

Postoperative adjuvant chemotherapy inhibits early recurrence of early gastric carcinoma

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Summary. Data on 300 patients with early gastric carcinoma who underwent curative resection were analyzed for the suppressive effects of postoperative adjuvant chemotherapy on early recurrences. Retrospective grouping was done as follows: no chemotherapy (NC) group (169 patients), mitomycin C (MMC) group (108), and another group (23). In all, 24 patients (16 in the NC, 6 in the MMC, and 2 in the other group) who died of other diseases within 5 years after surgery were excluded. Therefore, data on 153 individuals in the NC and 102 in the MMC group were analyzed. The recurrence rate in patients with Pen A type carcinoma, with a propensity toward an early recurrence in the liver, was 37.5% in the NC and 9.1% in the MMC group. Among 27 Pen A type patients, 3- and 4-year survival was significantly higher in those receiving MMC (100%) than in those given NC (62.5%). Recurrences in the liver occurred in 6/14 of the NC patients within 3 years after surgery, whereas there were no recurrences in 11 MMC patients. Thus, the postoperative adjuvant chemotherapy with mitomycin-C has an inhibitory effect on early recurrence in patients with Pen A type early gastric carcinoma.

Introduction

The prognosis of patients with early gastric carcinoma is favorable, both in Japan and in Western countries [1, 2, 6–8, 18, 20]. A small number of highly malignant cases were included among those with early gastric carcinoma; these were separated and defined as Pen A type, with invasion of the submucosa and a wide and expansive penetrating fashion [16, 19]. In all, 25% with Pen A type carcinoma had metastases to lymph nodes; the 5-year survival was 64.8% and was generally poor due to an early recurrence in the liver, even after curative surgery. Hence, specific anticancer chemotherapy was recommended for Pen A type early carcinoma [16]. As postoperative anticancer chemotherapy for patients with early gastric carcinoma has been given little attention in the literature, we report our data on such patients.

Materials and methods

A total of 300 Japanese patients with early gastric cancer underwent curative resection in the Second Department of

Surgery in Kyushu University Hospital from 1951–1981; all were followed for over 5 years. The three groups included the no chemotherapy (NC) group, 169 patients who had not been prescribed anticancer or immunochemotherapy before and/or after surgery, the MMC group, 108 individuals who were given 10–20 mg mitomycin C (MMC) i.v. on the day of surgery, with or without the oral administration of Futraful and the remaining group of 23, who were prescribed anticancer drugs (except MMC) or were given radiotherapy or only immunotherapy. The prognosis of patients with early gastric cancer is favorable, and death is usually due to a nonmalignant disease or other malignant diseases. Therefore, 24 patients (16 in the NC, 6 in the MMC, and 2 in the remaining group) who died within 5 years after surgery were excluded because of the link to other diseases.

A precise analysis was made of 153 patients in the NC and 102 in the MMC group, the objective being to assess the efficacy of postoperative adjuvant chemotherapy. The location, macroscopic appearance, and histologic type of the tumors were based on the general guidelines of previous gastric cancer studies in Japan [13] and on the growth pattern reported by Kodama et al. [16]. The Super type is a superficially spreading carcinoma with a diameter of >4 cm, occurring with or without submucosal invasion. The Pen type is a carcinoma with a diameter of <4 cm that has widely invaded the submucosa; this type of carcinoma is further divided into two subtypes according to the mode of submucosal invasion. Pen A is an expansively penetrating type and Pen B is an infiltratively growing type. The small mucosal type is a carcinoma with a diameter of <4 cm, either restricted to the mucosal layer or mostly restricted to the mucosal layer with slight invasion of the submucosal layer (Fig. 1).

Although the present study was not a prospective randomized trial, the distribution of patients between the NC and the MMC groups according to clinicopathologic characteristics was balanced (Table 1). The effect of treatment was evaluated according to the same factors, particularly those influencing prognosis, including the depth of cancer invasion, presence or absence of metastasis to lymph nodes, and growth patterns. The generalized Wilcoxon and Z-tests were used for statistical analysis.

