Positive Results of Combined Therapy of Surgery and Intraperitoneal Hyperthermic Perfusion for Far-advanced Gastric Cancer

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To evaluate the clinical efficacy of intraperitoneal hyperthermic perfusion (IPHP) for far-advanced gastric cancer, particularly with peritoneal seeding, we investigated the survival times of 59 patients who underwent distal subtotal gastrectomy, total gastrectomy, or total gastrectomy combined with concomitant resection of some of the remaining intra-abdominal organs. In all the 30 patients given IPHP, no cancer cells were present posthyperthermically in the lavage from the Douglas pouch. The 30 patients given IPHP lived longer than the 29 patients not given IPHP ($p = 0.001$), with a 1-year survival rate of 80.4% in the former group compared to 34.2% in the latter. With respect to a comparison of survival time of patients with peritoneal seeding, 7 patients not given IPHP had a 6-month survival rate of 57.1% and did not survive more than 9 months, whereas 20 patients given IPHP had 1- and 2-year survival rates of 78.7% and 45.0%, respectively; here the difference was significant ($p = 0.001$). The IPHP and control groups without peritoneal metastasis included 10 and 22 patients, respectively, and the 1-year survival rates are 85.4% and 45.3%, respectively. The survival rates of the former exceeded those of the latter, with $p = 0.015$ by the generalized Wilcoxon test. Thus this combined therapy offers the promise of extended survival for patients with far-advanced gastric cancer.

THE POOR PROGNOSIS of patients with advanced gastric cancer is caused by peritoneal or hepatic recurrence developed from cancer cells scattered before operation on the peritoneal surface or in the portal vein. Various attempts were made to treat the peritoneal recurrence and/or metastasis; however the results left much to be desired. To prevent peritoneal recurrence after surgical resection, continuous hyperthermic peritoneal perfusion was performed by Koga et al.[1] with good results. We reported that intraperitoneal hyperthermic perfusion (IPHP) led to a remarkable antitumor effect on peritoneal dissemination and peritoneal recurrence from gastric cancer.[2,3] We report here data on 30 far-advanced gastric cancer patients given IPHP, most of whom underwent total gastrectomy. The survival time of these 30 gastric cancer patients given IPHP was compared with data on patients with gastric cancer treated only surgically.

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Subjects and Methods

Patients

From February 1986 IPHP was performed soon after surgery for 30 far-advanced gastric cancer patients, the objective being to treat peritoneal dissemination or to prevent peritoneal recurrence (IPHP group). In contrast 29 patients with far-advanced gastric cancer underwent surgery without IPHP, within the same period of time (control group). The distribution of clinical characteristics in these patients is shown in Table 1.

Intraperitoneal Hyperthermic Perfusion and Antitumor Treatment for the Control Group

Intraperitoneal hyperthermic perfusion was applied, using an apparatus designed for IPHP, as a closed circuit.[2,3] The equipment needed for IPHP (Mera IPH-2, Senkosha, Tokyo, Japan) was inserted into the Douglas pouch and the upper abdominal cavity just before temporary closure of the abdominal wall after the surgical treatment; and in advance of IPHP, the prehyperthermic hypothermia (31 to 32°C) was induced by means of a cooling mat and ice bags (Fig. 1). Successively IPHP, using 3000 to 5000 mL of the perfusate containing 10 μg/mL of mitomycin C

TABLE 1. *Clinicopathologic Features of Patients*

Factors	IPHP Group (n = 30)	Control Group (n = 29)
Age	52.1 ± 12.6	60.5 ± 10.9
Sex (male/female)	14/16	17/12
TNM classification[5]		
T3	11	18
T4	19	11
N0	4	6
N1	3	4
N2	23	19
Distant metastasis to peritoneum	17 (3)*	7
Organs Involved		
1 organ	8	7
2 organs	11	4
Type of Histology		
Differentiated	5	12
Undifferentiated	25	17
Type of Surgery		
Distal subtotal gastrectomy	5	7
Pancreatico-duodenectomy	1	0
Total gastrectomy	2	9
Total gastrectomy plus splenectomy	3	7
Total gastrectomy, splenectomy plus oophorectomy	5	0
Total gastrectomy, splenectomy plus colectomy and/or partial pancreatectomy	8	6
Total gastrectomy, splenectomy, oophorectomy plus partial pancreatectomy	6	0

* Number in parentheses indicates the patient with cytologically positive results of peritoneal lavage.

