Original Article

# Adjuvant chemo-radiotherapy in patients with gastric cancer

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## Abstract

**BACKGROUND:** The role of adjuvant therapy in gastric cancer has been controversial. **AIM:** In this study, we report our experience with adjuvant chemotherapy and radiotherapy in patients with non-metastatic gastric cancer. **SETTINGS AND DESIGN:** Fifty patients were reviewed and assigned to three therapeutic groups. **MATERIALS AND METHODS:** Twenty patients received radiotherapy with concomitant administration of 5-fluorouracil and leucovorin on the first and last three days of radiotherapy; 20 patients received a five-day cycle 5-fluorouracil and leucovorin followed four to five weeks later by radiotherapy concomitant with the administration of fluorouracil on the first and the last three days of radiotherapy. Four weeks after radiotherapy two more five-day cycles of chemotherapy were administered; 10 patients received three cycles of cisplatin/docetaxel followed by radiotherapy and three additional cycles of chemotherapy after the completion of radiotherapy. **STATISTICAL ANALYSIS:** Patients were evaluated for treatment-related toxicity, local recurrences, distant metastases and deaths. We also aimed to make any possible comparisons between different chemo-radiation protocols. **RESULTS:** Within a median follow-up of 21,5 months seven patients developed local recurrence and 17 patients developed distant metastases. The overall death proportion was 42% (95% CI 28.2-56.8%). Despite the limited number of patients, no statistically significant differences in local recurrences, distant metastases and deaths were observed between the three protocols. Acute and long-term treatment-related toxicity was low and no treatment-related deaths were observed. **Conclusion:** Despite variations of chemotherapy, our study demonstrated that combined chemo-radiotherapy for patients with resected gastric cancer can be administered safely, with acceptable toxicity.

**Keywords:** Chemotherapy, gastric cancer, radiotherapy



## Introduction

The prognosis of gastric cancer remains poor despite the improvement in interventions during the last years. Although surgery remains the mainstay of potentially curative treatment for early stage gastric cancer, the long-term survival even in patients with complete resection and negative surgical margins is guarded. The five-year survival ranges from 70% for early stage gastric cancer to less than 10% for patients who have extensive lymph node involvement.[1,2] Numerous adjuvant efforts have been performed in the past decades to improve survival of these patients, after complete resection. However, the role of adjuvant therapy in gastric cancer has been controversial, since many randomized trials have lacked demonstrating a significant survival benefit so far.[3-6] Moreover, the benefit of aggressive adjuvant approaches has been compromised by the increased treatment-related morbidity and mortality.[3,7] Interest in adjuvant radiation therapy (RT) stems from the observation that over 80% of patients who die from gastric cancer, have experienced a local recurrence during the disease.[8] Almost all postoperative RT trials have included concurrent low dose chemotherapy -usually with 5-fluorouracil (5-FU)- to improve the efficacy of radiation

("radiation sensitization").

Undoubtedly, a renewed interest in gastric cancer treatment has arisen after the US Intergroup trial (0116), which demonstrated a clear survival advantage of adjuvant chemo-radiotherapy and strongly supported the integration of this treatment as part of standard care for patients who have undergone curative resection for high-risk adenocarcinoma of the stomach and gastroesophageal junction.[9] An updated report of this trial has confirmed that this benefit is still maintained at the long term.[10] These results have changed the standard of care in many countries following potentially curative resection of gastric cancer from observation alone to adjuvant combined chemo-radiotherapy, although the optimal regimen for postoperative chemo-radiotherapy has not been established yet.

In the present study we present our department's experience with adjuvant chemotherapy and RT in patients with non-metastatic gastric cancer that had undergone curative resection. We have tried to evaluate the possible benefits of such a combined treatment modality, to assess its tolerability and also aimed to make any possible comparisons between different chemo-radiation protocols.

