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Special Contribution

Scirrhous Gastric Cancer: Therapeutic Strategy

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The prognosis of patients with scirrhous gastric cancer is extremely poor. The management protocol for this type of cancer has not well been documented. In this paper, recent therapeutic outcomes of this type of gastric cancer are reviewed, and we introduce a new treatment protocol for scirrhous gastric cancer.

Key words: intraperitoneal chemotherapy; laparoscopy; real-time reverse transcription-polymerase chain reaction; scirrhous gastric cancer

Clinicopathological characteristics of scirrhous gastric cancer

Scirrhous gastric cancer, designated as linitis plastica or Borrmann type 4 gastric cancer, is unique among gastric carcinomas. It is characterized by poorly differentiated carcinoma cells or signet-ring cells which diffusely infiltrate the gastric wall with provoking reactive fibrosis. Scirrhous gastric cancerous cells are located predominantly in the submucosa, making it difficult to identify scirrhous gastric cancer using endoscopy. Although accuracy in the diagnosis of other gastric carcinomas has undoubtedly improved with the advent of endoscopy (Qizilbash et al., 1980), the sensitivity of detection of scirrhous gastric cancer by endoscopy was reported to be only 33 to 73% (Evans et al., 1985; Levine et al., 1990). Moreover, Park et al. (2004) indicated that detection of scirrhous gastric cancer using upper gastrointestinal series or endoscopic examinations at an early stage was quite difficult. Contrary to normal cases of gastric cancers, scirrhous gastric cancer tends to spread over the peritoneum with a rapid growth and early metastasis (Aranha et al., 1989; Kanter et al., 1986). Thus, prognosis is poor in patients with this disease, and the 5-year survival rate is low.

Prognosis of patients with scirrhous gastric cancer

Despite curative gastrectomy, the 5-year survival rate following gastric resection for patients with scirrhous cancer (13%) is significantly lower than that of patients with other types of carcinoma (67%) (Otsuji et al., 2004). High incidences of serosal invasion and peritoneal metastasis have been reported in scirrhous gastric cancer, and many reports indicated that palliative resection of the stomach resulted in poor outcomes for affected patients (Takahashi et al., 2000; Yoshikawa et al., 2001). Even when curative gastrectomy is performed, survival of patients remains low. Thus, Aranha et al. (1989) suggested that scirrhous gastric cancer was not a surgical disease.

In our previous study, between 1991 and 2001, scirrhous gastric cancer was detected in 58

Abbreviations: CEA, carcinoembryonic antigen; CY, cytology of peritoneal washing; P, peritoneal metastasis; RT, reverse transcription

(7.5%) of 774 patients with gastric cancers treated at the Tottori University Hospital. Gastrectomy was performed in 39 (67.2%) patients; and in the other 19 patients, gastrectomy was not performed (nine of them already had pleural effusion or ascites at diagnosis of scirrhous gastric cancer, and the other 10 were operated on, but gastrectomy was halted because metastasis was widely detected in the peritoneal cavity). Peritoneal intraoperative cytology of washings (CY) from the Douglas cavity was performed for the 39 patients immediately after laparotomy, according to a previously demonstrated method (Ikeguchi et al., 1994). Of the 39 scirrhous gastric cancer patients who underwent gastrectomy, the 5-year survival rate of 19 patients with no peritoneal metastasis (P) and no peritoneal washing cytology [P(–)/CY(–)] was 11.6%, and 13 patients with P(+)/CY(+) or 7 patients with P(–)/CY(+) died within 3 years of operation. The survival curve of patients with P(–)/CY(–) was better than that of patients with P(–)/CY(+) (P = 0.007), and survival curve of 7 patients with P(–)/CY(+) was not different from that of 13 patients with P(+)/CY(+) (Fig. 1, P = 0.262). Moreover, the 50% survival periods of 20 patients with P(–)/CY(+) or P(+)/CY(+) who underwent gastrectomy (5 months) was almost the same as that of 10 patients who were operated with only laparotomy (because of extended peritoneal metastasis, 6 months, P = 0.725). Our data strongly suggested that in scirrhous gastric cancer, gastrectomy should be performed for patients with P(–)/CY(–). Similar results have been reported by Kikuchi et al. (2000).

