Postoperative chemoradiotherapy for gastric cancer


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Received 19 February 2003; revised 16 April 2003; accepted 14 May 2003

Background: We report the results of postoperative chemoradiotherapy after curative resection in gastric cancer patients.

Patients and methods: Patients with gastric cancer staged IB to IV(M0) were treated with chemoradiotherapy after curative resection with extensive (D2) lymph node dissection. Nodal metastases were observed in 261 (90%) patients. The chemotherapy consisted of fluorouracil 400 mg/m² plus leucovorin 20 mg/m² for 5 days, followed by 4500 cGy of radiotherapy for 5 weeks with fluorouracil and leucovorin on the first 4 days and the last 3 days of radiotherapy. Two 5-day cycles of chemotherapy were given 4 weeks after the completion of radiotherapy.

Results: Of 290 patients accrued, 229 (79%) patients completed chemoradiotherapy as planned. With a median follow-up of 49 months, 114 (34%) patients have relapsed: 33 (29%) locoregional relapses, 76 (67%) peritoneal relapses and 41 (36%) distant metastases. The 5-year overall and relapse-free survivals were 60% and 57%, respectively. Tolerance was acceptable, the main toxicity being neutropenia.

Conclusions: This postoperative chemoradiotherapy after curative resection of gastric cancer was feasible, with acceptable toxicities. Whether this adjuvant therapy in gastric cancer patients that have undergone a D2 lymph node dissection impacts on survival or reduces the incidence of relapses remains to be studied.

Key words: adenocarcinoma, chemoradiotherapy, gastric, postoperative

Introduction

Gastric cancer is the most frequently occurring malignancy in Korea, and is one of the main causes of cancer death. According to the Ministry of Health and Welfare, the high mortality rate for gastric cancer has remained stable over the past two decades, being 29.7/100000 inhabitants in 1983 and 24/100000 inhabitants in 2001 [1, 2].

Complete surgical resection is the only potentially curative therapy available to patients with gastric cancer. However, even after a complete resection with negative margins, many patients will experience recurrence, and in general only palliative therapy is possible, reflecting the fact that most cases are diagnosed at an advanced stage [3].

The high rate of recurrence after curative resection makes it important to consider postoperative adjuvant therapy for patients with gastric cancer. However, most previous adjuvant trials have failed to show significant survival advantage in gastric cancer [4, 5]. Although there is no prospective study comparing postoperative chemotherapy and surgery alone in patients with gastric cancer in Korea, postoperative chemotherapy has been frequently given based on the evidence of survival benefit compared with historical control data [6].

The aim of this study was to evaluate the possible benefit of postoperative adjuvant chemoradiotherapy after curative resection in gastric cancer patients. We assessed overall and relapse-free survival, incidence and patterns of relapse, as well as the toxic effects.

Patients and methods

Patients

All patients were required to have histologically confirmed adenocarcinoma of the stomach. All patients also had a complete resection of the tumor, defined as resection performed with curative intent (D2 type) and resulting in resection of all tumor with negative margins; disease stage IB to IV(M0) according to the 1997 staging criteria of the American Joint Commission on Cancer [7]; an Eastern Cooperative Oncology Group performance status of ≤1 [8]; adequate function of major organs (including cardiac, hepatic and renal functions); adequate bone marrow function (hemoglobin >10 g/dl; leukocyte count ≥4000/µl; platelet count ≥100000/µl); a caloric intake >1500 kcal per day by oral route; treatment beginning no more than 6 weeks after surgery, but delay of a week was allowed to permit full recovery with restoration of reasonable
nutritional intake. Patients who had coexisting malignancy or who could not tolerate chemotherapy due to systemic disease were excluded. All patients underwent chest radiographs and abdominopelvic computed tomography to exclude distant metastases. Patients with any evidence of peritoneal seeding or distant metastasis were excluded. Informed consent was obtained from each individual before the enrollment. This study protocol was reviewed and approved by the Samsung Medical Center Institutional Review Board.

Surgery
The surgical requirement for eligibility was resection with curative intent and en bloc resection of the tumor with negative margins. All patients had undergone extensive (D2) lymph node dissection. This procedure entails the resection of all perigastric nodes and some celiac, splenic or splenic-hilar, hepatic artery, and cardiac lymph nodes, depending on the location of the tumor [9].

Chemoradiotherapy
Therapy was administered on an outpatient basis. The regimen of fluorouracil and leucovorin was developed by the North Central Cancer Treatment Group [10] and was administered before and after radiation. Chemotherapy for 5 days with fluorouracil 400 mg/m²/day and leucovorin 20 mg/m²/day was administered on day 1 and was followed by chemoradiotherapy beginning 4 weeks after the start of the initial cycle of chemotherapy. Chemoradiotherapy consisted of 4500 cGy of radiation at 180 cGy/day, 5 days/week for 5 weeks, with fluorouracil and leucovorin on the first 4 days and the last 3 days of radiotherapy. Four weeks after the completion of radiotherapy, two 5-day cycles of chemotherapy were given 4 weeks apart. Planned total doses of leucovorin and fluorouracil were 440 mg/m² and 8800 mg/m², respectively. The dose of leucovorin was kept constant, and the dose of fluorouracil was reduced according to toxicity.

