

## Gross Appearance and Curability Are Predictive Factors of a Better Prognosis After Gastrectomy in Gastric Cancer Patients with Metastasis to the Adjacent Peritoneum of the Stomach

Hiroaki Saito, Yusuke Kono, Yuki Murakami, Hirohiko Kuroda, Tomoyuki Matsunaga, Yoji Fukumoto, Tomohiro Osaki and Yoshiyuki Fujiwara

Division of Surgical Oncology, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504, Japan

### ABSTRACT

**Background** Gastric cancer patients with peritoneal metastasis have an extremely poor prognosis. The aim of the current study was to clarify the predictive factors of a better outcome in gastric cancer patients with peritoneal metastasis.

**Methods** We analyzed the records of 2262 gastric adenocarcinoma patients who underwent gastrectomies at our institution between January 1980 and December 2010.

**Results** The 5-year survival rates for advanced gastric cancer patients with P1 ( $n = 43$ ), P2 ( $n = 56$ ), and P3 ( $n = 36$ ) metastasis were 16.3%, 0%, and 0%, respectively. The prognosis of P1 gastric cancer patients was significantly better than that of either P2 ( $P = 0.0003$ ) or P3 patients ( $P < 0.0001$ ). A multivariate analysis identified gross appearance and curability as independent prognostic indicators in P1 gastric cancer patients. In fact, the prognosis was good for patients in whom an R0/1 resection had been performed and with tumors having a gross appearance of other than type 4, with a 40% 5-year survival rate and a 29-month median survival time.

**Conclusion** Our data indicated a good prognosis for P1 patients in whom an R0/1 resection could be performed and with tumors having a gross appearance of other than type 4. Therefore, radical surgery and adequate adjuvant chemotherapy should be performed in these patients.

**Key words** gastric carcinoma; peritoneal metastasis; prognosis; recurrence

Gastric cancer disseminates by hematogenous and lymphatic routes and by direct implantation on peritoneal surfaces. Peritoneal dissemination is the most frequent pattern of metastasis and recurrence in patients with gas-

tric cancer.<sup>1–3</sup> Concomitant peritoneal metastases are frequently observed at the time of diagnosis in patients with advanced gastric cancer. The prognosis for patients with peritoneal metastasis is extremely poor, with a median survival of about 6 months.<sup>4,5</sup> Therefore, systemic chemotherapy is generally administered to these patients. Although the prognosis for gastric cancer patients with peritoneal dissemination has been gradually improving because of improvements in systemic chemotherapy, it is not yet satisfactory. Because of the poor prognosis, surgery is not typically a treatment option for these patients unless there is obstruction or bleeding. However, some previous studies have documented positive effects of palliative gastric cancer resection on survival in gastric cancer patients with peritoneal carcinomatosis.<sup>6–12</sup> These results indicate that there might be patients who receive survival benefit by gastrectomy in gastric cancer patients with peritoneal metastasis. Therefore, it is extremely important to identify the patients with peritoneal metastasis whose prognosis can be improved by gastrectomy. However, there is little information on this regard thus far. Therefore, the aim of the current study was to clarify the predictive factors of a better prognosis after gastrectomy in gastric cancer patients with peritoneal carcinomatosis

### MATERIALS AND METHODS

#### Patients

We examined the records of 2262 consecutive gastric adenocarcinoma patients who underwent gastrectomies at our institution between January 1980 and December 2010. The data were collected retrospectively. Patients' ages ranged between 20 and 100 years with an average of 62.0 years; 1447 patients were male and 815 were female. Clinicopathological findings were generally determined according to the 14<sup>th</sup> edition of the Japanese Classification of Gastric Carcinoma, except for the classification of peritoneal metastasis and the definition of a curative operation.<sup>13</sup> The diagnosis of peritoneal dissemination was based on the operative and histological identification of peritoneal nodules at the time of the operation. The classification of peritoneal metastasis was

Corresponding author: Hiroaki Saito, MD, PhD

sai10@med.tottori-u.ac.jp

Received 2017 June 20

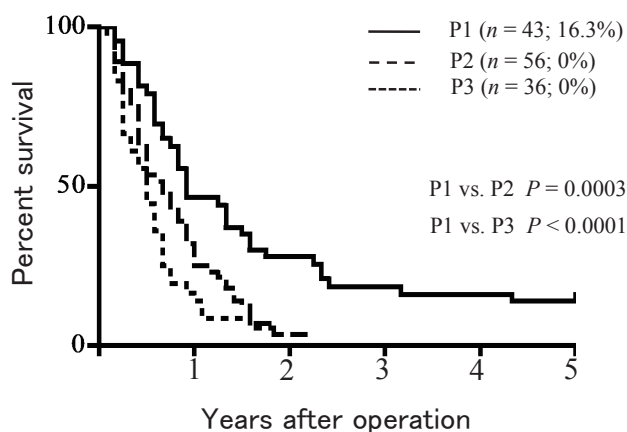
Accepted 2017 August 3

Abbreviations: CHPP, continuous hyperthermic peritoneal perfusion; MMC, Mitomycin C; MST, median survival time