Therapeutic procedures and outcomes of scirrhous gastric cancer

To prolong the survival periods of patients with scirrhous gastric cancer, some surgeons have performed more radical operations such as en bloc total gastrectomy including the pancreatic body and tail, the spleen, the gallbladder, the transverse colon and the left adrenal gland (Furukawa et al., 1997). However, such radical surgeries may result in increased risks of operative mortality. Although other treatments have been attempted such as chemotherapy (Kobayashi et al., 2002), radiotherapy (Willett, 2002), hormonal therapy (Furukawa et al., 1994) or immunotherapy (Kim et al., 2001), their antitumor effects have been insufficient to improve prognosis of patients with scirrhous gastric carcinoma.

Common features of scirrhous gastric cancer include remarkable fibrosis, rapid invasive progression and high frequency of metastasis to the peritoneum. Using a nude mouse model, Hippo

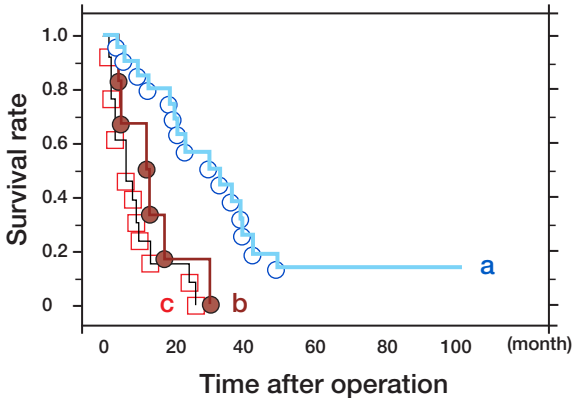

Fig. 1. Our therapeutic results for patients with scirrhous gastric cancer who underwent gastrectomy between 1991 and 2001. Survival curves of 39 patients.
Line a: 19 patients with no peritoneal metastasis (P) and no peritoneal washing cytology [P(–)/CY(–)].
Line b: 7 patients with P(–)/CY(+).
Line c: 13 patients with P(+)/CY(+).

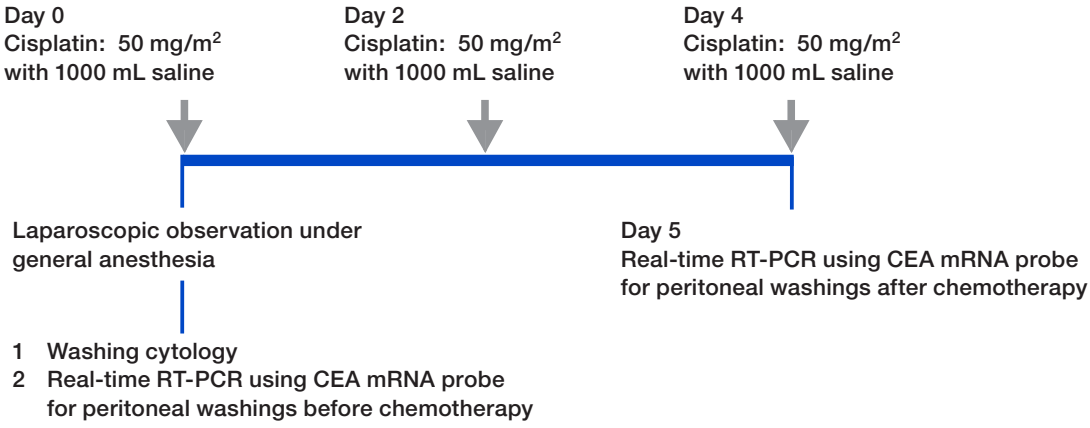

Fig. 2. Our new treatment design for scirrhous gastric cancer using laparoscopic cisplatin-based intraperitoneal chemotherapy.

et al. (2001) globally analyzed differential gene expression in scirrhous gastric cancer cells, and they indicated that scirrhous gastric cancer cells showed a particularly high potential for metastasis to the peritoneal cavity. Thus, development of new therapeutic approaches to prevent peritoneal metastasis is an important issue.

