Evaluation of Treatment for Gastric Cancer With Liver Metastasis

KAZUAKI OKUYAMA, MD, KAICHI ISONO, MD, IEE-KUNG JUAN, MD, SHOICHI ONODA, MD, TAKENORI OCHIAI, MD, YOSHIKAZU YAMAMOTO, MD, YOSHIO KOIDE, MD, AND HIROSHI SATOH, MD

In 161 cases of gastric cancer with liver metastasis but without peritoneal dissemination, evaluations were executed to find effective treatment. The most favorable results with best prognosis were obtained in the group receiving gastrectomy + hepatectomy + chemotherapy, followed by gastrectomy + chemotherapy, and gastrectomy alone. The most unfavorable outcome was in nonresected cases. Chief chemotherapy to be used after gastrectomy was FML (5-fluorouracil (5-FU) + mitomycin C [MMC] + lentinan) continuous intra-arterial infusion. Hepatectomy was found to be effective as an active measure for tumor reduction in cases of liver metastasis so far as the metastatic lesions are only a few scattered ones in both lobes.

Cancer 55:2498–2505, 1985.

UNTIL several years ago, to detect hepatic metastasis from the gastrointestinal tract was impossible except through the palpation of hepatomegaly.[1] However, by virtue of the rapid prevalence of echography and computed tomography (CT) scanning as well as the development of new tumor markers, we can diagnose hepatic metastasis even quantitatively before the operation without giving any pain to the patients.[2] Therefore, we can often encounter metastatic tumor of the liver in daily practice. Some reports concerning the treatment of colorectal cancer with liver metastasis had been seen. Aggressive treatments with hepatectomy and removal of the primary lesion followed by chemotherapy were used with acceptable results.[3,4] However, in Japan we have many patients that have gastric cancer with liver metastasis that had been reported with especially poor prognosis.[5] How to treat these patients has become a major problem.

In the current study, prospective pre- and intraoperative selection of patients for various therapeutic trials was carried out in order to obtain the best method of treatment.

Materials and Methods

During the last 24 years, from 1959 to 1982, there was a total of 3217 gastric cancer patients receiving surgical intervention. Among them, synchronous hepatic metastasis was found in 283 patients. In order to evaluate the effect of treatment under the same conditions as far as possible, only 161 patients without peritoneal dissemination were discussed. Before 1975, we had 96 such patients undergoing laparotomy alone without postoperative chemotherapy being used as the control, as it was in the current study. Since 1976 we have selected patients for different treatments according to the pre- and intra-operative information obtained consisting of the grade of liver metastasis and local invasion.

The following four groups of patients undergoing various kinds of treatment were obtained: (1) group I (9 patients): receiving gastrectomy, hepatectomy and chemotherapy; (2) group II (21 patients): receiving gastrectomy and chemotherapy; (3) group III (35 patients): gastrectomy alone; and (4) group IV (96 patients): nonresected.

Prognosis was compared among these subgroups by the survival rates calculated by the method of Kaplan and Meier.[6]

According to The General Rules for the Gastric Cancer Study in Surgery and Pathology of Japan,[7] in the current study patients with liver metastasis without peritoneal dissemination are defined as P0H(+). As to the grade of liver metastasis, metastasis limited to one of the lobes is defined as H1, few scattered metastases (two or three) to both lobes as H2, and numerous scattered metastases to both lobes as H3.

Results

Survival Rate on Presence or Absence of Gastrectomy

In order to determine whether gastrectomy is valuable in improving the prognosis of gastric cancer with liver

From the Second Department of Surgery, School of Medicine, Chiba University, Chiba, Japan.

Address for reprints: Kazuaki Okuyama, MD, PhD, Second Department of Surgery, School of Medicine, Chiba University, 1-8-1 Inohana-cho, Chiba 280, Japan.

Accepted for publication June 1, 1984.

metastasis or not, the prognosis shown by the Kaplan and Meier survival rate curves were compared between 65 cases of P0H(+) receiving gastrectomy and 96 cases of P0H(+) without gastrectomy as the control group (Fig. 1).

The control group did not receive postoperative chemotherapy, and the longest survival time was only 15 months. However, in the group with gastrectomy six cases including one case with the longest survival time of 39 months are still living. The Cox-Mantel test[8] revealed significant difference ($P < 0.05$) at z = 2.85 between them, favoring the group with gastrectomy.

To show the homogeneity of both groups, background factors that are considered to affect prognosis including distribution of sex and age, grade of liver and lymph node metastases, and depth of serosal invasion were analyzed by the chi-square test. As shown in Table 1, there was no significant difference between the group with gastrectomy and the group without gastrectomy in all background factors except for significantly ($P < 0.01$) lower incidence of S3 in the former group than in the latter group, according to macroscopic depth of serosal invasion.