(MMC), was carried out for 117 ± 17 minutes, with special attention given to the cardiorespiratory functions and to the rising temperatures in the pulmonary artery.[2-4]

Throughout this IPHP treatment, temperature was measured with six thermometer probes: at the points of inflow and outflow on the abdominal wall, at three spots in the peritoneal cavity, and at the pulmonary artery (Fig. 1). Temperatures in the pulmonary artery were measured by means of an inserted Swan-Ganz catheter and did not exceed 41°C during this treatment. During this IPHP temperatures at the inflow point and in Douglas' pouch were maintained at 45.0 to 47.3°C and 43.6 to 45.1°C, respectively.

On the other hand, for the 29 patients of the control group, 30 to 50 mg of MMC was given intraperitoneally and/or intravenously. There was no statistical difference between both the groups with regard to the doses of MMC.

Statistical Analysis

Survival curves were calculated using the Kaplan–Meier method[6] and survival rates were analyzed using a generalized Wilcoxon test[7] and log-rank test.[8] Background factors were compared between these two groups and chi square test or Student's t test was used to determine the statistical difference.

Results

Clinicopathologic Features of Patients

The mean age in the IPHP group was younger (p = 0.009) than that in the control group (Table 1). As shown in Table 1, of 30 patients given IPHP, 17 proved to have malignant ascitic effusion and 3 of the remaining 13 patients had positive cytologic examination with peritoneal lavage at laparotomy. The remaining 10 patients had serosal invasion of T3. In the IPHP group, total gastrectomy, subtotal gastrectomy, or pancreaticoduodenectomy was performed and 22 of the 30 patients underwent splenectomy, transverse colectomy, right hemicolectomy, partial pancreatectomy, and/or oophorectomy.

The control group included seven patients with malignant ascitic effusion and 18 of the remaining 22 had serosal invasion of T3 (Table 1). Of 29 patients not given IPHP, 16 underwent distal subtotal or total gastrectomy and, the remaining 13 were operated on for total gastrectomy plus splenectomy, colectomy, and/or partial pancreatectomy.

The incidence of peritoneal seeding was higher (p = 0.001) in the IPHP group, compared with the control group, and the ratio of T3 and T4 differed at p = 0.052 between the groups. There were no significant differences between the groups with regard to sex, nodal involvement, and organs involvement. Patients in the IPHP group underwent excision of multiple organs, with a statistical difference at p = 0.028, compared to the control group. In comparison of histology, the IPHP group had a high incidence of 'undifferentiated' tumors (p = 0.036), compared to the control group.

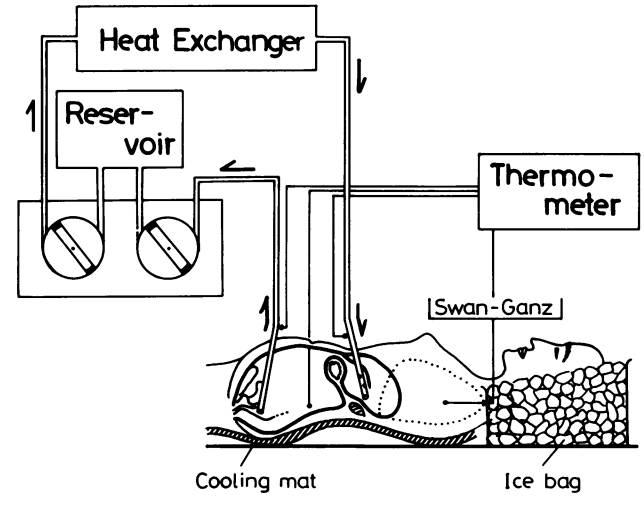

FIG. 1. Schematic drawing of IPHP. Arrows indicate flow direction of the perfusate.

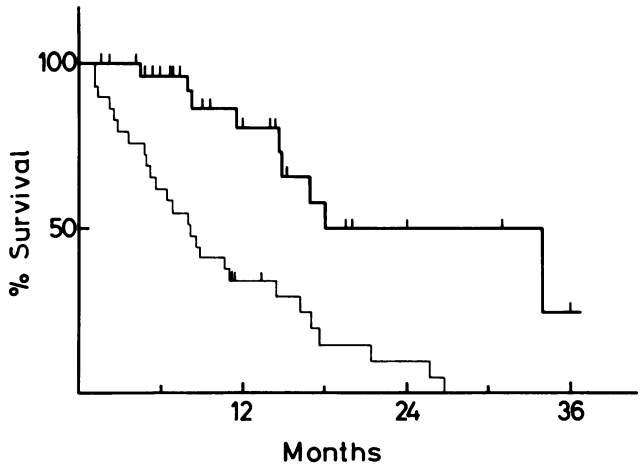

FIG. 2. Survival curves of patients with far-advanced gastric cancer. ——, IPHP group (n = 30); ——, control group (n = 29). The difference between the IPHP and control groups was statistically significant (p = 0.001 by generalized Wilcoxon test and log-rank test).