## Materials and Methods

The medical records of patients (stored as electronic files in the institution), who were treated with postoperative chemotherapy and RT for histologically confirmed adenocarcinoma of the stomach between January 1996 and December 2004, were reviewed by two independent investigators (AC, EEP). All patients had a complete clinical and laboratory staging preoperatively that included a detailed clinical examination and blood measurements, a bone scan and a computed tomography (CT) scan of the thorax, abdomen and pelvis. A complete gastric cancer resection with curative intent was performed (total or subtotal gastrectomy). Patients were staged according to the International Union Against Cancer TNM staging system.[11] All patients had recovered sufficiently from their operations before adjuvant therapy and all had adequate major organ function at the commencement of treatment (including cardiac, hepatic, renal and bone marrow function). Patients with metastatic disease were excluded from the analysis. We also excluded from the study patients whose clinical data could not be found or was remotely informative.

Patients received combined adjuvant chemo-radiotherapy if they had at least one of the following criteria: a) serosa invasion, b) extension to adjacent organs or c) metastases to the regional lymph nodes d) positive surgical margins. Chemotherapy was administered on an outpatient basis. Before 2001 (the year the intergroup trial 0116 was published), all patients received radiotherapy with concomitant administration of 5-fluorouracil (400 mg/m$^2$) and leucovorin (20 mg/m$^2$) on the first and last three days of RT (Group A). After the year 2001, the intergroup 0116 treatment plan was adopted. According to this protocol, patients received a five-day cycle of bolus 5-fluorouracil at 425 mg/m$^2$ and leucovorin at 20 mg/m$^2$ followed four to five weeks later by radiotherapy concomitant with the administration of fluorouracil on the first and the last three days of radiotherapy. Four weeks after completion of radiotherapy, two more 5-day cycles of chemotherapy was administered with a four-week interval (Group B). Finally, a subgroup of patients received chemotherapy according to an institutional protocol consisting of three cycles of cisplatin/docetaxel followed by radiotherapy and three additional cycles of chemotherapy after the completion of radiotherapy (Group C).

External beam radiotherapy was delivered by a linear accelerator (6-MV photons). Two parallel-opposed fields (antero-posterior, postero-anterior) were used. Both fields were treated on each treatment session. Oral barium contrast was given to the patients during the simulation procedure for better target volume definition [Figure 1]. The tumor bed, the anastomosis, the stump and the loco-regional lymph nodes were treated. Antiemetics were administered orally one hour before irradiation. A two-D planning (Mevaplan-Siemens) was applied. The target volume was covered by the 95% isodose curve. Treatment was given for five days per week for five weeks. The daily radiation dose ranged from 1.8 to 2.0 Gy and the median total radiation dose was 45.0 Gy (range 40.0-50.04).

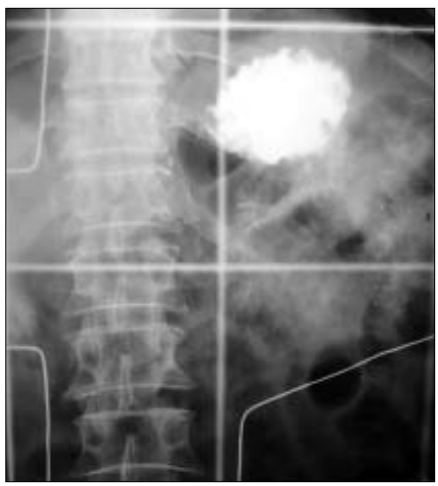

**Figure 1: Simulator film of the treatment field after oral barium contrast administration**

All patients were followed up in an out-patient basis, after the end of radiotherapy, every three months for the first two years, every six months for the third and fourth year and annually thereafter. Their evaluation included a physical examination, blood count and biochemical analyses. A chest radiograph, CT scans of the pelvis and abdomen and endoscopic examination were performed once a year. Bone scans and skeletal X-rays were obtained on indication. Patients were evaluated for treatment related toxicity, local recurrences and distant metastases. The treatment related toxicity was graded according to world health organization classification.[12] All patients or their families were contacted by phone call, if they had not responded to their last programmed visit and they were asked to provide additional data about their current condition.

