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Postoperative adjuvant chemotherapy with 5-fluorouracyl, adriamycin and cisplatin (FAP) in resectable gastric cancer

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The effectiveness of combined chemotherapy FAP as an adjunct to surgery was investigated in resected gastric cancer patients. Of 40 pts, 33 were evaluable. All patients were randomly assigned to surgery plus adjuvant FAP or surgery alone. The results have shown no benefit of adjuvant FAP in overall and disease free survival of patients with resectable gastric cancer. In addition, gastrointestinal intolerance presented a severe drawback and compromised the patients' quality of life.

Key words: stomach neoplasms – drug therapy; postoperative period

Introduction

Gastric cancer remains a major health problem in Slovenia, despite its decrease during the last decades. The prognosis in patients is poor; the overall five year survival rates are modest and have not increased over 5 % to 12 %.[1] The only chance of cure is still offered by surgery, although at the time of diagnosis only 20–30 % of patients will be amenable to operation.[1,2] Up to two thirds of patients, who have undergone curative resection, present with a recurence and die due to locoregional failure or metastatic disease. In the Western countries there has been no improvement in the prognosis over the past 40 years. The Japanese have however documented both better resectability and improved survival rates during the past 30 years. Extended lymphadenectomy has been reported to modify the survival in Stage II gastric cancer, while in stage III only 15 % patients can be cured by surgery alone.[3–5]

The failure of surgery to control the disease has led to several trials on adjuvant therapy.[5–14] The combination of the drugs used is often the one that has shown satisfactory results in the treatment of advanced gastric cancer. The combination of 5 FU, adriamycin and cisplatinum (FAP) is one of the several chemotherapeutic regimens that have proved active against advanced disease and have yielded 50 % response rate.[15] This paper, presents the results of a prospective randomized controlled study of adjuvant chemotherapy using FAP combination in operable gastric cancer.

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Materials and methods

Patients included in the study had undergone resection for histologically proven gastric adenocarcinoma. The UICC TNM classification

was used to define the stage of the disease. Histological subtyping of tumors was done by means of Lauren classification. The patients were randomized either to surgery plus chemotherapy or to surgery alone. Chemotherapy was started within 6 weeks following surgery. The chemotherapy consisted of 5 fluorouracil (5-FU) 500 mg/m^2 by rapid i.v. infusion on day 1 through day 5, doxorubicin 30 mg/m^2 i.v. on day 1, CDDP 20 mg/m^2 in 1500 ml of 0.5 normal saline i.v. over 2 hours on day 1 through day 5. The cycle was repeated every 4 weeks. Six consecutive cycles were planned to be given to each patient. Antiemetic therapy was administered routinely. Chemotherapy related toxicity was evaluated using WHO score. Appropriate dose adjustment or discontinuation of therapy was made if extensive toxicity was experienced during the proceeding course or if the patient refused further treatment. In addition, any histologically proven evidence of local recurrence or metastatic disease necessitated cessation of FAP treatment. Criteria for recurrence were histological proof or X-ray evidence of metastases.

Before entry to trial and after completed chemotherapy staging was carried out using chest radiology, ultrasonography or/and CT scan, hepatic and renal function tests and blood count. The patients were followed up in three month intervals; the check comprised a complete physical examination and blood chemistry, while repeated staging including gastroscopy was performed every six months in the first two postoperative years, and thereafter in 6 - month intervals.

The end point of the protocol was to determine the impact of adjuvant FAP on the survival and disease-free interval in patients treated by chemotherapy compared to those treated by surgery alone.

Survival and disease-free interval were calculated using Kaplan-Meier's method. The survival was assessed from the day of surgery until death or the most recent visit. The differences between groups were evaluated using log-rank test.

Results

The trial was conducted between January 1985 and January 1990. Fourty patients were entered into the trial; of these 33 were evaluable while 7 patients were lost to follow up. Patients' characteristics are shown in Table 1. There were 17 females and 16 males. Of 33 patients, 9 underwent total gastrectomy and 24 had subtotal gastrectomy. Seven patients underwent gastrectomy with incomplete removal of the primary (infiltrated tumor margins). For 11 patients surgery was the sole therapy, 21 cases received surgery plus FAP chemotherapy.