Antitumor Efficacy

In the 30 patients in the IPHP group, repeated cytologic examinations of the lavage in Douglas' pouch were negative posthyperthermically. With respect to preoperative ascitic effusion of 17 patients with peritoneal seeding in the IPHP group, the ascitic effusion disappeared soon after IPHP.

Survival Rates

The survival rates for the IPHP and control groups are shown in Figure 2. One-, two-, and three-year survival rates for the IPHP group were 80.4%, 49.1%, and 24.5%, respectively, whereas those for the control group were 34.2%, 9.8%, and 0%, respectively. The survival rates for the IPHP group were significantly higher than those for the control group, with a statistical difference of p = 0.001 by the generalized Wilcoxon test and log-rank test (Fig. 2).

The results in terms of 27 patients with peritoneal seeding are shown in Figure 3. Six-, twelve-, and twenty-four-month survival rates of 20 patients with IPHP were 94%, 78.7%, and 45%, respectively, while the 6-month survival rate for 7 patients without IPHP was 57.1%. The survival rates of these 20 patients given IPHP were significantly better than those of the 7 patients treated with surgery alone, with a statistical difference of p = 0.001, as determined by both the generalized Wilcoxon test and log-rank test.

Findings in the cases of 32 patients without peritoneal metastasis are shown in Figure 4. One- and two-year survival rates of 10 patients given IPHP were 85.4% and 56.5%, respectively, while those of 22 patients without IPHP were 45.3% and 12.9%, respectively. Survival rates for the IPHP group were significantly better than those for the control group (p = 0.011 by the log-rank test; p = 0.015 by the generalized Wilcoxon test).

Data on the cause of death are shown in Table 2. The incidences of death due to peritoneal recurrence were 6.7% (2 of 30 patients) in the IPHP group and 51.7% (15 of 29 patients) in the control group, and the difference was statistically significant at p = 0.0001 as determined using the chi square test. With regard to patients with peritoneal seeding at the time of laparotomy, the incidence of death caused by peritoneal dissemination was 10% in the IPHP group and 100% in the control group. With respect to

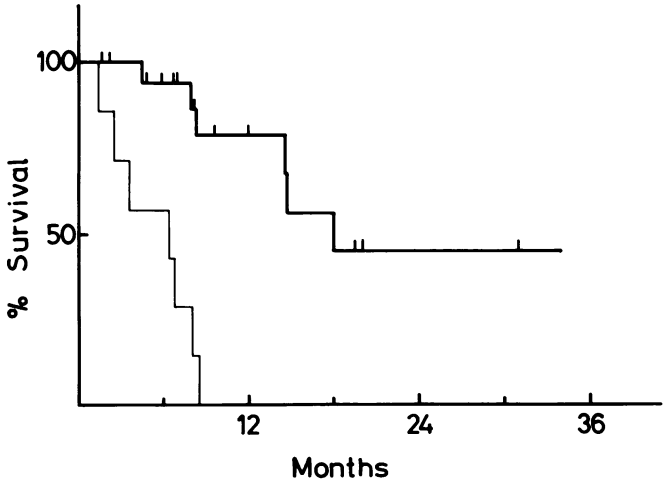

FIG. 3. Survival curves of patients with peritoneal seeding. ——, IPHP group (n = 20); ——, control group (n = 7). There was a significant difference between the survival curves of the IPHP and control groups (p = 0.001 by generalized Wilcoxon test and log-rank test).

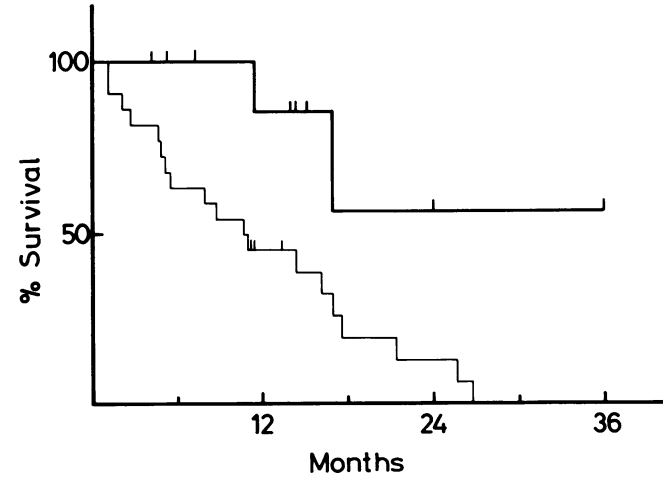

FIG. 4. Survival curves of 32 patients without peritoneal seeding. ——, IPHP group (n = 10); ——, control group (n = 22). There is a statistical difference between the IPHP and control groups (p = 0.015 by generalized Wilcoxon test; p = 0.011 by log-rank test).