We present the incidence of disease progression (local recurrence or metastasis) and death and we have estimated overall survival and disease-free survival for all patients included in our study. We also aimed to make any possible comparisons between the different therapeutic approaches. Kaplan-Maier analysis was used for overall and disease-free survival. The group differences were tested using exact inference (Fisher's test) or the Mann-Whitney test, as appropriate. Differences in survival functions were evaluated with the log-rank test. $P<0.05$ were considered formally statistically significant; all p-values were two-tailed. All statistical analyses were performed using the statistical package for social sciences (SPSS 11.0 Inc, Chicago IL).

## Result

Fifty patients with gastric adenocarcinoma treated with combined surgery and chemo-radiotherapy with available clinical data were eventually included in the present study. The median age (IQR) of patients was 62.0 (54-68) and the male/female ratio was 2.85 (37 males and 13 females). A total gastrectomy was performed in 24 patients (48%) while 26 patients (52%) underwent a subtotal gastrectomy. The mean number of resected lymph nodes (LNs) was 24 (range 3-76), while in 23 patients more than 20 LNs were dissected. Forty-six patients (92%) had positive LNs, while in four patients (8%) no LN infiltration was detected. According to the TNM staging system, three patients were stage II, 18 stage IIIA, 18 stage IIIB and 11 patients were stage IV. Forty patients (80%) had negative surgical margins. The main patient characteristics are presented in Table 1.

Twenty patients (40%) received chemotherapy according

**Table 1: Characteristics of eligible patients included in the study**

| | Overall | Group A | Group B | Group C |
|---|---|---|---|---|
| Gender | | | | |
| Male | 37 (74%) | 15 | 16 | 6 |
| Female | 13 (26%) | 5 | 4 | 4 |
| Median age (range) | 62 years (40-75) | 63.0 (35-75) | 63.5 (39-71) | 60.0 (41-71) |
| Gastric resection | | | | |
| Total | 26 (52%) | 12 | 11 | 3 |
| Subtotal | 24 (48%) | 8 | 9 | 7 |
| Surgical margins | | | | |
| Negative | 40 (80%) | 17 | 13 | 10 |
| Positive | 8 (16%) | 2 | 6 | 0 |
| Not available | 2 (4%) | 1 | 1 | 0 |
| Lauren classification | | | | |
| Diffuse | 24 (48%) | 8 | 12 | 4 |
| Intestinal | 17 (34%) | 9 | 5 | 3 |
| Mixed | 1 (2%) | 1 | 0 | 0 |
| Not available | 8 (14%) | 2 | 3 | 3 |
| Location of tumor | | | | |
| Lower | 24 (48%) | 7 | 10 | 7 |
| Medium | 21 (42%) | 11 | 8 | 2 |
| Upper | 5 (10%) | 2 | 2 | 1 |
| LN staging | | | | |
| N0 | 4 (8%) | 3 | 0 | 1 |
| N1 (£6) | 23 (46%) | 9 | 10 | 4 |
| N2 (6-15) | 15 (30%) | 6 | 5 | 4 |
| N3 (>15) | 8 (16%) | 2 | 5 | 1 |
| Pathological staging | | | | |
| II | 3 (6%) | 2 | 0 | 1 |
| IIIA | 18 (36%) | 8 | 8 | 2 |
| IIIB | 18 (36%) | 7 | 5 | 6 |
| IV (M0) | 11 (22%) | 3 | 7 | 1 |
| Toxicity | | | | |
| No | 14 (28%) | 5 | 4 | 5 |
| Mild | 23 (46%) | 11 | 8 | 4 |
| Severe | 13 (26%) | 4 | 8 | 1 |

LN: lymph nodes

Group A: radiotherapy with concomitant administration of 5-fluorouracil and leucovorin on the first and last three days of radiotherapy

Group B: Five-day cycle 5-fluorouracil and leucovorin followed four to five weeks later by radiotherapy concomitant with the administration of fluorouracil on the first and the last three days of radiotherapy and at four weeks after radiotherapy two more five-day cycles of chemotherapy.