Intraperitoneal chemotherapy for scirrhous gastric cancer

Various investigators have attempted to develop therapies against peritoneal metastasis in scirrhous gastric carcinoma. Hagiwara et al. (1992) reported prognostic effectiveness of intraperitoneal administration of mitomycin-C at the time of operation in patients with advanced gastric cancer. In addition, we have previously reported that intraperitoneal chemotherapy showed a survival benefit for patients with advanced gastric cancer who had free cancerous cells in their peritoneal cavities (Hamazoe et al., 1994). Thus, we suggested that intraperitoneal chemotherapy might have prognostic benefits for patients with scirrhous gastric cancer, by preventing peritoneal metastasis. Moreover, Tsujitani et al. (1993) reported that foci of peritoneal seeding were more sensitive to cisplatin than to mitomycin C or to adriamycin. Thus, we used cisplatin in our new treatment protocol (using intraperitoneal chemotherapy) for scirrhous gastric cancer patients.

Our new treatment design for scirrhous gastric cancer

Shiraishi et al. (1999) reported that laparoscopy was useful for evaluating peritoneal metastatic statuses. Therefore, to avoid unnecessary laparotomy, we used laparoscopy for the diagnosis of macroscopic peritoneal metastases or to perform peritoneal washing cytology for patients with scirrhous gastric cancer. Moreover, we used intraperitoneal chemotherapy with cisplatin during laparoscopy for these patients regardless of peritoneal status. We started this new treatment for patients with scirrhous gastric cancer from 2002 (Fig. 2). Patients with scirrhous gastric cancer without pleural effusion, ascites, liver metastasis or extended lymph nodes metastasis by computed tomography, were treated using laparoscopic diagnosis of peritoneal metastasis and peritoneal washing cytology under general anesthesia. During this procedure, intraperitoneal chemotherapy with cisplatin (50 mg/m^2) in 1000-mL saline was performed through a drain tube located in the left sub-diaphragm; and following 1 h after clamping

of the drain tube, saline with cisplatin was discharged from the drain tube located at the pouch of Douglas (Fig. 3). This type of intraperitoneal chemotherapy was performed thrice on every other day (initial chemotherapy was performed during laparoscopic diagnosis under general anesthesia, but following intraperitoneal chemotherapies were performed without anesthesia). Following the end of intraperitoneal chemotherapy, patients were treated with systemic chemotherapy using 5-fluorouracil (500 mg/m^2) and cisplatin (10 mg/m^2), intravenously for 4 days/week. Systemic chemotherapy was maintained for 4 weeks. Patients who were diagnosed as P(–) at initial laparoscopy underwent gastrectomy with lymphadenectomy after systemic chemotherapy. Patients who were diagnosed as P(+) received intraperitoneal chemotherapy using laparoscopy under general anesthesia for more than twice (Ikeguchi et al., 2005).

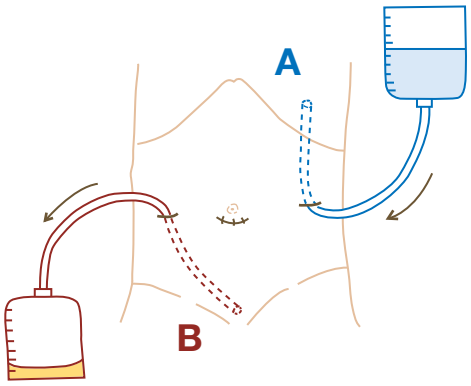

Fig. 3. Locations of tubes during intraperitoneal chemotherapy. **A:** drain tube located in the left subdiaphragm. **B:** drain tube located at the pouch of Douglas.

Detection of cancerous cells in peritoneal washing samples using real-time RT-PCR

In order to investigate therapeutic effects of intraperitoneal chemotherapy for patients with gastric cancer, we analyzed numbers of cancerous cells in peritoneal washing samples obtained just prior to and after intraperitoneal chemotherapy using carcinoembryonic antigen (CEA) mRNA based real-time reverse transcription (RT)-PCR. One hundred and fifty milliliters of saline were introduced into the Douglas cavity of each individual at the beginning of laparoscopic operations, and aspirated after gentle stirring. Fifty-milliliter samples of each peritoneal washing were prepared for cytological diagnosis of free cancerous cells, and other 50-mL samples were used for RNA extraction. At post-operative day 5 (after the end of intraperitoneal chemotherapy), peritoneal cavities of scirrhous patients were washed with 150-mL saline from the tube located on the left sub-diaphragm. Fifty milliliters of peritoneal washing were then collected from the tube located at the pouch of Douglas for RNA extraction. Cytological examination was not performed at this time, because it was usually difficult to gather sufficient volume of samples for cytological examination.