During 5-year observation period, 20 patients

Table 1. Characteristics of evaluable patients.

	Total	FAP	Control
Number of patients	33	22	11
Sex: male/female	16/17		
Age (years): median (range)	50 (37-62)		
Site of primary tumor			
Pylorus or antrum	20	10	10
Body	9	9	0
Cardia or fundus	4	3	1
Histological type			
Intestinal	12	9	3
Diffuse	21	13	8
Surgical procedure			
Subtotal gastrectomy	24	14	10
Total gastrectomy	9	8	1
Surgical margins status			
Negative	26	16	10
Positive	7	6	1
TNM stage			
T2	7	4	3
T3A	17	10	7
T3B	7	7	0
T4	2	1	1
N stage			
N0	7	4	3
N1	17	9	8
N2	8	8	0
N3	1	1	0
Stage			
II	11	7	4
IIIA	12	5	7
IIIB	8	8	0
IV	2	2	2

FAP = 5-FU, adriamicin, cisplatinum

Table 2. Causes of death.

Clinical cause of death	Total No.	FAP No.	Control No.
Metastatic disease	11	8	3
Local recurrence	9	7	2
Not recorded	3	3	0
Tumor unrelated	3	2	1
Total deaths	26	20	6

FAP = 5-FU, adriamycin, cisplatinum

in the treated arm and 6 in the control arm have relapsed and died. The causes of death are shown in Table 2.

At five years, 7 patients have been alive – 2 patients treated by chemotherapy and 5 controls. The overall survival for the whole group was 70% at two years, and 24% at 5 years (Figure 1), the corresponding numbers for NED being 52% and 24% respectively (Figure 2).

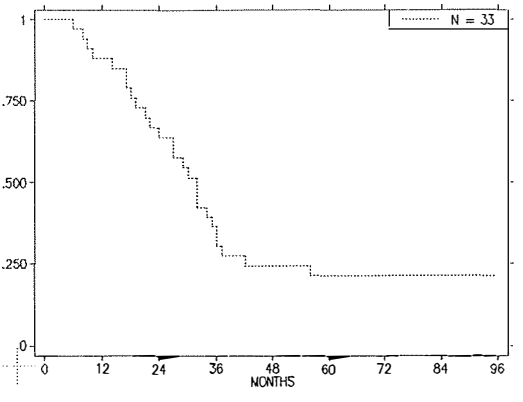

Figure 1. Overall survival of 33 patients with resectable gastric cancer.

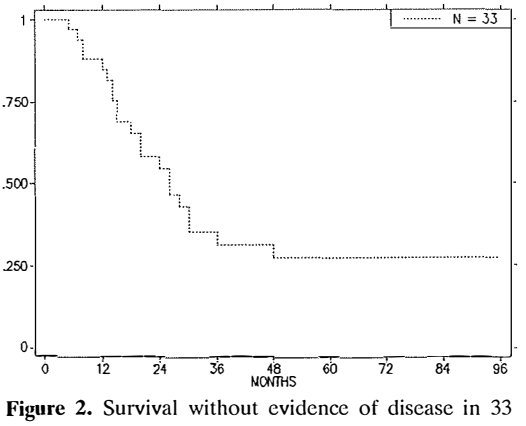

Figure 2. Survival without evidence of disease in 33 patients with resectable gastric cancer.

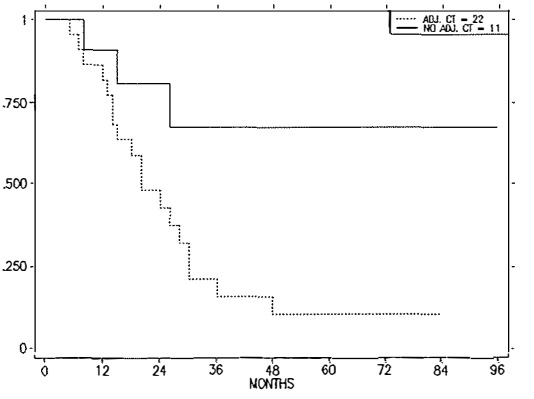

Figure 3. Survival without evidence of disease in 22 patients treated by adjuvant FAP (5-FU, adriamycin, cisplatinum) and 11 patients treated by surgery alone.