Among 65 cases of the group with gastrectomy, the macroscopic depth of serosal invasion was judged as S3 in 20 cases. In only 5 cases, 25%, was the histologic depth of serosal invasion assessed as si (direct infiltration to neighboring tissues was observed histologically). Because removed specimens with S3 were found to be si in only 25% of the cases, patients with si appear to account for a low percentage in 55 S3 patients of the nonresected group.

In cases of gastric cancer with liver metastasis, gastrectomy combined with resection of directly infiltrated neighboring tissues will solve the problems concerning the depth of serosal invasion even in S3 patients as long as they are P0. Consequently, active use of gastrectomy is valuable for improving the prognosis in these cases.

Survival Rates on Presence or Absence of Postoperative Chemotherapy

In order to determine whether tumor reduction itself, obtained by gastrectomy, contributed to improved prognosis in patients with gastrectomy or not, comparisons of prognosis were made by classifying gastrectomied patients into two groups according to the presence or absence of postoperative chemotherapy. The nonresected group was used as the control (Fig. 2).

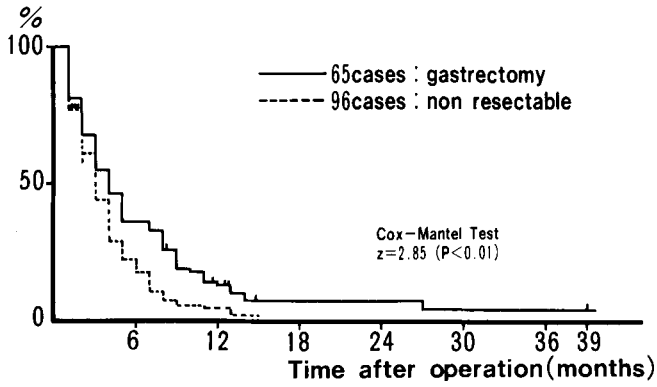

FIG. 1. Effect of gastrectomy on gastric cancer patients with hepatic metastasis but without peritoneal dissemination.

The distribution of grade of liver metastases, is shown in the upper right part of Figure 2. In 30 cases with gastrectomy + chemotherapy, H1 cases accounted for 30% of the cases, H2 23.3%, and H3 46.7%, as compared to corresponding values of 37.1% for H1, 45.7% for H2, and 17.2% for H3 cases in the group with gastrectomy alone. Thus, despite the fact that H3 cases accounted for a significantly higher percentage in the group with gastrectomy + chemotherapy, the prognosis given by the Kaplan and Meier survival rate curve was significantly ($P < 0.01$) favorable in this group with the Cox-Mantel test at z = 3.12.

Between the group with gastrectomy alone and the group without gastrectomy, no significant difference was seen both in grades of liver metastasis and survival rate curves.

Therefore, gastrectomy alone could not improve prognosis. Gastrectomy could produce favorable prognosis only when it was combined with chemotherapy, showing effectiveness of postoperative chemotherapy.

Then, 30 patients of P0H(+) gastric cancer undergoing gastrectomy combined with chemotherapy were classified

TABLE 1. Background Data for the Patients

	Sex		Age (yr)					Grade of liver metastasis			Grade of lymph node metastasis				Depth of cancerous invasion in stomach wall			
	M	F	<40	40–50	51–60	61–70	>71	H1	H2	H3	N(−)	N1(+)	N2(+)	N3,4(+)	S0	S1	S2	S3
Gastrectomy	50	15	0	12	18	21	14	22	24	19	1	12	33	19	2	4	39	20
Nonresectable	73	23	5	13	28	39	11	36	29	31	1	10	45	40	0	4	37	55
Statistical test	NS				NS				NS				NS				$P < 0.01$	

H1: metastasis limited to one of the lobes; H2: a few scattered metastases to both lobes; H3: multiple metastases to both lobes; N(−): no suspected lymph node metastasis by the macroscopic examination; N1(+): metastasis to Group I lymph nodes; N2(+): metastasis to Group II lymph nodes; N3,4(+): metastasis to Group III and IV lymph nodes; S0: no serosal invasion; S1: suspected serosal invasion; S2: definite serosal invasion; S3: invasion to contiguous structures.

NS: not significant; chi-square test; *P*; Fisher's exact probability test.

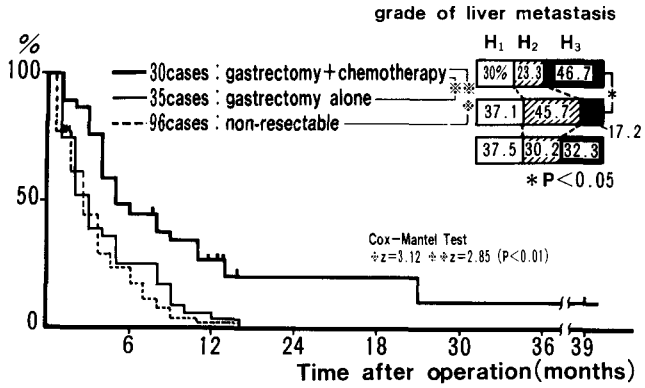

FIG. 2. Effect of postoperative chemotherapy on gastric cancer patients with hepatic metastasis but without peritoneal dissemination.

