CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

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ABSTRACT

Background Surgical resection of adenocarcinoma of the stomach is curative in less than 40 percent of cases. We investigated the effect of surgery plus postoperative (adjuvant) chemoradiotherapy on the survival of patients with resectable adenocarcinoma of the stomach or gastroesophageal junction.

Methods A total of 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of 425 mg of fluorouracil per square meter of body-surface area per day, plus 20 mg of leucovorin per square meter per day, for five days, followed by 4500 cGy of radiation at 180 cGy per day, given five days per week for five weeks, with modified doses of fluorouracil and leucovorin on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of fluorouracil (425 mg per square meter per day) plus leucovorin (20 mg per square meter per day) were given one month apart.

Results The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemoradiotherapy group; the hazard ratio for death was 1.35 (95 percent confidence interval, 1.09 to 1.66; $P=0.005$). The hazard ratio for relapse was 1.52 (95 percent confidence interval, 1.23 to 1.86; $P<0.001$). Three patients (1 percent) died from toxic effects of the chemoradiotherapy; grade 3 toxic effects occurred in 41 percent of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32 percent.

Conclusions Postoperative chemoradiotherapy should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastroesophageal junction who have undergone curative resection. (N Engl J Med 2001;345:725-30.)

THE curative treatment of stomach cancer requires gastric resection.[1] However, most patients are not cured by this surgery. A review of data from the National Cancer Data Base on 50,169 patients in the United States who underwent gastrectomy between 1985 and 1996 found a 10-year survival rate of 65 percent among patients with stage IA disease (tumor confined to the gastric mucosa), but the 10-year survival rates among those with more advanced disease ranged from 3 percent to 42 percent, depending on the extent of disease.[2]

The high rate of relapse after resection makes it important to consider adjuvant treatment for patients with stomach cancer. However, adjuvant chemotherapy has not resulted in higher survival rates than surgery alone.[3-5]

Local or regional recurrence in the gastric or tumor bed, the anastomosis, or regional lymph nodes occurs in 40 to 65 percent of patients after gastric resection with curative intent.[6-9] The frequency of such relapses makes regional radiation an attractive possibility for adjuvant therapy. A phase 3 trial[10] found clinically limited but statistically significant improvement ($P=0.009$) in survival after preoperative regional radiotherapy in patients with cancer of the gastric cardia. Small phase 3 trials have suggested that survival is improved after postoperative radiation, with or without fluorouracil,[11] and after intraoperative radiation.[12]

Phase 3 trials have found that 12 to 20 percent of patients with residual or locally unresectable gastric cancer are long-term survivors after treatment with radiation plus fluorouracil.[13,14] We undertook a study to determine the efficacy of chemoradiotherapy in patients with resected gastric cancer. The trial was initiated in 1991 to compare surgery followed by fluorouracil plus irradiation of the gastric bed and regional lymph nodes with surgery alone.

METHODS

Eligibility

The eligibility criteria included histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction; complete resection of the neoplasm, defined as resection performed with curative intent and resulting in resection of all tumor with the margins of the resection testing negative for carcinoma; a classification of the resected adenocarcinoma of the stomach or gastroesophageal junction as stage IB through IVM0 according to the 1988 staging criteria of the American Joint Commission on Can-

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cer[15]; a performance status of 2 or lower according to the criteria of the Southwest Oncology Group; adequate function of major organs (indicated by a creatinine concentration no more than 25 percent higher than the upper limit of normal; a hemogram within the normal limits; a bilirubin concentration no more than 50 percent higher than the upper limit of normal; a serum aspartate aminotransferase concentration no more than five times the upper limit of normal; and an alkaline phosphatase concentration no more than five times the upper limit of normal); a caloric intake greater than 1500 kcal per day by oral or enterostomal alimentation; registration between 20 and 41 days after surgery, with treatment beginning within 7 working days after registration; and the provision of written informed consent according to institutional and federal guidelines. When a patient was registered, surgeons and pathologists from the Southwest Oncology Group reviewed the patient's surgery and pathology reports to confirm the completeness of the resection.

