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Positive Results of Adjuvant Mitomycin-C in Resected Gastric Cancer: A Randomised Trial on 134 Patients

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In order to evaluate the results on successful adjuvant chemotherapy in resected gastric cancer we performed a randomised trial on 134 patients in two arms: a control one with no further treatment after surgery versus a treatment arm given mitomycin-C (MMC), 20 mg/m² intravenously one day every 6 weeks for four courses, starting before the sixth week after surgery. The median follow-up was 105 months. In the control arm, 49 out of 66 patients died due to recurrence, versus 40 out of 68 patients in treatment arm. Actuarial survival curve was statistically significant ($P < 0.025$) in favour of the treatment group. Liver metastases were lower in adjuvant group than in the control group (8/68 versus 19/66). Toxicity was mild. Main toxic effects were thrombocytopenia, leukopenia, nausea and vomiting. A pelvis renal cancer as a second malignancy 8 years after gastric cancer was observed. In that particular case MMC was given after surgery. We conclude that adjuvant chemotherapy based on MMC given in the early period after surgery, improves survival rate in gastric cancer resected patients.
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INTRODUCTION

GASTRIC CANCER has a poor prognosis, even in patients undergoing surgery. In a review of 1479 cases, Dupont *et al.* [1], observed that 50% of resected patients died within 2 years of "curative" surgery. In Japan, in the past 25 years there has been a progressive improvement in the cure rate and long term survivors among patients with gastric cancer [2]. The reason for this improved survival has been the emphasis on early diagnosis, on extensive surgical procedures and because of the routine use of adjuvant chemotherapy. For this reason we initiated a randomised trial with adjuvant mitomycin-C (MMC) preliminary results of which have been previously published [3]. The life-table probabilities of survival were significantly improved in the treatment arm relative to the control arm after 5 years of follow-up and persists after 10 years [4]. We have now continued the case entry up to 134.

We report the long term follow-up results in all patients.

PATIENTS AND METHODS

Between 1977 and 1983, 134 consecutive patients were recruited to a randomised clinical trial with two arms: first, a control arm given no further treatment after resected surgery; secondly, a treatment arm, given mitomycin-C (MMC), 20 mg/m² intravenously once every 6 weeks for four courses. The inclusion criteria consisted of a histological diagnosis of gastric adenocarcinoma in one of the following categories (according to the UICC staging system; Ref. 5): T1 either with

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N1 or N2; any T2, T3 with any N0, N1 or N2. Cases with T1 N0, or any N3, or M1 were excluded from the study. No patient with residual disease at initial surgery was included in the trial. Exclusion conditions were patients over 70 years old, or with serum creatinine more than 132 μmol/l, or severe intercurrent diseases.

Chemotherapy was given within 6 weeks of surgery. After treatment all patients were followed-up every 3 months for a year, every 6 months for the next 4 consecutive years and once a year thereafter. The follow-up control consisted in anamnesis, physical examination, routine laboratory tests (including haematological, hepatic and renal function tests), level of CEA, and chest X-ray.

Statistical analysis

Life table probabilities of overall survival were calculated by the method of Kaplan and Meier [6]. The differences in survival between both groups of patients were compared using the log-rank test [7]. Survival data were recorded according to the rules of Peto *et al.* [8]. Toxic effects were evaluated following WHO criteria [9].

RESULTS

Patients' details

66 patients were included in control arm, 44 were male and 22 female. The mean of age was 57 (range 30–70). Most patients had a local advanced cancer (19 T3N0, 22 T3N1 and 14 T3N2). 68 patients were entered in treatment arm. 44 were male and 24 female. The mean age was 56 (range 34–70). The staging was in the following categories: T3N0 in 17 patients, T3N1 in 22 or T3N2 in 15 other patients (Table 1).

Survival and effect of treatment

The median follow-up of all patients was 105 months. In the control arm, 49 out of 66 patients died because of recurrence, versus 40 out of 68 in adjuvant MMC treated group. The actuarial survival curve shows statistically significant differences ($P < 0.025$) between both arms in favour of the adjuvant group (Fig. 1). Recurrence sites are summarised in Table 2.

The estimated 5 and, 10 year survival rates were 41% and 39% respectively, for the patients treated with adjuvant MMC and 26% and 26% for the abstention group.

After 5 years a "plateau" can be observed in actuarial survival curve that persists after 10 years. 1 patient died 8 years after gastrectomy because of liver metastases.

Table 1. Patients' characteristics

	Control	Mitomycin
Number	66	68
Male	44	44
Female	22	24
Age (mean)	57	56
Age range	30–70	34–70
T1N1	2	2
T2N0	6	9
T2N1	3	3
T3N0	19	17
T3N1	22	22
T3N2	14	15

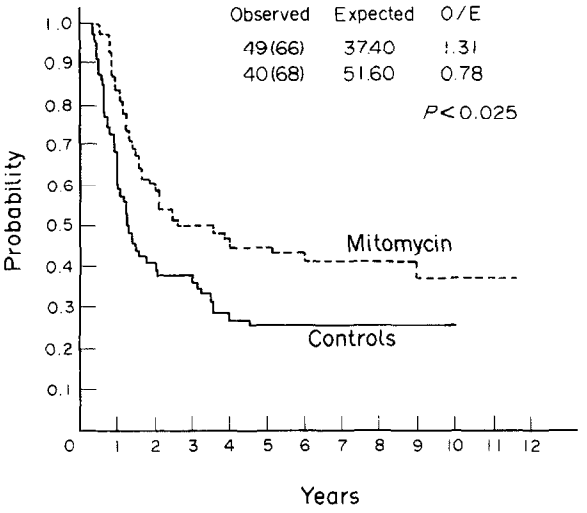

Fig. 1. Actuarial survival curve of all patients.