The comparison of the survival between both groups revealed statistically significant ($p < 0{,}0133$) difference in disease-free survival in favour of the untreated arm (Figure 3).

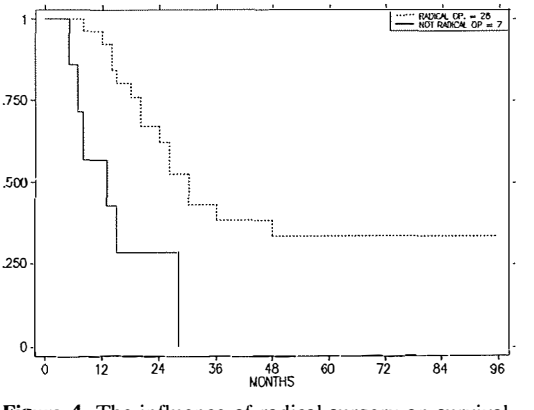

Figure 4. The influence of radical surgery on survival without evidence of disease.

A group analysis showed that patients who underwent radical surgery managed significantly better ($p < 0{,}0015$) than those who had incomplete resection (Figure 4). Adjuvant therapy worsened the survival in radically operated gastric cancer patients (Figure 5). The difference was however of borderline significance (p = NS). The histological type of the tumor has not exerted any influence on the survivals (P = NS) (Figure 6).

Side effects experienced by patients on chemotherapy are summarized in Table 3. Chemo-

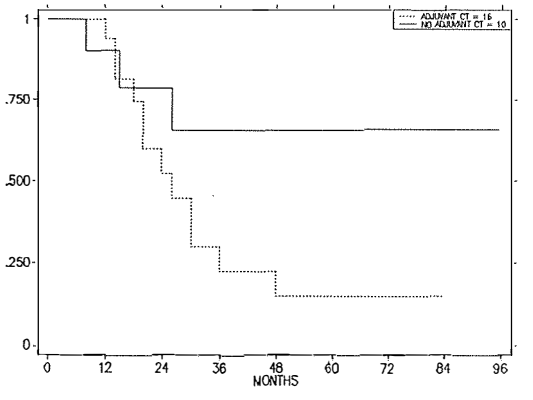

Figure 5. The influence of adjuvant chemotherapy on the survival without evidence of disease in 26 radically operated gastric cancer patients.

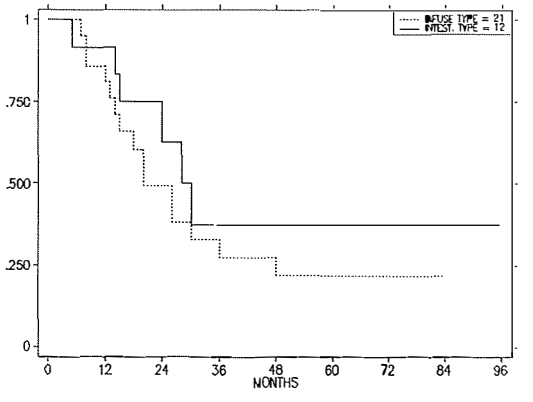

Figure 6. The influence of histology (Lauren classification) on the survival without evidence of disease in 33 resected gastric cancer patients.

therapy was discontinued after two or three courses in 9 (46%) patients because of poor gastrointestinal tolerance. Only 12 patients (54%) completed the planned therapy. There were no deaths related directly to chemotherapy in this study.

Table 3. Side effects of treatment with FAP (5-FU, adriamycin, cisplatinum).