Treatment Plan

After undergoing gastrectomy, patients were randomly assigned to surgery alone or to the postoperative combination of fluorouracil plus leucovorin and local–regional radiation. Randomization was performed 20 to 40 days after surgery by means of a dynamic balancing procedure that included stratification according to the tumor stage (T1 to T2, T3, or T4) and the nodal status (no positive nodes, one to three positive nodes, or four or more positive nodes).

The regimen of fluorouracil and leucovorin was developed by the North Central Cancer Treatment Group[16] and was administered before and after radiation. Chemotherapy (fluorouracil, 425 mg per square meter of body-surface area per day, and leucovorin, 20 mg per square meter per day, for 5 days) was initiated on day 1 and was followed by chemoradiotherapy beginning 28 days after the start of the initial cycle of chemotherapy. Chemoradiotherapy consisted of 4500 cGy of radiation at 180 cGy per day, five days per week for five weeks, with fluorouracil (400 mg per square meter per day) and leucovorin (20 mg per square meter per day) on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of fluorouracil (425 mg per square meter per day) plus leucovorin (20 mg per square meter per day) were given one month apart. The dose of fluorouracil was reduced in patients who had grade 3 or 4 toxic effects.

The 4500 cGy of radiation was delivered in 25 fractions, five days per week, to the tumor bed, to the regional nodes, and 2 cm beyond the proximal and distal margins of resection. The tumor bed was defined by preoperative computed tomographic (CT) imaging, barium roentgenography, and in some instances, surgical clips. The presence of proximal T3 lesions necessitated treatment of the medial left hemidiaphragm. We used the definitions of the Japanese Research Society for Gastric Cancer for the delineation of the regional-lymph-node areas.[17,18] Perigastric, celiac, local paraaortic, splenic, hepatoduodenal or hepatic-portal, and pancreaticoduodenal lymph nodes were included in the radiation fields. In patients with tumors of the gastroesophageal junction, paracardial and paraesophageal lymph nodes were included in the radiation fields, but pancreaticoduodenal radiation was not required. Exclusion of the splenic nodes was allowed in patients with antral lesions if it was necessary to spare the left kidney. Radiation was delivered with at least 4-MV photons. Doses were limited so that less than 60 percent of the hepatic volume was exposed to more than 3000 cGy of radiation. The equivalent of at least two thirds of one kidney was spared from the field of radiation, and no portion of the heart representing 30 percent of the cardiac volume received more than 4000 cGy of radiation. Fluorouracil (400 mg per square meter) and leucovorin (20 mg per square meter) were administered as an intravenous bolus on each of the first four days and the last three days of irradiation. This regimen was shown to be tolerable in a previous trial.[19]

Quality Assurance for Radiotherapy

Prior approval of the treatment plan for radiotherapy by the radiation-oncology coordinator was required before the initiation of radiotherapy. Treatment fields, dosimetry, surgery and pathology reports, and preoperative tumor imaging were submitted for review before treatment began. Plans that were not approved because of the risk of toxic effects on critical organs or the failure to treat the appropriate target volumes were corrected before therapy was begun. At these reviews, 35 percent of the treatment plans were found to contain major or minor deviations from the protocol, most of which were corrected before the start of radiotherapy. A final quality-assurance review of radiotherapy (conducted after the delivery of radiation) revealed major deviations in 6.5 percent of the treatment plans.

Follow-up of Patients

Follow-up of both groups occurred at three-month intervals for two years, then at six-month intervals for three years, and yearly thereafter. Follow-up consisted of physical examination, a complete blood count, liver-function testing, chest radiography, and CT scanning as clinically indicated. The site and date of the first relapse and the date of death, if the patient died, were recorded.

Statistical Analysis

Our study was originally designed to include 350 patients. With a two-sided alpha level of 0.05, the study had an estimated 80 percent power to detect a 50 percent relative difference in survival (equivalent to a hazard ratio for death of 1.5) and an estimated 95 percent power to detect a 60 percent relative difference in relapse-free survival (a hazard ratio for death or relapse of 1.6). However, since enrollment was higher than expected, the data and safety monitoring committee approved an amendment to expand the enrollment to 550 eligible patients, which ensured 90 percent power to detect a 40 percent difference in survival (a hazard ratio of 1.4) and a 40 percent difference in relapse-free survival.