into continuous intra-arterial infusion group in which the main postoperative chemotherapy was continuous intra-arterial infusion and systemic chemotherapy. The main chemotherapy was MFC (MMC [mitomycin C] + 5-fluorouracil [5-FU] + cytosine arabinoside [Ara-C]) treatment. Between these two groups, comparisons of the prognosis were made as shown in Figure 3. The continuous intra-arterial infusion group had 15 patients (solid line) and the systemic chemotherapy group also had 15 patients (dotted line). Between these two groups the Cox-Mantel test revealed no significant difference in the Kaplan and Meier survival rate curves at z = 0.106.

However, the distribution of grades of liver metastasis, shown in the right upper part of Figure 3, revealed that H3 cases accounted for 60% in the continuous intra-arterial infusion group and 26.6% in the systemic chemotherapy group. Because the percentage of H3 cases was significantly higher ($P < 0.05$) in the continuous intra-arterial infusion group, this kind of postoperative chemotherapy can be considered as an effective method.

Continuous Intraarterial Infusion Therapy and Method of Administration

Protocol of continuous intraarterial infusion: In order to determine the effect of continuous intra-arterial infusion therapy for liver metastasis, two groups of intra-arterial infusion using different drugs and different administration methods were studied and their prognosis was compared.

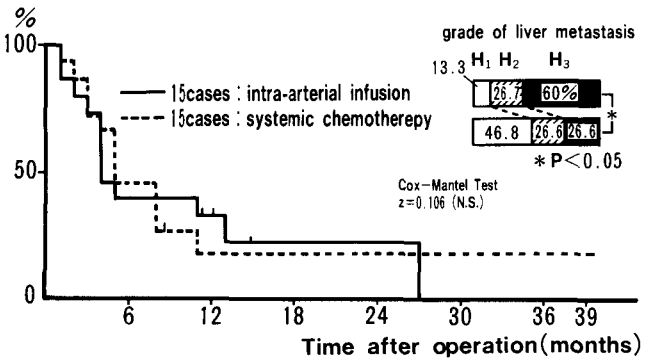

FIG. 3. Effect of postoperative continuous intra-arterial infusion therapy on gastric cancer patients with hepatic metastasis but without peritoneal dissemination.腹膜傳播

Usually, at our department, the intra-arterial infusion was performed by the protocol as shown in the lower part of Figure 4. Namely, 5-FU + MMC (FM) continuous intra-arterial infusion was used consisting of 5-FU 1000 mg/week given on consecutive days and 10 mg of MMC (mitomycin C) as one shot intra-arterial once a month. However, many patients whose general conditions worsened during the course of FM continuous intra-arterial infusion had a poor prognosis. Therefore, a method consisting of continuous intra-arterial infusion of 5-FU given every other week combined with an immunostimulant to enhance immunity was used. We therefore devised a protocol of FM treatment that substitutes bleomycin (BLM) in BM therapy of Miyamoto *et al.*[9] by 5-FU combined with daily intra-arterial infusion of lentinan, which can be administered intravenously. This activates the hepatic reticulo-endothelial system by direct infusion into the hepatic artery and produces an anti-cancer effect through the combined use of an antitumor agent. This protocol is shown in the upper part of Figure 4 as FML continuous intra-arterial infusion.

By this protocol of FML continuous intra-arterial infusion, lentinan should be given daily for a total dose of 20 mg per week. The dose of 5-FU was 1000 mg per week. On the seventh day after administration of 5-FU, 10 mg of MMC should be given as a one shot intra-arterial injection. These constitute one course. At least four courses of treatment should be given for an extended period in each patient.

Prognosis following continuous intra-arterial infusion: Continuous intra-arterial infusion was performed on 15 patients with P0H(+) gastric cancer having gastrectomy, including 7 patients undergoing FM continuous intra-arterial infusion and 8 patients undergoing FML continuous intra-arterial infusion (Fig. 5).

The FM group and FML group were compared in terms of prognosis as determined by the survival rate curves of Kaplan and Meier. The generalized Wilcoxon test[9] revealed a significant difference ($P < 0.05$) at z = 2.32 favoring the FML group.

As far as the distribution of grade of liver metastases was concerned, no significant difference was seen between these two groups.