Side effect (Grade 3–4)	No (%)
Nausea/vomiting	15 (68%)
Alopecia	16 (72%)
Nephrotoxicity	2 (9%)
Neurotoxicity	1 (4,5%)
Hemotoxicity	6 (27%)

Discussion

The role of systemic combination chemotherapy in the standard treatment for stomach cancer is limited to palliation. The most popular regimens used in gastric cancer treatment in Europe and the United States, such as FAB, FAM and FAP induce an objective response rate of 30–40%.[12,13,15,16] The FAP combination has been shown to be the most promising chemotherapy schedule at the beginning of the study, with a 50% response rate in advanced gastric cancer patients.[15] These results have suggested that FAP should be tested in patients with resectable gastric cancer.

The discussion of whether adjuvant chemotherapy is of any benefit in the treatment of gastric cancer is still open. Conflicting results have been obtained so far.[6,7,9–12,15] Therefore this kind of chemotherapy is used in resectable gastric cancer solely in randomized clinical trials. Several studies of adjuvant chemotherapy using different drug combinations have been conducted but have failed to demonstrate any benefit in improved survival.[3,6,7,9,12] There was however a suggestion that patients with T3 – T4 tumors do benefit from such treatment. Even though no statistically significant differences in the survival were established, a lower number of recurrences was found in the treated arms.[6]

The Japanese[5] have however reported a significant beneficial effect of combined chemo-immunotherapy in 1805 resected gastric cancer patients followed up for 5 years. Patients given immuno-chemotherapy survived longer than those treated by surgery alone. A curatively operated stage III subgroup seems to benefit the most from postoperative immuno-chemotherapy,[4,5,17] the beneficial effect was related to tumor infiltration by dendritic cells.[17] A combination of mitomycin, tegafur and PSK has become the most popular regimen for adjuvant treatment of gastric cancer in Japan.[5,16]

In adjuvant studies the stage of the disease (TNM), was shown to be the most important prognostic factor; this was followed by subtype

using Lauren classification, and site of the primary tumor.[1,17,18]

The results of this study have shown that the overall survival of all patients from both arms is not inferior to the survival data reported in patients with potentially curative resection for gastric cancer.[1,2] The finding of a significantly higher survival in nontreated arm compared to the treated arm, however, disagreed with other reports. By additional analysis of subgroups with different prognostic factors, it was shown that despite the random selection of operated patients, the unfavorable prognostic factors were all more prominent in the treated group. The treated group comprised six nonradically resected cases and all cases with N2 and N3 nodal involvement, vs. one nonradically resected and none N2 and N3 case in the control arm. In the German Gastric study, the survival was shown to be mainly dependent[19] on the absence of residual tumor. Non-radical resection shortened the survival. The results of the present study are in accordance with that finding. However the Gastrointestinal Tumor Study Group have found a 5 year survival rate of 17% obtained by chemotherapy plus radiotherapy in patients with microscopic locally recurrent or residual gastric cancer after surgery.[20] In our treated group none of the patients survived 5 years and all were dead within the first postoperative year.

Diffuse type carcinoma has been connected with worse prognosis in gastric cancer patients.[17,18] Statistically insignificant difference was shown also in the present study. Diffuse type was found to be the predominant histological type in the whole observed group with no difference between the two arms. The result shows that the worse outcome in the treated group was not related to the difference in tumor histology.

Adverse effects of the drug combination, especially gastrointestinal toxicity, posed a severe problem and required cessation of therapy in 46% of patients. Nausea and vomiting grade 3 and 4 were the reasons for patients' refusal of further therapy.

The results reported here indicate that as best this regimen can not be of benefit to patients with operable gastric cancer. In fact, there was a decreasing trend in the survival of the FAP treated patients. In view of the negative impact on survival, it would be reasonable not to conduct any further trials with this drug combination in adjuvant settings. However, the study included only 33 patients, and group evaluation revealed that despite randomisation, the differences between arms were very prominent. In future, studies of adjuvant therapy must comprise a sufficient number of cases to enable satisfactory evaluation.

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