The two stratification factors, the T stage (three levels) and the N stage (three levels), were included as covariates in the Cox regression analysis.[20] The examination of other potential covariates (age, race, the extent [D level] of the dissection, and the location of the primary tumor) yielded no significant effects, and these variables were not included in the analysis. All eligible patients were included in the analyses of survival and relapse-free survival according to the intention-to-treat principle.

The sites of relapse were classified as follows: the relapse was coded as local if tumor was detected in the surgical anastomosis, residual stomach, or gastric bed, as regional if tumor was detected in the peritoneal cavity (including the liver, intraabdominal lymph nodes, and peritoneum), and as distant if the metastases were outside the peritoneal cavity. All eligible patients in the chemoradiotherapy group who received any treatment were included in the analysis of toxic effects.

The study was monitored by the data and safety monitoring committee of the Southwest Oncology Group. At two planned interim analyses, the committee assessed whether the trial could be terminated early according to protocol-specified guidelines. Both interim analyses resulted in the continuation of the study until the planned time for the reporting of final data.

RESULTS

Demographic Characteristics

Between August 1, 1991, and July 15, 1998, 603 patients were registered. Forty-seven patients (8 percent) were deemed ineligible because they had positive surgical margins, had disease other than adenocarcinoma on pathological examination, or were registered after the specified time limit. Of the remaining 556 patients, 275 were randomly assigned to surgery only and 281 to surgery plus chemoradiotherapy. Demographic factors (Table 1) were similar between the two

TABLE 1. CHARACTERISTICS OF THE PATIENTS AND THE TUMORS.*

CHARACTERISTIC	SURGERY-ONLY GROUP (N=275)	CHEMORADIOTHERAPY GROUP (N=281)
Age (yr)		
Median	59	60
Range	23–80	25–87
Performance status of 0 or 1 (%)	94	94
Male sex (%)	71	72
Race (%)		
White	73	75
Black	16	16
Asian	7	5
Other	4	4
T stage (%)		
T1 or T2	31	31
T3	61	62
T4	8	6
No. of positive nodes (%)		
0	16	14
1–3	41	42
≥4	43	43
Location of primary tumor (%)		
Antrum	56	53
Corpus	25	24
Cardia	18	21
Multicentric	<1	2

*Because of rounding, not all percentages total 100.

groups; 94 percent of the patients were ambulatory or asymptomatic after surgery.

Most tumors were in the distal stomach. Lesions were present in the gastroesophageal junction in approximately 20 percent of the patients. The patients were at high risk for relapse; more than two thirds of them had stage T3 or T4 tumors, and 85 percent had nodal metastases (Table 1).

Treatment

Of the 281 patients assigned to the chemoradiotherapy group, 181 (64 percent) completed treatment as planned (Table 2); 17 percent stopped treatment because of toxic effects (investigators were not required to indicate the specific toxic effect that prompted the cessation of treatment). Eight percent declined treatment, 5 percent had progression of disease while receiving treatment, 1 percent died during the course of treatment, and 4 percent discontinued treatment for other reasons. Twelve patients (eight assigned to receive chemoradiotherapy and four assigned to receive surgery only) declined to continue the assigned therapy but are included in the assigned study group according to the intention to treat. The eight patients who declined to receive the protocol-specified chemoradiotherapy could not be evaluated for toxic effects.

Surgical Procedures

The only surgery-related requirements for eligibility were resection with curative intent and en bloc resection of the tumor with negative margins. Also required was a statement from the operating surgeon that no metastatic or unresected adenocarcinoma was present. Gastric resection with an extensive (D2) lymph-node dissection was recommended. This procedure entails the resection of all perigastric lymph nodes and some celiac, splenic or splenic-hilar, hepatic-artery, and cardial lymph nodes, depending on the location of the tumor in the stomach.[17] However, since patients were usually identified postoperatively, we could not require specific surgical procedures. The operating surgeon completed a form defining the extent of lymphadenectomy. Of 552 patients whose surgical records were reviewed for completeness of resection, only 54 (10 percent) had undergone a formal D2 dissection. A D1 dissection (removal of all invaded [N1] lymph nodes) had been performed in 199 patients (36 percent), but most patients (54 percent) had undergone a D0 dissection, which is less than a complete dissection of the N1 nodes.