Results

Recurrence rates according to the presence or absence of metastasis to lymph nodes, depth of cancer invasion, and

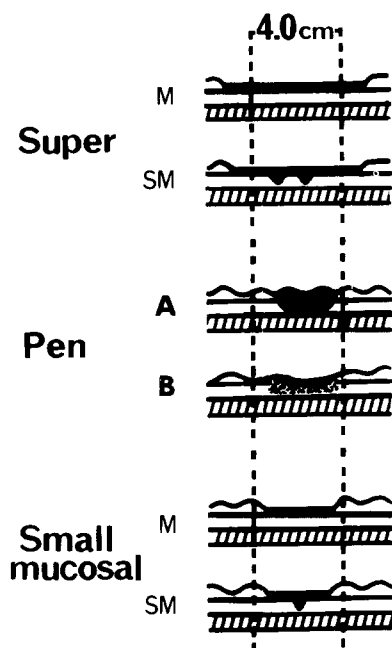


Fig. 1. Various growth patterns seen in early gastric cancer

growth patterns are summarized in Table 2. Of 153 NC group 8, (5.9%) underwent recurrences, whereas 3 (2.9%) of 102 in the MMC group had a recurrence. In those with mucosal carcinoma and no lymph node metastasis, none of the MMC patients had a recurrence, although a small number of NC patients did. In those with submucosal carcinoma and lymph node metastasis, a similar number of recurrences was observed between the MMC and NC groups. In those with the small mucosal, Super, and Pen B types, the recurrence rates were low in both the NC and MMC groups. However, in those with the Pen A type, the rate was 37.5% in NC patients but only 9.1% in the MMC group.

Postoperative survival curves for the NC and MMC groups are shown in Fig. 2, and those for patients with Pen A type carcinoma are shown in Fig. 3. The 3- and 4-year survival for the MMC group was significantly higher than that for the NC group ($P < 0.01$).

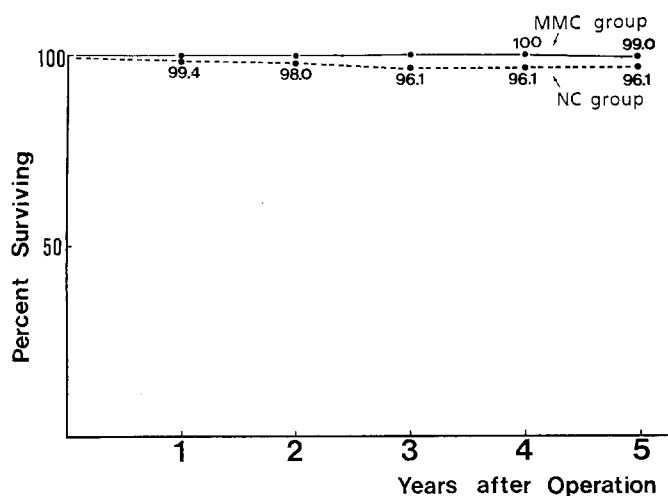


Fig. 2. Survival curves of the MMC group (solid line) and the NC group (dotted line)

Table 1. Clinicopathologic Factors

	Number of cases	
	NC group (n = 153)	MMC group (n = 102)
Age (years)		
Range	24–85	23–75
Mean	54.7	52.8
Sex		
Men	112 (73.2)	67 (65.7)
Women	41 (26.8)	35 (34.3)
Location		
Upper (C)	12 (7.8)	8 (7.8)
Middle (M)	80 (52.3)	52 (51.0)
Lower (A)	61 (39.9)	42 (41.2)
Macroscopic appearance		
Elevated	44 (28.8)	21 (20.6)
Flat	2 (1.3)	1 (1.0)
Depressed	107 (69.9)	80 (78.4)
Size (cm)		
0–<2	35 (22.9)	19 (18.6)
2–<4	61 (39.9)	50 (49.0)
4–<6	36 (23.5)	19 (18.6)
6–<8	15 (9.8)	7 (6.9)
8–<10	3 (2.0)	6 (5.9)
10–	3 (2.0)	1 (1.0)
Histologic type		
Papillary, well-differentiated	66 (43.1)	31 (30.4)
Moderately differentiated	16 (10.5)	20 (19.6)
Signet, poorly differentiated	71 (46.4)	51 (50.0)
Depth of cancer invasion		
Mucosa	80 (52.3)	48 (47.1)
Submucosa	73 (47.7)	54 (52.9)
Lymph node metastasis		
Negative	139 (90.9)	87 (85.3)
Positive	14 (9.1)	15 (14.7)
Growth pattern		
Small mucosal	67 (43.8)	49 (48.0)
Super	57 (37.2)	33 (32.4)
Pen A	16 (10.5)	11 (10.8)
Pen B	13 (8.5)	9 (8.8)