Group C: Three cycles of cisplatin/docetaxel followed by radiotherapy and three additional cycles of chemotherapy after the completion of radiotherapy.

to Group A protocol, 20 patients (40%) according to Group B protocol and 10 patients (20%) according to Group C chemotherapeutic protocol. All patients received adjuvant radiotherapy within a median period of 71 days (range 57-106) from surgery. Forty-seven patients (94%) tolerated irradiation without interruption of their treatment and completed radiotherapy as planned.

Acute toxicity was mild and there were no treatment-related deaths. The most common hematological toxicity was grade III leucopenia. Severe thrombocytopenia was uncommon. Three patients developed grade III myelotoxicity, which resulted in a delay of completion of radiotherapy for one to three weeks. Gastrointestinal toxicity was generally mild and manageable and no prolongation in treatment was attributed to it. The most common grade I/II gastrointestinal toxicities were nausea and vomiting, mucositis and diarrhea. Three patients developed grade 3 diarrhea, which were manageable. The acute toxic side effects are listed in Table 2. A trend for increased severe treatment-related toxicity (Grade III) was observed in the Group B protocol, but the differences were not statistically significant ($P$=0.23, 4 degrees of freedom [df]). Long-term toxicity was negligible in the three therapeutic groups. Two patients had to be re-operated due to intestinal obstruction. In the first patient peritoneal carcinomatosis was diagnosed and he died one month later due to disease progression. In the second patient, the obstruction was due to fissures, but he recovered fully with no evidence of disease.

Within a median follow up of 21,5 months (range 6-110 months) seven patients developed a local recurrence (14% with 95% confidence interval [CI] 5.8-26.7%) and 17 patients developed distant metastases (34%, 95% CI 21.2-48.8%). The most common site of metastasis was the liver (11 patients). Peritoneal carcinomatosis, bone and lung metastases were also reported. From the seven patients that developed local recurrences, three belonged in group A, two in group B and two in group C, while the respective numbers for distant metastases per group were five, ten and two. Among the 24 patients that had a relapse (local recurrence or distant metastasis) 21 patients died of the disease (7 Group A, 12 Group B, 2 Group C). Three of the relapsed patients were still alive with liver metastases at the time of this writing. The overall death proportion was 42% (95% CI 28.2-56.8%). Despite the limited number of patients and the heterogeneity in the follow-up of each group, no statistically significant differences in local recurrences, distant metastases and deaths were observed between the three therapeutic protocols although a trend for decreased overall survival was observed in Group B patients ($P$=0.08, 2 df) [Figures 2 and 3].

The univariate analysis performed on different variables like surgical lymph nodes dissection, type of gastric resection, Lauren histology, tumor site, sex and LN status did not confirm their potential value in respect to overall survival. However, we observed a statistically significant lower disease free and overall survival in patients with advanced disease stage (stage IIIB, IV) ($P$=0.01 with 3 df and $P$=0.03 with 3 df respectively). The positive surgical margins were also associated with decreased disease-free and overall survival but the difference was strongly statistically significant only for the later ($P$=0.02 with 2 df).