One patient, a 65-year-old man, presented with gastric cardia cancer with liver metastasis (Fig. 6) and had excellent results after continuous intra-arterial infusion. Gross findings at laparotomy revealed the primary lesion located at the posterior wall of the cardia belonging to P0, S2, and N2. There were three metastatic lesions as demonstrated by preoperative CT scan shown in the left

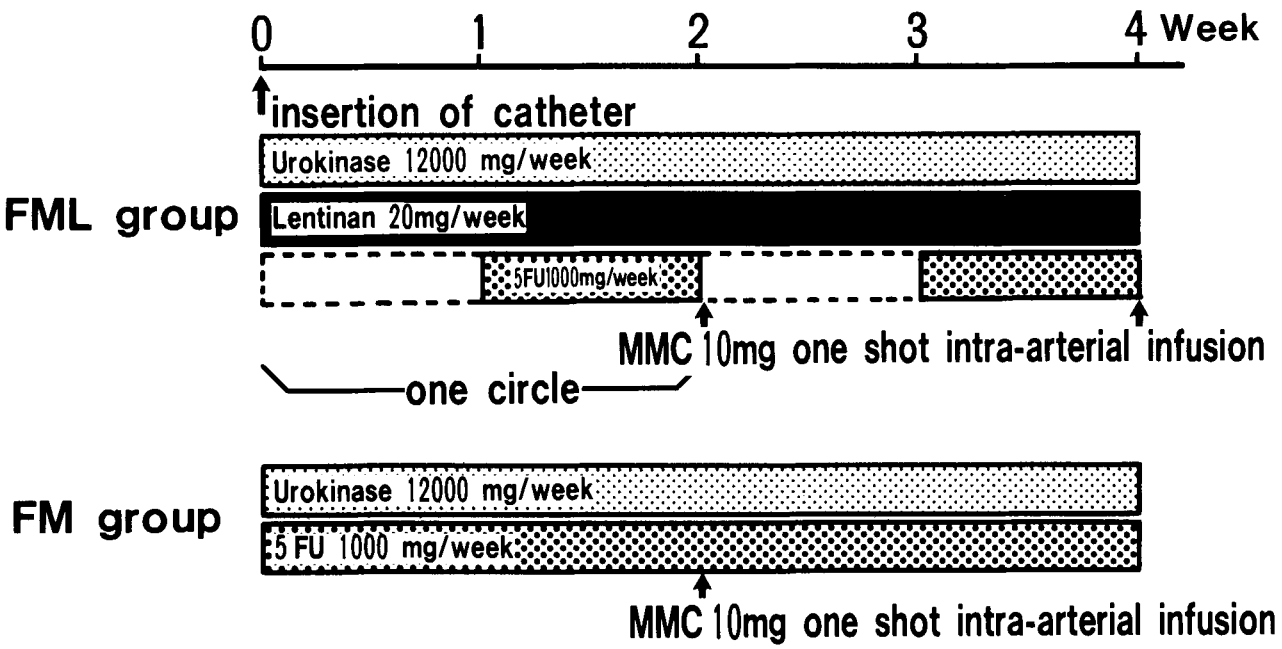

FIG. 4. A protocol of continuous intra-arterial infusion therapy.

lower part of Figure 6. Two lesions of 5.4 × 5.0 cm and 3.9 × 3.9 cm in size, respectively, were detected in the right lobe, whereas the remaining lesions, 7.5 × 7.0 cm in size, occupied the entire left lateral segment. All three metastatic lesions were confirmed at operation.

As the metastatic lesions in the lateral segment was judged to be resectable, lateral segmentectomy was added to total gastrectomy combined with extensive lymph node dissection.

In order to give selective continuous intra-arterial infusion postoperatively for the metastatic lesion of the right lobe, a catheter for continuous intra-arterial infusion was inserted into the common hepatic artery through the gastroduodenal artery.

Using the protocol of FML continuous intra-arterial infusion shown in Figure 4, 25,000 mg of 5-FU, 80 mg of MMC, and 8000 mg of lentinan were administered for a period of 10 months. The catheter containing the continuous intra-arterial infusion was then extracted spontaneously. One month after the operation, margins of two metastatic lesions remained in the right lobe. These lesions, possessing irregular borders and marked with an arrow in the preoperative CT scan (Fig. 6), were found to be stabilized. Measurements by planimeter at this time revealed reduction of 16.4% for large-sized tumors and 23.5% for small-sized tumors. Five months later, 80% and 90% reduction were observed for large and small tumors, respectively. No measurable metastatic lesion was revealed by CT scan at 10 months after operation.

However, recurrence occurred at the distant lymph nodes (left cervical and left axillary nodes) 1 year and 3 months after treatment and metastases to bilateral lungs developed 2 years later, from which the patient died 2 years and 3 months after operation.

Pathologic section of the remaining right lobe at autopsy revealed only one or two small metastatic lesions, 0.5 × 0.5 cm in size, indicating the excellent effect of continuous intra-arterial infusion for liver metastatic lesions.

Survival Rate After Gastrectomy

Simultaneous hepatectomy was performed in combination with gastrectomy in nine cases of gastric cancer with synchronous liver metastasis as shown in Table 2.

There were three H1 cases, four H2 cases, and two H3 cases.