Table 2. Recurrence rates according to factors influencing prognosis

	Recurrence rate (%)	
	NC group (n = 153)	MMC group (n = 102)
Lymph node metastasis		
Negative	5.0 (7/139)	0 (0/87)
Positive	14.3 (2/14)	20.0 (3/15)
Depth of cancer invasion		
Mucosa	3.8 (3/80)	0 (0/40)
Submucosa	8.2 (6/73)	5.6 (3/54)
Growth pattern		
Small mucosal	1.5 (1/67)	2.0 (1/49)
Super	3.5 (2/57)	3.0 (1/33)
Pen A	37.5 (6/16)	9.1 (1/11)
Pen B	0 (0/13)	0 (0/9)
Total	5.9 (9/153)	2.9 (3/102)

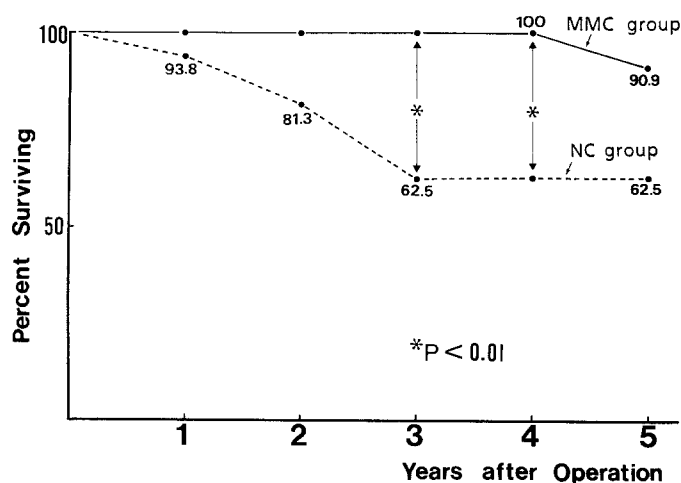


Fig. 3. Survival curves in Pen A type carcinoma patients for the MMC (solid line) and NC groups (dotted line)

The postoperative course in patients with the Pen A type is shown in Fig. 4. In the NC group, six died of disease recurrence in the liver within 3 years after surgery (Fig. 5a), whereas only one patient in the MMC group, a 51-year-old woman, died of such recurrence in the liver at 4 years and 4 months after curative gastrectomy (Fig. 5b). This patient had been given 20 mg MMC i.v. once on the day of surgery, and no chemotherapy was prescribed thereafter. In 10 of 16 NC patients and 10 of 11 in the MMC group, there were no recurrences (Fig. 5c).

Discussion

Chemotherapy for advanced gastric carcinoma is not extremely effective [3, 4, 9, 10], yet significant effects have been obtained for surgically curable or nonadvanced cases [5, 12, 15]. The fewer the remaining tumors, the greater the efficacy of the chemotherapy [21]. Hence, cancer chemotherapy is considered to be effective for micrometastases, to halt the growth of remaining tumor cells and clinically suppress the recurrence of the carcinoma after curative surgery. In a small but definite number of patients with early recurrence in the liver, which has been defined as Pen A type carcinoma [16], in those with early gastric carcinoma, micrometastases to the liver may have been present at the time of surgery; for such patients, adjuvant chemotherapy should be effective.