**Table 2: Treatment - associated side effects based on the world health organization classification**

| Type of side effect | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| **Gastrointestinal** | | | |
| Nausea/vomiting | 14 (28) | 6 (12) | 0 |
| Mucositis | 6 (32) | 5 (10) | 0 |
| Diarrhea | 110 (20) | 5 (10) | 3 (6) |
| Fatigue | 7 (14) | 3 (6) | 0 |
| Hematological | | | |
| Leucopenia | 6 (12) | 18 (37) | 3 (6) |
| Anemia | 15 (28) | 8 (16) | 1 (2) |
| Throm/penia | 0 (20) | 4 (8) | 1 (3) |

Figures in parentheses are in percentage

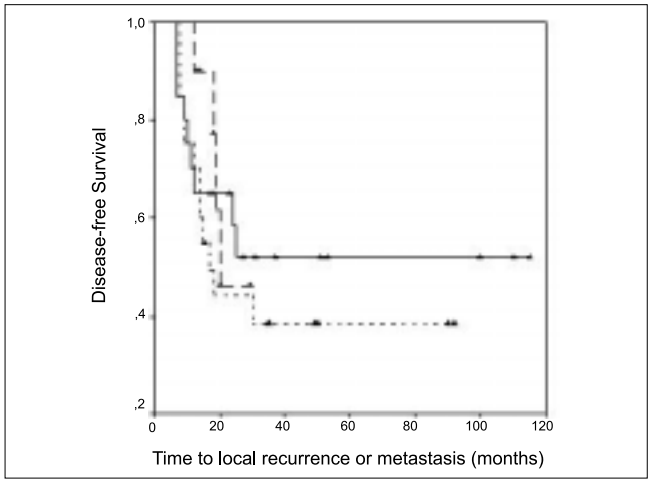


**Figure 2: Disease-free survival plots for patients with gastric cancer treated with the three therapeutic protocols (Group A protocol: continuous line, Group B protocol: dotted line and Group C protocol: line with dashes). Censoring is indicated by triangles**

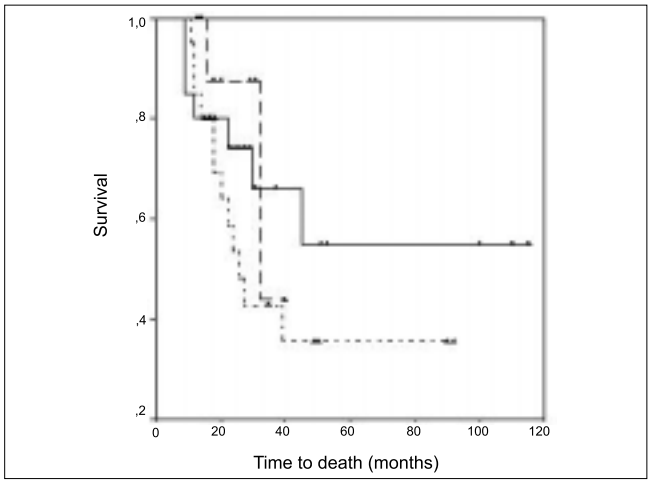


**Figure 3: Survival plots for patients with gastric cancer treated with the three therapeutic protocols (Group A protocol: continuous line, Group B protocol: dotted line and Group C protocol: line with dashes). Censoring is indicated by triangles**

## Discussion

The present retrospective study suggests that postoperative chemotherapy combined with radiotherapy can be administered safely and effectively in patients with radically resected gastric cancer. Almost half of the patients included in the analysis developed a relapse (loco-regional recurrence and/or distant metastasis), while approximately 40% of patients died overall in the three therapeutic protocols used. No statistical significant differences according to the intervention used were observed, although patients in Group A protocol showed a trend to improved outcomes compared to the other 2 protocols. However, the limited number of patients included in each group precluded solid analyses. Finally, both the acute and long-term treatment-related toxicity was low and no treatment-related deaths were observed.