As to the three H1 cases, the primary lesion required subtotal gastrectomy in Case 1 and total gastrectomy in

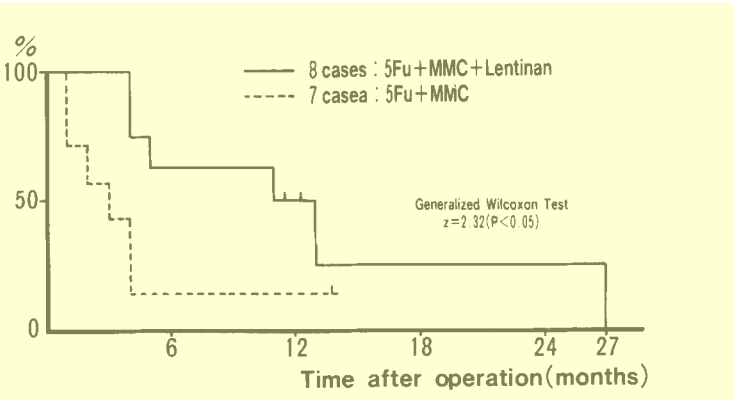

FIG. 5. Survival rate curves of gastric cancer patients with hepatic metastasis receiving postoperative continuous intra-arterial infusion of chemoimmunotherapy.

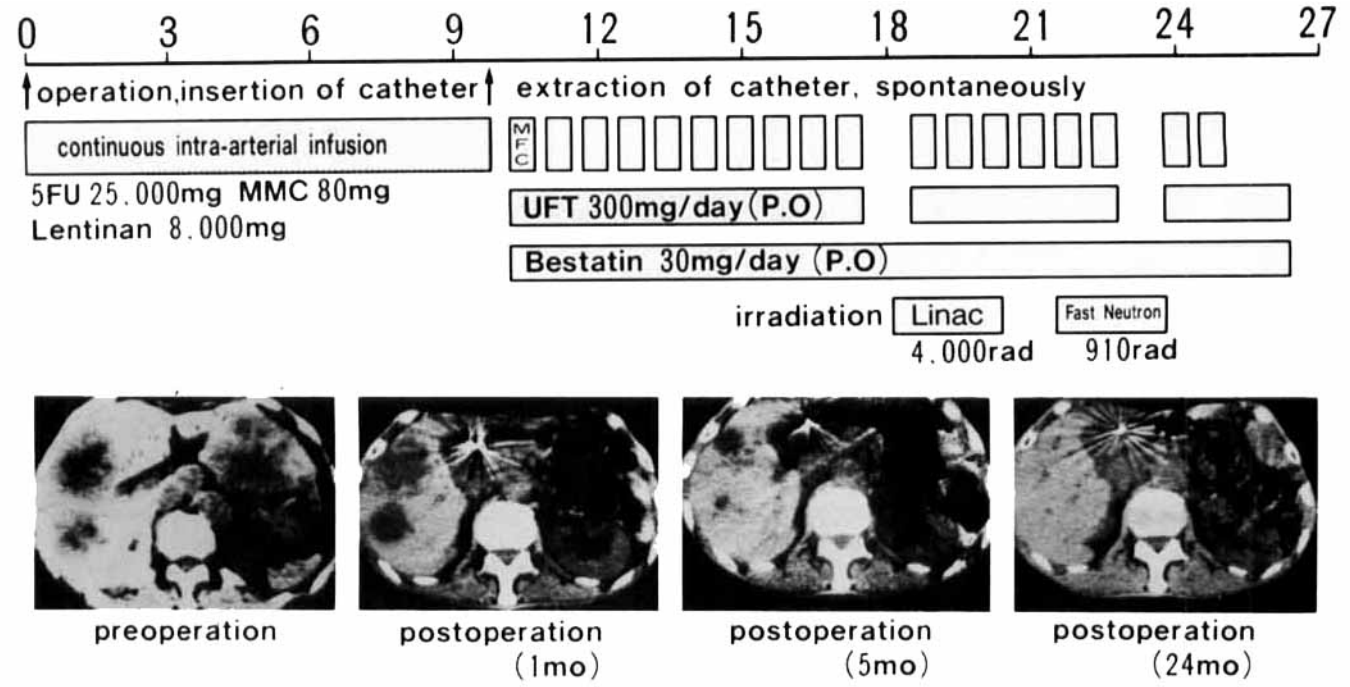

FIG. 6. Presentation of a case, a 65-year-old man, with a diagnosis of gastric cancer with liver metastasis. He received continuous intra-arterial infusion with FML for 10 months after operation. Following spontaneous extraction of the intra-arterial catheter, intravenous systemic chemotherapy of MFC accompanying oral UFT 300 mg/day (UFT containig futraful (FT) 300 mg and uracil 672 mg) and bestatin 30 mg/day [3-(R)-amino-(S) hydroxy-phenylbutanoyl-(S)-leucine] were administered. Because lymph node recurrence at left cervical area was observed 18 months after operation, linac 4000 rad and fast neutron 910 rad were irradiated at that area.

Cases 2 and 3. Hepatectomy was performed in the posterior inferior segment in Case 1 and in the lateral segment in Cases 2 and 3. In all of these cases radical resection could be performed.