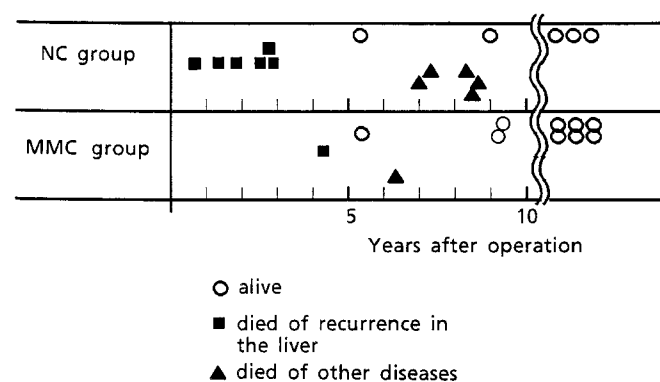


Fig. 4. Postoperative outcome of Pen A type carcinoma patients

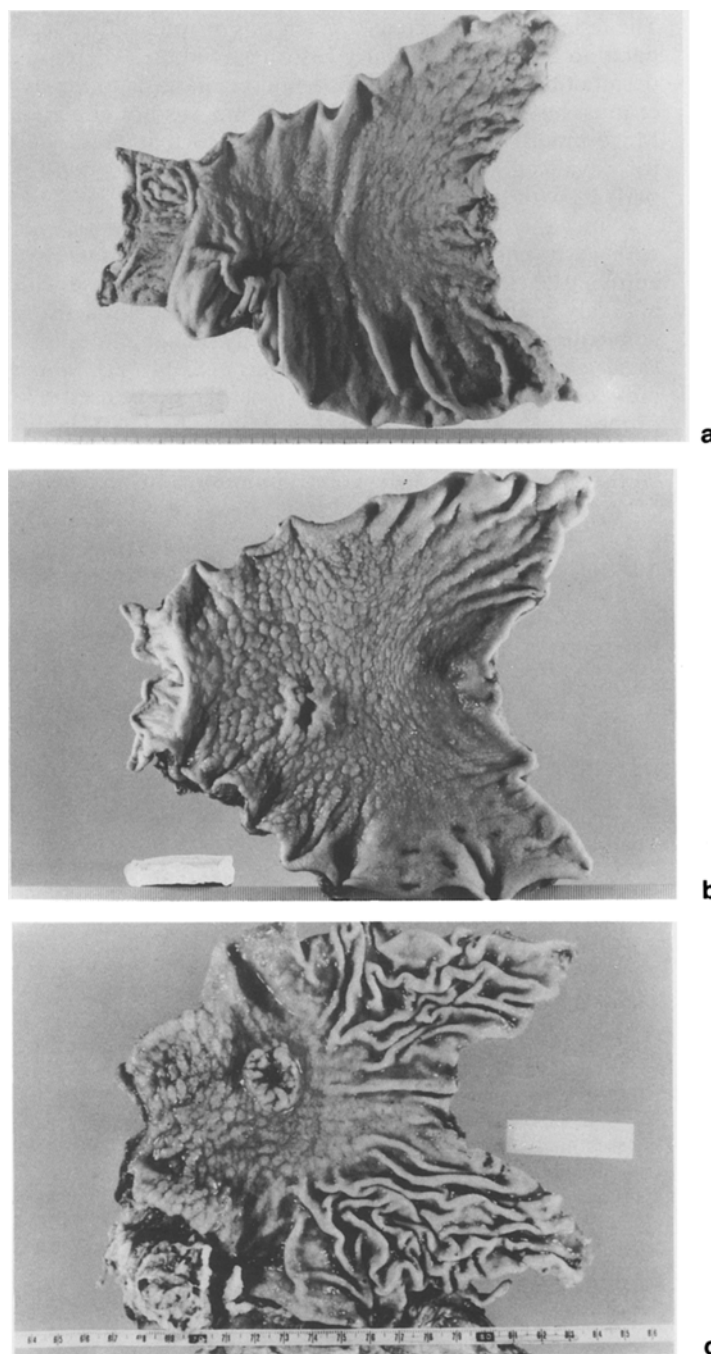


Fig. 5. Examples of the resected stomachs with Pen A type carcinoma. a: No chemotherapy and early recurrence; 78-year-old woman, 2.2 × 1.4 cm tumor, IIa + IIc in macroscopic appearance, papillary adenocarcinoma with extensive submucosal invasion. b: Chemotherapy but late recurrence; 51-year-old woman, 2.5 × 1.3 cm tumor, IIa + IIc in macroscopic appearance, well differentiated adenocarcinoma with extensive submucosal invasion. c: Chemotherapy and no recurrence; 47-year-old woman, 2.0 × 1.8 cm tumor, IIa + IIc in macroscopic appearance, papillary adenocarcinoma with extensive submucosal invasion

The possible suppressive effects of postoperative adjuvant chemotherapy on early recurrence in the liver among patients with the highly malignant type of early gastric cancer thus have to be considered. One patient who died of a late recurrence in the liver had been given 20 mg MMC i.v. on the day of surgery and no drugs thereafter.

The lesion in the resected stomach was histologically elucidated to be Pen A type early gastric carcinoma. Therefore, despite the curative resection, a micrometastasis to the liver must have existed; thus, MMC alone was not effective. More intensive chemotherapy, similar to that prescribed for advanced gastric carcinoma [12], is recommended for patients with the highly malignant type.

Since the prognosis for most surgically treated patients with early gastric carcinoma is favorable, postoperative adjuvant chemotherapy should be reserved for those with a highly malignant lesion. An accurate diagnosis using conventional tools is difficult for highly malignant lesions; thus, cytophotometric DNA analysis [11, 14, 17], which makes it feasible to detect such lesions, should be used. We propose that the detection of these lesions by DNA analysis plus pre- and/or postoperative, intensive adjuvant chemotherapy will lead to a great diminution in recurrence of the cancer in the liver.

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