The 4500 cGy of radiation was delivered in 25 fractions 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 imaging. We used the definition of the Japanese Research Society for Gastric Cancer for the delineation of the regional lymph node areas [9, 11]. This regimen of chemoradiotherapy was shown to be tolerable in a previous trial [12].

Patient evaluation
We followed up patients at 3-month intervals for 1 year, at 6-month intervals for the next 2 years and yearly thereafter. Follow-up consisted of physical examination, a complete blood count, liver function tests, chest radiography, abdominopelvic computed tomography, and gastroscopy as clinically indicated. During the follow-up period, any suspected relapse was confirmed by biopsy, if possible. Typical nodules in liver or lung with imaging studies and typical lesions in the radioisotope bone scan and plain X-ray were accepted as relapse without histological confirmation. The site and date of the first relapse and the date of death, if the patient died, were recorded.

The site of relapse was classified as follows: the relapse was coded as loco-regional if the tumor was detected within the radiation fields (including surgical anastomosis, remnant stomach or gastric bed); as peritoneal if the tumor was detected in the peritoneal cavity; and as distant if there was liver metastasis or the metastases were outside the peritoneal cavity.

Statistical considerations
Initially, we designed this study as a prospective randomized study comparing postoperative chemoradiotherapy with surgery alone. However, we were failing to accrue patients on the control group because most patients wanted to receive postoperative therapy, thus we had to change the design to a single-arm study.

Two important outcome measures in this study were overall and relapse-free survival rates. Relapse-free survival was defined as the time from surgery to the recurrence of cancer, occurrence of a second primary carcinoma, or death without evidence of recurrence or second primary. The Kaplan–Meier product-limit method was used to estimate survival rates. To assess the importance of potential prognostic factors, we performed univariate and multivariate analyses using log-rank test and Cox’s proportional hazards regression model. A P value <0.05 was considered significant. All analyses were performed using SPSS for Windows 10.0 software.

Results

Patient characteristics
Two-hundred and ninety patients who underwent surgery at Sung Medical Center, Seoul, Korea, were entered in this study between August 1995 and January 1999. Two (1%) patients had previously undergone gastric surgery for peptic ulcer. All patients were ambulatory or asymptomatic after surgery. Sixty per cent of the patients underwent subtotal gastrectomy and most tumors were located in antrum or corpus. Almost two-thirds of the patients had stage III or IV tumors, and 90% had nodal metastases confirmed with surgical specimen (Table 1).

Treatment
Of the 290 patients enrolled in this study, 229 (79%) patients completed treatment as planned (Table 2); 26 (43%) patients stopped treatment because of toxic effects. Fourteen patients declined further treatment, 12 had progression of disease while receiving treatment, and nine patients discontinued treatment because of their poor performances.

Median total dose of administered fluorouracil was 7240 mg/m² [95% confidence interval (CI) 7045–7434 mg/m²], which was 82% of the planned dose (95% CI 80% to 84%) (Table 3).

Toxicity
Toxicities were graded as 1–4 based upon the National Cancer Institute Common Toxicity Criteria [13]. The toxicities classified as grade 3 or higher are summarized in Table 4, the most common toxicity being neutropenia. Five (2%) patients underwent adhesiolysis during the treatment due to intestinal obstructions that were not a result of tumor recurrence. No toxic death was observed.

Survival and relapse
With a median follow-up period of 49 months, 98 (34%) patients died (Figure 1). The 3-year survival rate was 68% and the 5-year survival rate was 60%.

One-hundred and fourteen (39%) patients relapsed during the follow-up period. Of these, 44 (39%) patients showed early relapse within the first year, whereas 11 (10%) patients showed late relapse after 3 years of surgery. The rate of relapse-free survival at 3 years was 62%, and at 5 years was 57%. Locoregional recurrence occurred in 33 (29%) of the relapsed patients. Peritoneal relapse was reported in 76 (67%) patients and 41 (36%) patients had distant relapses (Table 5).

Prognostic factors
We compared the incidence of relapse and survival rates by grouping median dose intensity and failed to detect any differ-
ences between the above- and below-median groups (Table 6). In the univariate analysis, subtotal gastrectomy, completion of chemo-radiotherapy and early stage were associated with a better survival, and subtotal gastrectomy and early stage were also associated with a lower risk of relapse. In the multivariate analysis, we found that advanced stage (Figure 2) and relapse were related to decreased survival.

