjuvant treatment. Numerous known prognostic factors for gastric cancer were analyzed to assess their value after neoadjuvant chemotherapy. This analysis revealed that T stage, nodal positivity, and the number of positive nodes were all significant prognostic factors for disease-free and overall survival by univariate analysis (Table 3). Tumor location approached but did not reach statistical significance. Other variables, including tumor grade, differentiation, and the specific chemotherapy protocol, were analyzed

Table 3. PROGNOSTIC FACTORS AFTER NEOADJUVANT CHEMOTHERAPY AND CURATIVE RESECTION: UNIVARIATE ANALYSIS

Prognostic Factor	Log Rank
T stage (T1 + T2 *vs.* T3 + T4)	$p < 0.001$
Nodal positivity	$p < 0.001$
# of positive nodes (0, 1–3, >3)	$p < 0.001$
Response (complete + partial *vs.* stable + progression)	$p < 0.001$
Location (Proximal vs. body/distal vs. linitis plastica)	$p < 0.08$
Chemotherapy regimen (EFP *vs.* EAP *vs.* FIP)	$p = 0.28$
Differentiation (Well + moderate *vs.* poor)	$p = 0.29$

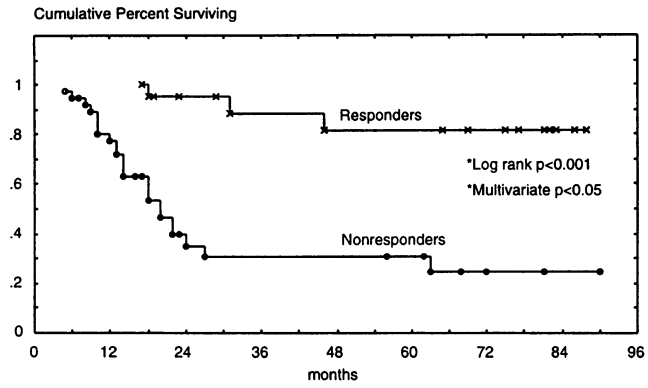

Figure 2. Overall survival after neoadjuvant chemotherapy and curative resection.

and were not found to be significant predictors of survival. When response to chemotherapy was analyzed, this was also found to be a significant prognostic factor. Responders had an actuarial 5-year survival of 83% *versus* 31% for nonresponders (Fig. 2). The median survival for nonresponders was 20 months, whereas the median survival for responders has not been reached at a median follow-up of 26 months.

When the factors identified by univariate analysis were subjected to a multivariate analysis, response to chemotherapy was found to be the only independent prognostic factor for overall survival (Table 4). Identical findings were obtained when the analysis was repeated for disease-free survival. The relative risk for responders *versus* nonresponders was 0.44 (confidence interval 0.2 to 0.9), indicating that response to neoadjuvant chemotherapy was associated with a more than twofold increment in overall survival. The three patients in whom a complete pathologic response to treatment was observed remain alive and free of disease at 48, 58, and 63 months of follow-up.

DISCUSSION

The poor prognosis of gastric cancer has prompted investigation of novel therapeutic strategies, among them the use of neoadjuvant chemotherapy. The application of neoadjuvant chemotherapy to the treatment of gastric adenocarcinoma was first reported by Wilke et al,[11] who treated patients with locally advanced, unresectable tumors. Shortly thereafter, phase II trials were expanded to examine patients with potentially resectable disease.[12–14,17–20] The goal of these phase II trials has been to achieve at least a 10% rate of pathologic complete response before embarking on a phase III randomized study. This goal rate is adapted from the neoadjuvant experience in the treatment of locally advanced breast cancer, in which significant improvements in long-term survival were noted when pathologic complete response rates reached the 10% level.[21,22] In the latest M.D. *Anderson phase* II trial of 5-FU, α-interferon, and cisplatin, this response level was reached.

On review of the data from all three phase II trials, it was striking that patients who had a significant response to neoadjuvant therapy appeared to have significantly prolonged disease-free and overall survival. In the absence of any published phase III trials directly comparing neoadjuvant chemotherapy plus resection to resection alone, we thought it of interest to analyze survival as a function of response to neoadjuvant chemotherapy. In addition, because preoperative treatment is becoming increasingly common, we thought it important to reassess the predictive value of known prognostic factors for gastric cancer (*i.e.*, T stage, nodal positivity, number of positive nodes) in the context of neoadjuvant chemotherapy.[3] Interestingly, although the known prognostic factors of survival after curative resection of gastric cancer held statistical significance on univariate calculation, these prognostic variables did not maintain significance on multivariate analysis. Although this may be a result of patient numbers, response to neoadjuvant chemotherapy remained predictive of survival on multivariate analysis. Further, patients who did respond to neoadjuvant therapy had an actuarial 5-year survival of 83%, despite a 44% incidence of positive lymph nodes. This survival rate is significantly better than any previously reported Western series of surgical resection alone.