Treatment of early-stage gastric carcinoma poses a therapeutic challenge. Only a small minority of patients accounting for only 10% of all gastric cancer cases will experience long overall survival and potentially cure. Even definite surgical treatment does not result in cure and the majority of patients will relapse and die of disease irrespective of the operation performed.[13] Despite the large amount of published trials the reported results are conflicting and no uniform treatment modality has been widely adopted and implemented. After the publication of the INT0116 results,[9] a shift towards a more homogenous treatment has been made. In this large, multi-institutional trial that enrolled 556 patients randomly assigned to either adjuvant chemo-radiotherapy (consisted of fluorouracil plus leucovorin followed by 4500 cGy of radiation) or surgery alone, postoperative chemo-radiotherapy offered a significant improvement in the three-year disease-free and overall survival. The three-year disease-free and overall survival was 48% and 50% respectively in the chemo-radiotherapy group and these rates were statistically significant higher than the respective rates in patients treated with surgery alone. A recent updated report has shown that the benefits of this combined adjuvant protocol, are maintained in the long term.[10]

The results of this study have been confirmed by later studies with similar interventions.[14-17] Among them, the largest one that enrolled a total of 990 patients (544 that received chemo-radiotherapy and 446 controls) recently reported that the postoperative chemo-radiotherapy identical to the 0116 protocol, can prolong survival and decrease recurrence in D2-resected gastric-cancer patients.[14] Another recent large randomized trial for operable gastric cancer, the MAGIC trial,[18] showed that patients with operable gastric adenocarcinoma may benefit from perioperative chemotherapy. However, despite the fact that the trial showed that periopeartive chemotherapy decreased tumor size and stage and significantly improved progression-free and overall survival, no radiotherapy was used in the eligible patients and the study didn't provide the harm–benefit ratio for specific subsets of patients with different extent of surgery and tumor stage. In our study, the different chemotherapy regimens that were used reflect the shift of the approach of adjuvant chemo-radiotherapy over the last decade. The Group B chemo-radiotherapeutic protocol is the same used in the INT 0116 trial. However, the limited number of patients (N=20) and the absence of a control group precluded any comparisons with the INT 0116 trial. Within a mean follow up of 33 months 12 patients had a relapse and finally died in the Group B protocol (60%, 95% CI 36-81%).

Nevertheless, the INT 0116 trial raised serious concerns about the adverse events of this adjuvant, combined treatment since the treatment-related toxicity was of high rate. Grade 3 and 4 toxic effects occurred in 41 and 32 percent of the chemo-radiotherapy group, respectively, while three patients (1%) died from treatment-related toxic effects. The most frequent grade 3 or worse adverse effects were hematologic (54%), gastrointestinal (33%), infectious (6%) and neurologic (4%). Taking into account the limitations of a retrospective analysis, in our series of 50 patients treated in one institution over a period of eight years with different chemotherapeutic regimens, toxicity was not a major concern. No significant toxicities were

documented and treatment-related deaths were not reported. The most troublesome toxicity was nausea and vomiting and grade III myelotoxicity was manageable and reversible without significant delays in treatment. Moreover, the results of the INT 0116 trial should be interpreted with caution since, only 64% of patients initially assigned in this adjuvant protocol completed treatment as planned. In our study only three patients (6%) had a delay in their treatment and no significant violations of the protocol were reported.

After the publication of the INT0116 study, a change in every day practice has been made and more patients received fluorouracil-based chemotherapy in addition to radiotherapy.[19] Employing chemotherapy in combination with radiotherapy in patients with high risk for relapse significantly reduces the chance of loco-regional recurrence, which has a considerable impact of morbidity and mortality. However, based on the high rates of reported adverse events of this protocol, there is still room in future randomized studies to evaluate the optimal regimen of chemotherapy that results in improved disease progression and survival outcomes combined with decreased treatment-related toxicity. The role of adding neo-adjuvant chemotherapy in postoperative chemoradiotherapy,[20] as well as the role of neo-adjuvant chemo-radiotherapy should also be defined.[21] Finally, new targeted therapies such as EGFR inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters and matrix metalloproteinases inhibitors should be examined by future investigators,[22] since they might represent novel treatment strategies in the battle against gastric cancer.

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