TABLE 2. REASONS FOR THE CESSATION OF CHEMORADIOTHERAPY AMONG THE 281 PATIENTS IN THE CHEMORADIOTHERAPY GROUP.

REASON FOR CESSATION	NO. OF PATIENTS (%)
Protocol treatment completed	181 (64)
Toxic effects	49 (17)
Patient declined further treatment	23 (8)
Progression of disease	13 (5)
Death	3 (1)
Other	12 (4)

Toxicity

The toxic effects classified as grade 3 or higher that occurred among the 273 patients who received postoperative chemoradiotherapy are summarized in Table 3. Hematologic and gastrointestinal toxic effects predominated. The most common hematologic toxic effect was leukopenia. Severe thrombocytopenia was uncommon. Gastrointestinal toxic effects included nausea, vomiting, and diarrhea. Other types of toxic effects occurred in less than 10 percent of the patients. Three patients (1 percent) died as a result of a toxic effect attributed to chemoradiotherapy (pulmonary fibrosis in one patient, a cardiac event in another, and sepsis complicating myelosuppression in the third).

Overall and Relapse-free Survival

With a median follow-up period of 5 years, the median duration of survival was 36 months in the chemoradiotherapy group and 27 months in the surgery-

TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

TYPE OF TOXIC EFFECT	NO. OF PATIENTS (%)
Hematologic	148 (54)
Gastrointestinal	89 (33)
Influenza-like	25 (9)
Infection	16 (6)
Neurologic	12 (4)
Cardiovascular	11 (4)
Pain	9 (3)
Metabolic	5 (2)
Hepatic	4 (1)
Lung-related	3 (1)
Death†	3 (1)

*Major toxic effects were defined as those of grade 3 or higher. Data are for the 273 patients who received chemoradiotherapy.

†One patient died from a cardiac event, one from sepsis complicating myelosuppression, and one from pulmonary fibrosis.

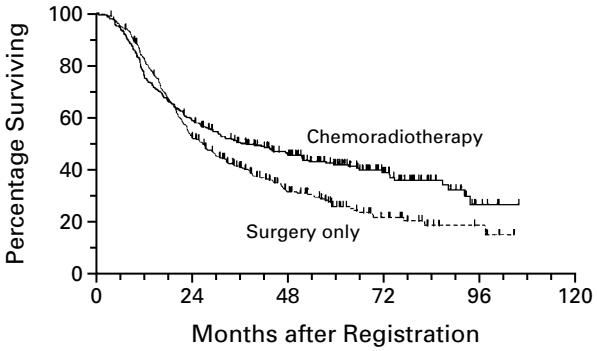

Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgery-only group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169 of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period.

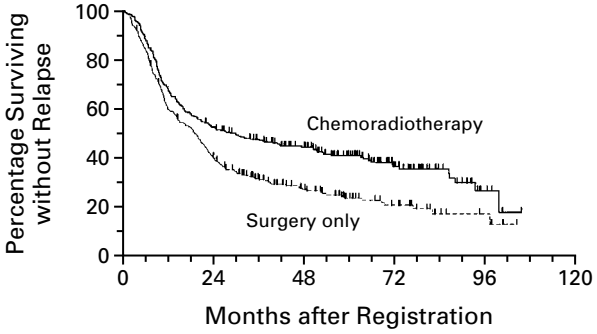

Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

The median duration of relapse-free survival was 19 months in the surgery-only group and 30 months in the chemoradiotherapy group. This difference in relapse-free survival was significant (P<0.001 by a two-sided log-rank test). A total of 174 of the 281 patients in the chemoradiotherapy group and 206 of the 275 patients in the surgery-only group died or had a relapse during the follow-up period.

only group (Fig. 1). The three-year survival rates were 50 percent in the chemoradiotherapy group and 41 percent in the surgery-only group. The hazard ratio for death in the surgery-only group, as compared with the chemoradiotherapy group, was 1.35 (95 percent confidence interval, 1.09 to 1.66; P=0.005).