Fifty milliliters of peritoneal wash samples were centrifuged for 10 min at 400 × *g*, and total RNA was extracted from the resulting pellets using an RNeasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. cDNA was synthesized from 1 μg total RNA using Ready-to-Go You-Prime First-Strand Beads (Amersham Pharmacia Biotech, Piscataway, NJ). Specific primers and a TaqMan probe for CEA were synthesized (Ikeguchi et al., 2003). PCR was carried out with incubation at 50°C for 2 min, denaturing at 95°C for 10 min, 45 cycles at 95°C for 15 s and 61°C for 1 min (Bustin et al., 1991).

Different concentrations of KATO-III cells (10–10^6) were added to 1.5-mL peripheral blood samples from 1 healthy volunteer (6 × 10^6 peripheral blood granulocytes). CEA mRNA expression levels from different concentrations of KATO-III cells were analyzed by real-time RT-PCR. All PCR experiments were done in triplicates. Numbers of cancerous cells were derived from the CEA calibration curve (Yajima et al., 1998) derived from plots representing the log of KATO-III cells in 6 × 10^6 granulocytes on the x-axis and cycle numbers on the y-axis. Therefore, formula for CEA expression was y = 40 – 3x (r^2 = 0.994)

(Fig. 4). For each peritoneal washing sample, relative numbers of cancerous cells (amounts of CEA mRNA) were determined from the standard curve (Nakanishi et al., 2000).

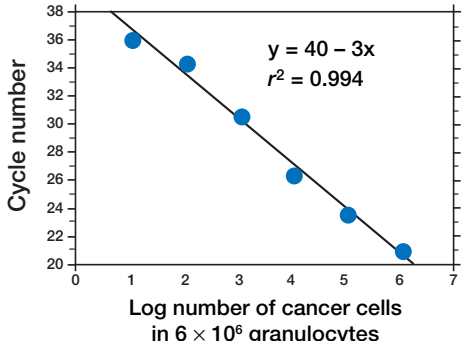

Fig. 4. The standard curve based on the different concentration of KATO-III cells in 6×10^6 granulocytes. The log of KATO-III cells in 6×10^6 granulocytes was set on the x-axis. The threshold line was set at an Rn of 0.1. The cycle numbers at which each amplification curve of the different concentration of KATO-III crossed the threshold (0.1) was set on the y-axis. For each sample, the number of cancer cells was estimated from this standard curve and it was described as the number of cancer cells/6×10^6 granulocytes.

Therapeutic benefits of laparoscopic intraperitoneal chemotherapy for patients with scirrhous gastric cancer

Between 2002 and 2005, 13 patients were diagnosed as scirrhous gastric cancer and diagnosed as no pleural effusion, no ascites, no liver metastasis or no extended lymph node metastasis by computed tomography. They were performed laparoscopic diagnosis for peritoneal metastasis followed by intraperitoneal chemotherapy. Details of these patients are summarized in Table 1. Four patients were diagnosed as P(+)/CY(+), 3 were as P(–)/CY(+) and 6 were as P(–)/CY(–). While, cancerous cells were detected in peritoneal washings of all 13 patients using CEA-based real-time RT-PCR. More than 90% of cancerous cells were removed from the peritoneal cavity following cisplatin intraperitoneal treatment in 8 patients (Table 1). Moreover, CEA-positive cells could not

Table 1. Characteristics of the 13 scirrhous gastric cancer patients treated with laparoscopic intraperitoneal chemotherapy

Patient number	Age (year)	Sex	P/CY	Number of cancerous cells/ 6×10^6 granulocytes		Cancerous cells† reduced after chemotherapy (%)	Gastrectomy after chemotherapy	Prognosis§ after intraperitoneal chemotherapy
				Before chemotherapy	After chemotherapy			
1	55	F	+/+	263,027	23,988	91	No	9 mo, dead
2	37	M	+/+	27,353	1148	96	No	9 mo, dead
3	62	M	–/–	14	22	0	Yes	22 mo, dead
4	68	F	+/+	707,946	109,648	85	No	4 mo, dead
5	82	F	+/+	2884	1288	55	No	14 mo, dead
6	45	F	–/+	2399	0	100	Yes	9 mo, dead
7	30	F	–/+	130	167	0	Yes	6 mo, dead
8	49	F	–/–	3311	0	100	Yes	12 mo, dead
9	79	M	–/–	49	0	100	Yes	28 mo, dead
10	69	M	–/–	9	0	100	Yes	5 mo, dead
11	74	M	–/–	1000	800	20	Yes	5 mo, dead
12	69	F	–/–	43	3	93	Yes	14 mo, alive
13	58	F	–/+	25,119	1995	92	Yes	8 mo, alive

CY, cytological free cancerous cells; F, female; M, male; mo, months; P, peritoneal metastasis.