TABLE 2. *Outcome of Treatment in Terms of Cause of Death*

	IPHP Group		Control Group	
	Peritoneal Seeding		Peritoneal Seeding	
Cause of Death	(+) n = 20	(−) n = 10	(+) n = 7	(−) n = 22
Peritoneal metastasis	2	0	7	8
Pleural metastasis	2	0	0	0
Intra-abdominal metastatic tumors	2	0	0	5
Hepatic metastasis	0	2	0	3
Others	1	0	0	3
Total	9/30		26/29	

other causes of death, there was no significant difference between the two groups.

Side Effects

Two of the thirty patients given IPHP and one patient in the control group had minor leakage at the anastomosis. The platelet count decreased immediately after IPHP but 7 days later normal ranges were observed. Serum GOT and GPT levels increased considerably after IPHP but at 2 to 3 weeks after normal ranges were recorded. Serum protein dropped during IPHP and reverted to preoperative levels 4 to 7 days later.

Discussion

'Total cell killing' is the objective of treatment for patients with malignant diseases. Even a cure can be achieved for patients with solid malignant tumors with regional nodal involvement when wide local excision with regional lymphadenectomy are carried out. However, when cancer cells invade the blood vessels, the combined treatment of surgery and chemotherapy is indispensable. Intra-arterial cancer chemotherapy has been prescribed for patients with colorectal liver hematogenous metastasis, with considerable success.[9] In many patients with advanced gastric cancer, occult metastatic foci are considered to have already been scattered at the time when surgery is done. To provide added support for the surgery, a clinically available antitumor means aimed at cancer cells in the portal vein and on the serosal surface was devised.

Hyperthermia is particularly effective for human cancers, when applied with chemotherapy.[10] However difficulties are encountered when attempting to apply hyperthermia for lesions of the abdominal cavity with its variously shaped organs. Spratt et al.[11] Koga et al.,[1] and Fujimoto et al.[2,3] performed intraperitoneal hyperthermic chemotherapy to eradicate cancer cells and/or cancerous tumors of small size on the peritoneal surface. An ideal application of hyperthermia is to expose the malignant lesions to a uniform, elevated temperature. The peritoneal surface is heated uniformly with the apparatus we used for IPHP and this IPHP treatment is safe as the temperature of the pulmonary artery is monitored by means of an inserted Swan-Ganz catheter.[2,3]

Yamada et al.[12] reported that the survival rates of 99 patients with an excised primary lesion and malignant effusion and those of 190 patients with an inoperable primary lesion and malignant effusion were 21% and 15% at 6 months after treatment for effusion, respectively, regardless of the intraperitoneal and intravenous administration of antitumor drugs. These results are inferior to the findings of the 7 patients with peritoneal seeding in our control group. Intraperitoneal wide-spread dissemination is probably due to the biologic behavior of gastric cancer cells, which is thought to differ essentially from colorectal cancer, yet to some extent resembles ovarian cancer.

All 7 patients in our control group with peritoneal seeding died within 9 months, while of the IPHP group with 17 patients with peritoneal seeding 2 died of peritoneal recurrence. Free-floating cancer cells and cancer cells on the peritoneal surface are exposed to the high concentration of MMC, in case of IPHP application.[2-4] For larger tumors, however, MMC given intraperitoneally diffuses into the tumoral tissue and MMC concentrations decline after a few layers of cancer cells. A similar phenomenon may be said to occur in case of conduction of heat by blood flow. Thus intraperitoneal tumors of small diameters are severely affected by this IPHP treatment. On the other hand, intraperitoneal large tumors and those that have invaded under or directly under the serosal or peritoneal surface may not be effectively treated by this IPHP with MMC. We reported elsewhere[2] that a patient with peritoneal dissemination underwent this IPHP treatment and at the second operation 5 weeks later, no peritoneal dissemination was found, despite partial residual implantations in the cecum and colon. These partial residual implantations would result from larger tumors and may be the origin of peritoneal recurrence of the two patients in the IPHP group who died.

Our data suggest that to treat patients with peritoneal seeding from gastric cancer, combined surgery and IPHP should be considered. A controlled randomized study remains to be performed. This IPHP treatment led to a favorable outcome for far-advanced gastric cancer patients who had been diagnosed as inoperable. This combined therapy offers promise of extended survival for patients with far-advanced gastric cancer.

Acknowledgment

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