In each of the four H2 cases there were a few scattered metastatic lesions in the right lobe with the longest diameter more than 4.0 cm. Therefore, lateral segmentectomy was performed in Cases 4, 5, and 6 for tumor mass reduction. As the postoperative chemotherapy Case 4 received MFC treatment 20 times, followed by one shot intravenous injections of 10 mg MMC once every 3 months. This case was under the oral administration of tegafur (masked compound of 5-FU).

In Cases 5 and 6, a catheter for continuous hepatic intra-arterial infusion was inserted during operation and FML continuous intra-arterial infusion was performed for metastatic lesions in the remaining right lobe.

In Case 7, in which the patient had only relatively small superficial metastatic lesions (one lesion of 1.4 × 1.4 cm in the medial segment and the other of 1.6 × 1.8 cm in the anterior–superior segment), both lesions were removed completely. However, the possible presence of micrometastatic lesions that had not been detectable even by intra-operative echography was suspected. A catheter for continuous hepatic intra-arterial infusion was therefore inserted during operation to perform FML continuous intra-arterial infusion postoperatively.

Regarding the two H3 cases (Cases 8 and 9), the metastatic lesion in the lateral segment was extremely large in size (13 × 12 cm in Case 8 and 14 × 13 cm in Case 9). In both of these cases lateral segmentectomy was added to total gastrectomy for tumor reduction as far as possible. Moreover, in Case 8 the catheter for continuous intra-arterial infusion was inserted into the hepatic artery during operation and intra-arterial infusion was performed postoperatively.

Looking into the prognosis of these nine cases having undergone hepatectomy simultaneously with gastrectomy, one (Case 3) of the three H1 cases expired at 5 months after operation, when liver metastasis to the right lobe occurred, possibly due to the fact that tumor in this case was si with direct infiltration to the pancreas. However, Case 1 and Case 2 have been maintained alive for 1 year and 1 months for the former case, and for 8 months for the latter case.

In Cases 4, 5, and 6, all of which were H2 cases, metastatic lesions in the remaining right lobe were reduced remarkably by postoperative chemotherapy. Case 4 has been maintained well for 3 years and 3 months and Case 6 for 1 year after operation.

Case 5 is the case presented in Figure 6. Even though metastatic lesions in the liver were well controlled, the patient died from metastases to both lungs at 2 years and 3 months after operation.

TABLE 2. Cases Receiving Resection Both of Gastric Cancer and Hepatic Metastasis

Case no.	Age & sex	Grade of hepatic metastasis	Primary lesion of gastric cancer*	Location of hepatic metastasis	Operative method	Pathologic findings of the specimen: Histologic pattern	Depth of cancerous invasion in stomach wall	Grade of lymph node metastasis	Cancer cell invsion into lymph vessels and the veins of the stomach wall	Outcome
1	62 M	H1	M	 4.5 × 4	Pg + S6	tub1	ss	n1(+)	(+)	Alive (13 mo)
2	56 M	H1	MA	 0.8 × 0.5	Tg + S3	tub2	se	n2(+)	(++)	Alive (8 mo)
3	73 M	H1	C	 3 × 3	Tg + S2.3	tub1	si	n1(+)	(++)	Died (5 mo)
4	57 M	H2	C	 3 × 3	Tg + S2,3	pap	se	n2(+)	(+++)	Alive (40 mo)
5	65 M	H2	C	 4 × 3	Tg + S2,3	pap	ss	n2(+)	(+++)	Died (27 mo)
6	65 M	H2	C	 0.9 × 0.8 0.6 × 0.5 2 × 2	Tg + S2,3	por	se	n2(+)	(+)	Alive (12 mo)
7	74 M	H2	A	 1.6 × 1.8 1.4 × 1.4	Pg + S4S8	tub1	sm	n2(+)	(++)	Died (3 mo)
8	67 M	H3	MC	 13 × 12	Tg + S2,3	tub2	se	n2(+)	(++)	Died (5 mo)
9	53 M	H3	MC	 14 × 13	Tg + S2,3	tub1	ss	n2(+)	(++)	Died (2 mo)

* The stomach is separated into the upper (C), middle (M), and lower (A) portions by drawing lines between the corresponding trisecting points on the greater and lesser curvatures.

† n1(+): metastasis to Group I lymph nodes; n2(+): metastasis to Group II lymph nodes.

‡ (+): minimal invasion; (++): intermediate invasion; (+++): severe invasion.

Pg: partial gastrectomy; Tg: total gastrectomy; S6: hepatectomy of posteror inferior segment; S3: hepatectomy of lateral inferior segment; S2,3: hepatectomy of lateral segment; S4: hepatectomy of median segment; S8: hepatectomy of anterior superior segment; tubl: tubular adenocarcinoma, well-differentiated type; tub2: tubular adenocarcinoma, moderately differentiated type; pap: papillary adenocarcinoma; por: poorly differentiated adenocarcinoma; sm: tela submucosa; ss: tela subserosa; se: cancer cells present on the serosal surface and exposed to the peritoneal cavity; si: cancer cells infiltrating the neighboring tissue.