The hazard ratio for relapse in the surgery-only group, as compared with the chemoradiotherapy group, was 1.52 (95 percent confidence interval, 1.23 to 1.86; P<0.001). The median duration of relapse-free survival was 30 months in the chemoradiotherapy group and 19 months in the surgery-only group (Fig. 2). The three-year rates of relapse-free survival were 48 percent in the chemoradiotherapy group and 31 percent in the surgery-only group. Relapses were reported in 64 percent of the patients in the surgery-only group and 43 percent of those in the chemoradiotherapy group.

We recorded information on the site of the first relapse only, and these sites were categorized as local, regional, or distant (Table 4). Local recurrence occurred in 29 percent of the patients in the surgery-only group and 19 percent of those in the chemoradiotherapy group. Regional relapse — typically, abdominal carcinomatosis — was reported in 72 percent of those in the surgery-only group and 65 percent of those in the chemoradiotherapy group; 18 percent of those in the surgery-only group and 33 percent of those in the chemoradiotherapy group had distant relapses. Because we only required documentation of a single site of first relapse, a statistical assessment of differences in these patterns of relapse rates would be biased by a lack of complete reporting of sites.

We were unable to detect differences in the effects of treatment according to sex, race, the location of the primary tumor, or the extent of the surgical procedure.

DISCUSSION

In patients with rectal carcinoma,[21] adenocarcinoma of the pancreas,[22] and incompletely resected stom-

TABLE 4. SITES OF RELAPSE.*

SITE	PATIENTS WITH RELAPSES	
	SURGERY-ONLY GROUP (N=177)	CHEMORADIOTHERAPY GROUP (N=120)
	no. (%)	
Local	51 (29)	23 (19)
Regional	127 (72)	78 (65)
Distant	32 (18)	40 (33)

*Because patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients in each group who had relapses.

ach cancer,[13,14] postoperative regional radiation plus chemotherapy reduces the risk of relapse and prolongs survival. The frequent occurrence of local and regional relapses after resection for gastric cancer provided the rationale for our evaluation of the combination of chemotherapy and radiation in patients with adenocarcinoma of the stomach or gastroesophageal junction. Our results demonstrate that chemoradiotherapy after resection for gastric cancer significantly improves relapse-free and overall survival among such patients. The apparent benefit of adjuvant therapy could not be the result of shorter-than-expected survival in the surgery-only group, since the duration of survival in this group closely approximated that observed in other studies.[4,23]

The adequacy of surgical resection in our patients is an important issue. Resection of all detectable disease was required for participation in the trial. An extensive (D2) lymph-node dissection was recommended, but patients were not excluded on the basis of the extent of lymphadenectomy. Only 10 percent of the patients underwent a D2 dissection, 36 percent had a D1 dissection, and 54 percent had a D0 lymphadenectomy (a resection in which not all of the N1 nodes were removed).

Although one would intuitively expect extensive nodal dissection to be beneficial in removing subclinical cancer, its value has been the subject of serious debate in surgical oncology.[24] Three randomized studies[25-27] have compared D1 dissection with D2 dissection. The two largest of these studies[26,27] found similar five-year survival rates after D1 and D2 procedures: 35 percent and 33 percent, respectively, in a study conducted in the United Kingdom and 45 percent and 47 percent, respectively, in a trial in the Netherlands. Both trials found significantly increased in-hospital mortality related to the distal pancreatectomy and splenectomy performed as part of the D2 procedure. Although these trials had their limitations — they did not control surgical technique precisely and had high overall mortality rates — no phase 3 trial to date has demonstrated a survival benefit resulting from D2 nodal resection. In our study, we were unable to detect any significant difference in relapse-free or overall survival according to the extent of the dissection ($P=0.80$).

In summary, our results demonstrate that local–regional radiotherapy plus fluorinated pyrimidine–based chemotherapy administered as adjuvant (postoperative) treatment significantly improves overall and relapse-free survival among patients with gastric cancer. Although this therapy may be delivered safely, radiation oncologists must be familiar with the proper techniques for the delivery of upper abdominal radiation in patients who have undergone gastrectomy, and the maintenance of adequate nutrition during therapy is essential. This study also indicates that a D0 lymphadenectomy is the most common type of lymph-node dissection performed in the United States during resection for gastric cancer. Adjuvant treatment with fluorouracil plus leucovorin and radiation should be considered for all patients with high-risk gastric cancer.

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