These findings must be interpreted with caution, however. The present study summarizes data from three independent, nonrandomized prospective trials, and therefore no definitive statements can be made regarding the ability of neoadjuvant chemotherapy to improve survival for patients with resectable gastric cancer. These results do raise several questions, however. First, do patients who respond to neoadjuvant chemotherapy simply have biologically more favorable tumors than nonresponders? If so, would this favorable biology have resulted in prolonged survival even without neoadjuvant therapy? Certainly it is clear that there is considerable tumor heterogeneity among patients with gastric cancer, as for other malignancies. However, favorable biology alone seems insufficient to account for the 83% 5-year survival figures seen in responders, particularly in light of the 30% survival rate for nonresponders, which is equivalent to surgery alone in most large series. The inci-

Table 4. MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS FOR OVERALL SURVIVAL AFTER NEOADJUVANT CHEMOTHERAPY AND CURATIVE RESECTION

Prognostic Factor	Cox Regression
T stage	p = NS
Nodal positivity	p = NS
# of positive nodes	p = NS
Response	$p < 0.05 \rightarrow$ Relative risk = 0.44 Confidence interval = 0.2–0.9

dence of nodal positivity in the group of responders was 44%. Because it is likely that some patients were downstaged by preoperative therapy, the true incidence of (pretreatment) nodal positivity may have exceeded 50%. Previous studies of adjuvant chemotherapy have consistently demonstrated 5-year survival rates of <35% for patients with positive nodes.[4–6] It therefore seems more likely that neoadjuvant treatment is identifying a subset of tumors with specific molecular markers that may regulate treatment response. Although these molecular markers may confer some survival advantage after resection alone, this advantage is greatly augmented by treatment with cytotoxic chemotherapy. Numerous studies have demonstrated that the presence of certain molecular markers, such as a wild-type p53 tumor suppressor gene, holds prognostic significance in gastric cancer.[23,24] Lenz et al[25] have reported that tumor thymidylate synthase levels are predictive of both response to neoadjuvant chemotherapy and survival in patients with gastric cancer. Unfortunately, such data are not yet available for the patients in the current series. It will be critical to link all future studies of neoadjuvant therapy in gastric cancer to a molecular analysis of tumor tissue obtained before treatment. Ideally, the identification of molecular markers that predict response to neoadjuvant therapy could be used to direct specific preoperative treatment to the patients most likely to benefit.

The data also suggest that standard staging and prognostic criteria may lose some of their predictive value after neoadjuvant therapy. This phenomenon was also observed in patients with gastric cancer who were treated with 5-FU–based neoadjuvant chemoradiation (Mansfield et al, manuscript in preparation). Despite radical lymphadenectomy performed by the same surgeons, patients who underwent neoadjuvant treatment had fewer nodes detected on pathologic examination. To evaluate the validity of these findings fully, it is critical that future neoadjuvant protocols incorporate state-of-the-art pretreatment staging modalities. The importance of laparoscopic staging to rule out occult metastatic disease in gastric cancer has been well documented.[26,27] To assess T and N staging accurately, endoscopic or laparoscopic ultrasound should also be routinely incorporated in neoadjuvant trial design.[28–30]

The results of this study also suggest that accurate evaluation of treatment response requires both clinical and pathologic criteria. In only 58% of cases was definitive evidence of both clinical and pathologic response present. This is not surprising given the pathologic characteristics of diffuse-type gastric carcinoma seen most commonly in Western patients, which often include chronic gastritis and abundant fibrous stroma. Lesions that contain dense stromal reaction may not demonstrate significant reductions in size after neoadjuvant treatment, and pathologic evaluation of such tumors is similarly difficult.

The present studies did not use radiation as part of the neoadjuvant treatment program. The rationale for the addition of radiation therapy to surgery and chemotherapy lies in the high rate of local/regional recurrence after gastrectomy, as documented by both autopsy and clinical studies.[31–33] Studies from Japan have focused on the use of intraoperative radiation therapy, whereas in the United States more effort has been directed toward investigation of chemoradiation strategies. Most data suggesting a potential benefit for adjuvant chemoradiation in gastric cancer are derived from single-institution phase II trials.[34–36] A randomized study from the Mayo Clinic did demonstrate a benefit to adjuvant chemoradiation *versus* surgery alone, but the study was flawed by randomization of patients who ultimately refused treatment.[37] A recent prospective randomized trial of neoadjuvant chemoradiation that included both esophageal and proximal gastric (cardia/gastroesophageal junction) adenocarcinomas did demonstrate an overall survival benefit for the treatment group.[38] Several other trials that incorporate radiation therapy into the treatment plan are ongoing or near completion. Intergroup 0116 has just completed accrual of patients randomized to receive gastrectomy or gastrectomy followed by 5-FU–based chemoradiation. Newer studies are evaluating the use of neoadjuvant chemotherapy, radiation, and surgery. The combination of 5-FU–based neoadjuvant chemotherapy, chemoradiation, and surgery is being examined in a phase II study coordinated by the Radiation Therapy Oncology Group. An institutional phase II trial at the University of Cincinnati is using preoperative paclitaxel (Taxol) and gemcitabine followed by chemoradiation with 5-FU and cisplatin before surgery in patients with proximal gastric and esophageal carcinomas. The outcome of such trials will define whether neoadjuvant chemotherapy alone or in combination with radiation is of benefit to patients with resectable gastric cancer.

CONCLUSIONS

Analysis of data from three consecutive phase II trials demonstrated that response to neoadjuvant chemotherapy was associated with markedly improved survival after curative resection for gastric carcinoma. Response to chemotherapy was the best predictor of overall survival. These data support further investigation of neoadjuvant therapies and molecular determinants of treatment response. Once molecular markers are identified that can accurately predict response to specific therapies, treatment can be individualized, toxicity minimized, and outcome improved for patients with gastric cancer.

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