The patient of Case 7 died at 3 months after operation from unknown causes with no improvement in general condition. The death was possibly due to old age.

In H3 cases, despite postoperative chemotherapy with continuous intra-arterial infusion as the main therapy, patients died at 5 months (Case 8) and 2 months (Case 9) after operation.

Consequently, it is advisable to confine indication of simultaneous hepatectomy in gastrectomy to cases with histologic depth of primary lesion up to se (cancer cells are present on the serosal surface and exposed to the peritoneal cavity) and grade of liver metastasis up to H2.

The survival rate curves of 9 patients receiving gastrectomy + hepatectomy + chemotherapy for gastric cancer with synchronous liver metastasis were compared with that of 21 undergoing gastrectomy + chemotherapy and 35 undergoing gastrectomy alone in Figure 7. A better prognosis was obtained for the gastrectomy + hepatectomy + chemotherapy group (thick solid line) than the gastrectomy + chemotherapy group (thin solid line) and the gastrectomy alone group (dotted line), the difference being statistically significant ($P < 0.01$) at $z = 2.1$ and 2.71, respectively.

As to the grade of liver metastasis, the chi-square test revealed no significant difference among the three groups.

Therefore, we believe that the effective treatment for gastric cancer with synchronous liver metastasis is a gastrectomy with radical lymph node dissection, combined with hepatectomy to remove the metastatic lesions for tumor reduction, and postoperative chemotherapy with continuous intra-arterial infusion.

Discussion

Gastrectomy for the treatment of gastric cancer with liver metastasis was reported by Hoshino[10] and Itoh[11] who compared the prognosis of patients having undergone gastrectomy with that of patients not undergoing

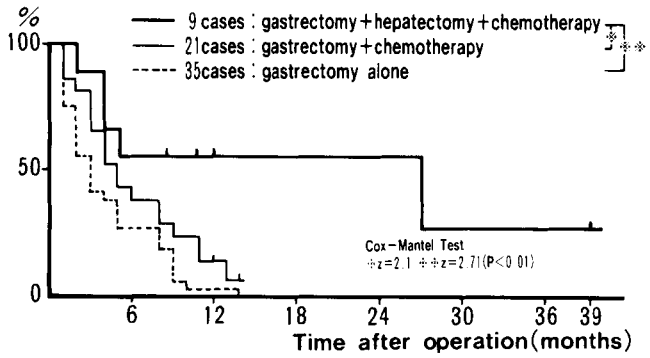

FIG. 7. Effect of hepatectomy in gastric cancer patients with hepatic metastasis, but without peritoneal dissemination.

resection. Beneficial effects were obtained in patients receiving gastrectomy. Statistical analysis for comparison of survival rates, however, was not carried out by them. We also have experienced the same beneficial effects among our patients. A stratification of gastrectomied patients into those with and without chemotherapy revealed that gastrectomy without chemotherapy cannot prolong the survival time of the patients, as compared with the nonresected. We believe that temporary beneficial effects, such as allowing oral intake and the control of pain or bleeding, can be obtained by gastrectomy without chemotherapy. However, the residual cancerous mass, including hepatic metastasis and lymph node metastasis, can rapidly grow after the surgical invasion to suppress the defense mechanism of the patient. Significant improvement in the survival time of patients with gastrectomy, compared with nonresected cases, has not occurred. Furthermore, if the residual cancer cells are too massive for control by anti-cancer chemotherapy, tumor cells can easily proliferate and the tumor can recur. We believe that to treat this disease, it is essential to reduce the size of the cancer cells as much as possible, so that chemotherapeutic agents can have some effects. Based on this consideration, we have performed radical gastrectomy with extensive lymph node dissection and hepatectomy in order to remove metastatic lesions. Using intra-operative echography, we can completely remove liver metastatic lesions in H1 cases, even in H2 cases with metastasis located at the lateral segment or marginal portion of the liver. In our series the survival rate can be improved when hepatectomy is combined with radical gastrectomy, so long as liver metastatic lesions remain those of H2 cases.