Table 2. Main relapse site

	Control	Mitomycin
Peritoneal	26	27
Local	4	2
Liver	19	8
Bone	1	—
Ovary	1	1
Brain	4	—
Lung	1	—
Adrenal	—	1
Skin	—	1
Nodes	—	1

Toxicity

Acute toxicity was mild (Table 3). Thrombocytopenia was observed in 25% of treated patients, invariably less than grade 4 with no episode of haemorrhage. Leukopenia was observed in 15 (22%) cases (grades 1, 2 or 3). Nausea and vomiting were the main gastrointestinal toxic effects developed in 12 (18%) patients always grade 1 or 2. Hair loss grade 1 was observed in a patient. Another patient had a second malignancy. In this patient a renal pelvic cancer was detected 8 years after gastrectomy and adjuvant chemotherapy. This second tumour was not resected owing to advanced stage at diagnosis and the patient died 3 months later. At this point he was recorded as being alive but lost to follow-up. No case of renal failure or haemolitic–uraemic syndrome was observed.

Table 3. Toxic effects

	$n = 68$	(%)
Thrombocytopenia	17	(25)
Leukopenia	15	(22)
Nausea and vomiting	12	(12)
Alopecia	1	(1)
Second malignancy	1	(1)

DISCUSSION

Our results suggest that adjuvant chemotherapy with MMC improves the long term actuarial survival in patients with resected gastric cancer. These results confirm our previous preliminary randomised study in 70 patients [3, 4]. With an increased number of patients and follow-up period, we observed persistent improvements in treatment group survival. On the other hand, late relapses are rare since a "plateau" appears in the actuarial survival curve after 5 years of follow-up. Patients whose life-span exceeds the period of time determined by the "plateau" can be considered cured after this period [10]. In the case of liver metastases after 8 years of follow-up, it was not possible to determine if they were caused by a relapse of the gastric cancer or by a second malignancy since the premature deterioration and death of the patient made it impossible to perform the diagnostic procedures required. In this case we considered it as a gastric cancer-related death. The treatment group had relatively fewer hepatic metastases than controls, which suggests a protective effect of adjuvant chemotherapy on blood borne dissemination and that it might be less effective in preventing local recurrences. Our results are similar to those obtained by Japanese authors [11–15], who generally speaking, use MMC associated with 5-fluorouracil derivates (with or without immunotherapy). In the United States only one study was positive, an association of 5-fluorouracil with methyl-CCNU starting in the immediate postoperative period [16]. On the other hand, there are at least two randomised studies with negative results [17–18]. In the first study performed by the Eastern Cooperative Oncology Group, chemotherapy was started 7 weeks after surgery. According to their authors, the great number of hospitals taking part might be the possible reason for the failure, because it might have caused dispersion of results [17]. In the second study performed by Veterans Administration Surgical Oncology Group, positive results favourable to the control group were shown in the first period of the follow-up, but these findings disappeared after 42 months of median follow-up [18]. Another randomised multicentre trial in the UK, with MMC-based adjuvant chemotherapy, showed no advantage in treated patients over the control group [19]. As mentioned in this report, The British Stomach Cancer Group recommends that patients with residual disease should be considered to have had a palliative resection and as such, should not be included in an adjuvant study, which we have observed in our trial. We support Douglass [2], who after an extensive review suggests that the most successful adjuvant chemotherapy would be the one started before the 6th week of the postoperative period and the use of chemotherapy based on MMC.

Acute toxicity was mild and treatment was well accepted by patients, especially due to the low rate of alopecia. Long term toxicity was non-existent apart from the secondary malignancy mentioned above. In our opinion MMC given over a short period has low carcinogenicity. This was also the conclusion of a study on 7672 cases with resected gastric cancer treated with adjuvant chemotherapy which included MMC in most cases; only in 22 of them a second malignancy in gastric remnant was observed [20]. Another study on 10 138 patients given similar adjuvant chemotherapy showed also a lower second malignancy rate than would be expected in a control group with no chemotherapy [21]. We had no cases of haemolytic–uraemic syndrome in this series. Nevertheless, a report by Lesesne *et al.* [22], suggests that once the cumulative dose of MMC reaches 60 mg, there should be a careful monitoring of renal function and haematological parameters.

In the light of these positive results and mild toxicity in patients treated with adjuvant MMC, we are considering the possibility of eliminating the abstention group in further trials on adjuvant chemotherapy in resected gastric cancer.

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