† Percentage of the reduced number of cancerous cells after intraperitoneal chemotherapy was calculated as follows: $(\mathbf{a} - \mathbf{b})/\mathbf{a} \times 100\%$; **a**, number of cancerous cells before intraperitoneal chemotherapy; **b**, number of cancerous cells after intraperitoneal chemotherapy.

§ dead, died of disease: alive, alive with disease.

be detected in peritoneal wash samples by real-time RT-PCR from 4 patients after chemotherapy. We grouped the 8 patients into the "intraperitoneal chemotherapy effective group". In the remaining 5 patients, the percentages of reduced numbers of cancerous cells after chemotherapy were less than 90% (Table 1). We named these patients as the "intraperitoneal chemotherapy ineffective group". In these patients, cancer cells may have resistance to cisplatin chemotherapy. The 50% survival period of the intraperitoneal chemotherapy effective group was longer (9 months) than that of the intraperitoneal chemotherapy ineffective group (6 months), but the difference was not significant (P = 0.342, Fig. 5) with a log rank test based on the Kaplan-Meier method.

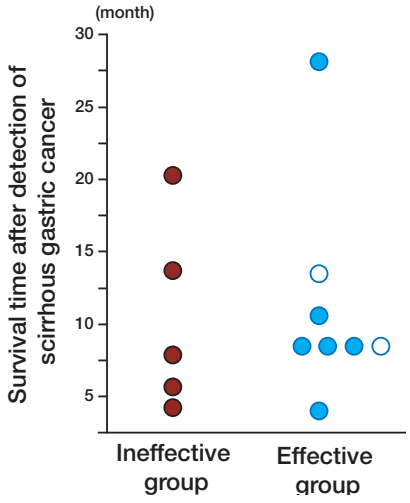

Fig. 5. Survival periods of 13 scirrhous gastric cancer patients treated with our new treatment protocol.

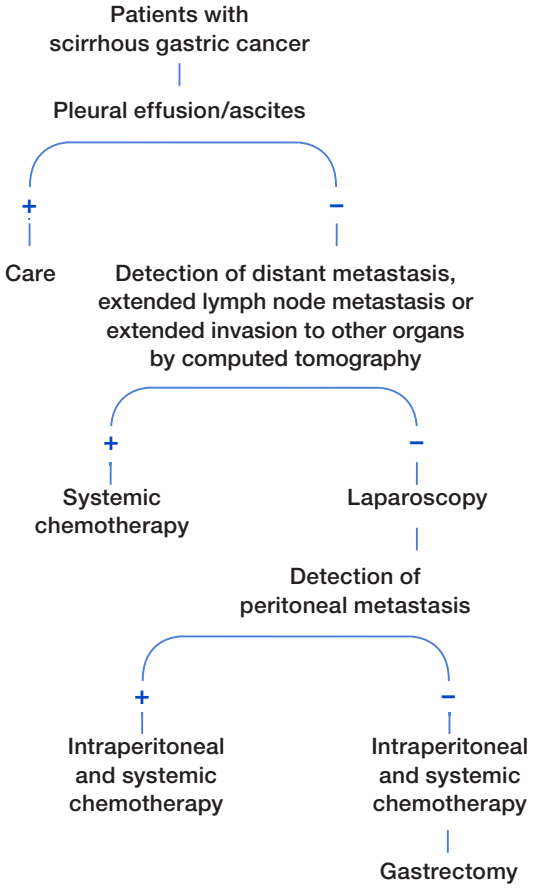

Fig. 6. Our treatment protocol for patients with scirrhous gastric cancer from 2002.

Our treatment protocol for patients with scirrhous gastric cancer

Our treatment protocol for patients with scirrhous gastric cancer is summarized in Fig. 6. In the present study, the observation period was too short to estimate survival benefits of cisplatin-based intraperitoneal chemotherapy for patients with scirrhous gastric cancer. Therefore, continuous follow-up is required.

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