Our data revealed that chemotherapy through the intra-arterial route is unable to contribute to a significant prolongation of survival time in comparison with therapy through the systemic route. The grade of liver metastasis is significantly ($P < 0.05$) higher in patients receiving intra-arterial infusion than in those receiving systemic administration. We believe that for the treatment of residual metastatic lesions in the liver, continuous intra-arterial infusion through the hepatic artery, so that anti-cancer agents can selectively reach the lesion, is effective in reducing tumor mass and side effects of the drugs. Tumor reductive hepatectomy performed on patients with H2 liver metastasis does not induce rapid growth of the lesions in the remaining liver; remarkable reduction in tumor size can occur as long as chemotherapy is added, especially by the intra-arterial route of administration. The effectiveness of chemotherapy depends on the drug and the way of administration. We proposed a method with reference to BM therapy of Miyamoto *et al.*[9] for pulmonary metastasis of uterine cervical cancer. We used 5-FU instead of bleomycin because all of our patients had adenocarcinoma. In addition, lentinan is added to constitute the 5FU-MMC-lentinan (FML) regimen for our continuous intra-arterial infusion. Lentinan is a polysaccharide that has a host-mediated antitumor effect and no direct cytocidal function.[12] It can restore cell-mediated immunity after suppression caused by tumors or by administration of chemotherapeutic agents.[13] We use lentinan in our continuous intra-arterial infusion in the immediate postoperative period, as the surgical invasion frequently jeopardizes the patient's defense mechanism. In order to obtain an anti-tumor effect by enhancement of the defense mechanism in the tumor-bearing host through the thymus and lymphatic system, and to obtain potentiated tumor reducing effects similar to those reported by Satoh *et al.*,[14] our department uses endoscopic topical infusion of BCG-CWS (bicolor guaiac cell wall skeleton). We administer lentinan intra-arterially into the liver, in combination with the anti-cancer agents 5-FU and MMC, so as to obtain lentinan concentrations at very high levels within the liver metastatic lesions.

Potentiation of antitumor effects by combining lentinan with other anti-cancer agents was demonstrated by Shiio *et al.* in animal experiments.[13] We report here that using lentinan in continuous intra-arterial infusion is effective in potentiating the anti-tumor effect of the drugs and in prolonging survival time of the clinical cases.

Conclusions

Evaluations were executed to obtain effective treatment for gastric cancer with synchronous liver metastasis with the following results: (1) subjects were divided into four groups: Group I consisting of cases receiving gastrectomy + hepatectomy + chemotherapy, Group II gastrectomy + chemotherapy, Group III gastrectomy alone, and Group IV nonresected cases. The prognosis was compared by survival rate curves according to the method

胃切除術 肝切除術

of Kaplan and Meier. The prognosis was in the order of Group I > Group II > Group III > Group IV. Between Group I and any of the other groups, a statistically significant difference was seen; (2) Immunochemical treatment using FML continuous intra-arterial infusion was used for chemotherapy after gastrectomy and was proven effective for improving prognosis; and (3) When hepatectomy was carried out at the same time as gastrectomy, radical excision was recommended for H1 cases. Moreover, even in H2 cases, hepatectomy was found to be effective for improving prognosis by reducing tumor mass as much as possible, followed by immunochemical treatment using postoperative intra-arterial infusion as the main treatment.

REFERENCES

1. Nishi M, Tamura T. Clinical study of stomach cancer with hepatic metastasis. *Jpn J Cancer Clin* 1962; 8:433–442 (in Japanese).
2. Shinagawa T, Ohto M, Kimura K *et al.* Real-time ultrasonographic diagnosis of hepatocellular carcinoma correlation of echograms and histopathological findings. *Jpn J Gastroenterol* 1981; 78:2402–2411 (in Japanese).
3. Adson MA, Van Heeden JA. Major hepatic resections for metastatic colorectal cancer. *Ann Surg* 1980; 191:576–583.
4. Goslin R, Steele G, Zamcheck N *et al.* Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon and rectum. *Dis Colon Rectum* 1982; 25:749–754.
5. Okuyama K, Chin F, Ryu M *et al.* The effect of chemotherapy against gastric cancer especially to metastatic cancer of liver. *J Clin Surg* 1980; 35:1049–1055 (in Japanese).
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:459–481.
7. Japanese Research Society for Gastric Cancer. The general rules for gastric cancer study in surgery and pathology. *Jpn J Surg* 1981; 11(2):127–139.
8. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; 50: 163–170.
9. Miyamoto T, Takabe Y, Watanabe M *et al.* Drastic remission effect of a sequential combination of bleomycin and mitomycin-C (B-M) on advanced cervical cancer. *Jpn J Cancer Chemother* 1977; 4: 273–291 (in Japanese).
10. Hoshino T. Evaluation of palliative operation for gastric cancer. *Jpn J Cancer Clin* 1967; 4:1543–1550 (in Japanese).
11. Itoh I. Treatment of metastatic liver cancer: Hepatectomy and chemotherapy. *J Clin Surg* 1967; 22:1543–1550 (in Japanese).
12. Chihara G, Maeda Y, Hamuro J *et al.* Inhibition of mouse sarcoma-180 by polysaccharide from Lentinus edodes (Berk) Sing. *Nature* 1969; 222:687–688.
13. Shiio T, Yoshihara T, Yugari Y. Effect of anti-tumor polysaccharide lentinan on immune response and its additive effect with other chemotherapeutic agents. *Jpn J Cancer Chemother* 1975; 2:45–51 (in Japanese).
14. Satoh H, Ochiai T, Satoh H. Immunotherapy for gastrointestinal cancer. *Gastroenterol Surg* 1979; 2:69–75 (in Japanese).