Discussion

Gastric cancer is usually diagnosed when it is locally advanced with extension to the serosa and/or lymph nodes, or with intra-
peritoneal spread far from the tumor bed. Surgery has been considered the only way to cure gastric cancer; however, survival rates are quite low despite tumors being curatively resected. Therefore, postoperative adjuvant therapy has been extensively studied for gastric cancer.

Meta-analyses of randomized trials failed to demonstrate significant improvement in survival with the use of postoperative chemotherapy in resected gastric cancer [4, 5]. Radical gastrectomy with extended lymph node dissection (D2 or higher) has been regarded as standard surgery in Korea and Japan. Although a survival advantage was not confirmed in randomized trials [14, 15], D2 lymph node dissection is beneficial in determining more accurate pathological staging.

In Western countries, it has been reported that the sites of treatment failure after surgical treatment were mainly locoregional, in the tumor bed. Thirty-eight per cent to 85% of the patients relapsed locally, and when there was lymph node involvement, the relapse rate was as high as 85% [16, 17]. Treatment failure sites were not restricted to the tumor bed only; 9–54% of patients sustained relapses in the abdomen but outside of the tumor bed [18]. The frequency of such relapses made regional radiation an attractive strategy for postoperative therapy [19]. However, in Korea and Japan where extensive (D2 or higher) lymph node dissection has been regarded as a standard surgical procedure for gastric cancer, distant organs and peritoneum were the main sites of recurrence [20, 21].

Recently, MacDonald et al. [22] reported the results of the Intergroup trial INT-0116 comparing the effect of postoperative chemoradiotherapy with that of surgery alone. They reported a significant improvement in survival with the use of chemoradiation as adjuvant therapy in resected gastric cancer.

Nevertheless, the Intergroup trial seems to have some weaknesses. First, it was difficult to assess precisely the treatment outcomes as only 181 out of 281 patients (64%) completed treatment as planned. Secondly, most patients in this study had undergone limited (D0 or D1) lymph node dissection, which might be substantially associated with increased risk of residual positive nodes and with a suspicion of inadequate nodal staging. The authors reported that 19% of the patients in the chemoradiotherapy arm had relapsed locally, whereas 29% had relapsed in the control arm, and the sites of relapse were mainly locoregional. This result may suggest the possibility of inadequate local control with limited (D0 or D1) lymph node dissection.

Our study was initially designed as a randomized trial but we failed to obtain consent from those patients randomized to the control arm, because most patients wanted to receive postoperative treatment. If we had been successful, we would have been able to draw more precise conclusions from this study. With this kind of limitation, our results demonstrate that postoperative chemoradiotherapy after resection of gastric cancer may be feasible with acceptable toxicities; however, it is still questionable that this kind of chemoradiotherapy may be of value as surgical adjuvant for gastric cancer.

Yoo et al. [21] reported that peritoneal recurrence was the most frequent (46%) in gastric cancer patients receiving D2 lymph node dissection. Randomized trials performed by Japanese investigators reported 5-year survivals of 46–68% in patients with D2–3 resected gastric cancer staged I to IV; these rates were comparable to our results [23]. Compared with the results from the large randomized Western studies performed by Dutch [14] and British

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients with relapse</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Locoregionalb</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Peritonealc</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Distantd</td>
<td>41</td>
<td>36</td>
</tr>
</tbody>
</table>

aBecause patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients with relapses.
bTumor detected within the radiation fields (including surgical anastomosis, remnant stomach or gastric bed).
cTumor detected in the peritoneal cavity.
dMetastases were outside the peritoneal cavity (including liver).

Table 5. Pattern of treatment failure (n = 114)

<table>
<thead>
<tr>
<th>Unfavorable factors</th>
<th>On relapse</th>
<th>On survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>0.62</td>
<td>0.60</td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lauren classification</td>
<td>0.30</td>
<td>0.21</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>0.17</td>
<td>0.09</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Failure to complete treatment</td>
<td>0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>Relative dose intensity</td>
<td>0.47</td>
<td>0.44</td>
</tr>
<tr>
<td>Relapse</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

P values are from χ²-test or Fisher’s exact test for categorical variables; Mann–Whitney test for continuous variables; and log-rank test or Cox’s regression for variables on survival.
operative chemoradiotherapy in patients undergoing D2 lymph node dissection. Therefore, we hope that this study will result in a prospective randomized phase III trial of postoperative chemoradiotherapy improves survival.

In the present study, 60% of the patients receiving postoperative chemoradiotherapy survived 5 years or more. It is still difficult to reach any definite conclusions on the influence of postoperative chemoradiotherapy on long-term survival for the patients with resected gastric cancer, especially for those who underwent D2 or higher lymph node dissection. Therefore, we hope that this study will result in a prospective randomized phase III trial of postoperative chemoradiotherapy in these patients.

References