**Table 1. Clinicopathologic characteristics according to peritoneal metastasis status**

Variables	P1 (n = 43)	P2 (n = 56)	P3 (n = 36)
<b>Gross appearance</b>			
Type 4	15 (34.9%)	26 (46.4%)	16 (44.4%)
Except type 4	28 (65.1%)	30 (53.6%)	20 (55.6%)
Tumor size	10.6 ± 5.2	11.1 ± 4.8	10.7 ± 4.4
<b>Serosal invasion</b>			
Absent	5 (11.6%)	2 (3.6%)	3 (8.3%)
Present	38 (88.4%)	54 (96.4%)	33 (91.7%)
Number of lymph node metastasis	15.3 ± 16.8	17.7 ± 17.7	15.8 ± 12.3
<b>Lymphatic vessel invasion</b>			
Absent	4 (9.3%)	9 (16.1%)	3 (8.3%)
Present	39 (90.7%)	47 (83.9%)	33 (91.7%)
<b>Blood vessel invasion</b>			
Absent	8 (18.6%)	18 (32.1%)	11 (30.6%)
Present	35 (81.4%)	38 (67.9%)	25 (69.4%)
<b>Liver metastasis</b>			
Absent	37 (86.0%)	50 (89.3%)	32 (88.9%)
Present	6 (14.0%)	6 (10.7%)	4 (11.1%)
<b>Curability</b>			
Curative	25 (58.1%)*	4 (7.1%)**	0 (0%)**
Non-curative	18 (41.9%)	52 (92.9%)	36 (100%)

\*versus \*\*  $P < 0.0001$



**Fig. 1.** Survival curves for advanced gastric cancer patients with peritoneal metastasis. The 5-year survival rates for advanced gastric cancer patients with P1, P2, and P3 metastasis were 16.3%, 0%, and 0%, respectively. The prognosis for P1 gastric cancer patients was significantly better than the prognosis for either P2 or P3 gastric cancer patients.

determined according to the 12<sup>th</sup> edition of the Japanese Classification of Gastric Carcinoma: P0, no dissemination; P1, disseminating metastasis to the adjacent peritoneum of the stomach; P2, a few scattered metastases to the distant peritoneum; and P3, numerous metastases to the distant peritoneum.<sup>14</sup> Institutional review board

approval was obtained on July 2017 (1607A051), and the informed consent requirement was waived for this study.

### Statistical analysis

Survival rates were constructed using the Kaplan–Meier method, and differences between survival curves were examined with the log rank test. Multivariate analysis was performed using the Cox proportional hazards model and a stepwise procedure. The accepted level of significance was  $P < 0.05$ . A StatView software package (Abacus Concepts, Berkeley, CA) was used for all statistical analyses.

### RESULTS

Among the study population, 43, 56, and 36 patients underwent gastrectomy for P1, P2, and P3 gastric cancer, respectively. Table 1 shows the clinicopathologic findings according to peritoneal metastasis status. Curative operations were more frequently performed in P1 patients than in P2 or P3 patients; the differences in curative resection rates between P1 and P2 or P3 patients were statistically significant. No significant differences were observed in the other clinicopathologic findings.

The 5-year survival rates for advanced gastric cancer patients with P1, P2, and P3 metastasis were 16.3%, 0%, and 0%, respectively. The prognosis for P1 gastric cancer patients was significantly better than the prognosis for either P2 or P3 gastric cancer patients (Fig. 1).

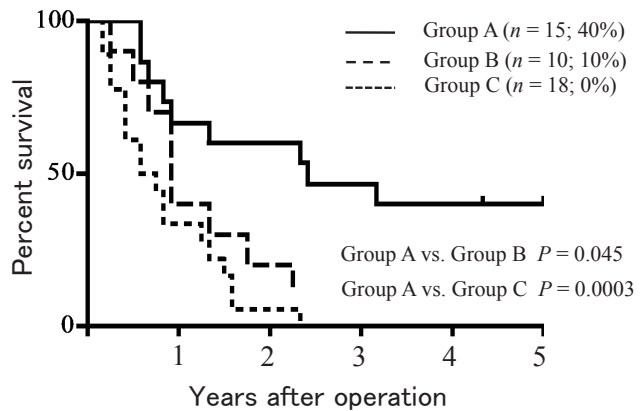
**Table 2. Multivariate analysis using the Cox proportional hazards model and a stepwise procedure in P1 gastric cancer patients**

	<i>P</i>	Hazard	95% CI
Curability (curative vs. non-curative)	0.0006	0.289	0.142–0.589
Gross appearance (Type 4 vs. others)	0.0357	2.104	1.051–4.212

CI, confidence interval.

Among 43 P1 patients, 37 patients (86.0%) underwent chemotherapy, while the remainder did not. It is likely that chemotherapy affect the prognosis of P1 patients. Since this study is retrospective study, various kind of chemotherapy was used. In brief, tegafur (FT-207, Taiho, Tokyo, Japan) was used in 14 patients and uracil-tegafur (UFT, Taiho) in 10 patients. These patients received either 600 to 800 mg of FT twice or 200 to 400 mg of UFT twice or three times daily orally. Tegafur-gimeracil-oteracil (S-1, Taiho) was used in 4 patients. In principle, 80 mg of oral S-1 per square meter of body-surface area per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. This 6-week cycle was repeated. Mitomycin C (MMC) was used in 26 patients as follows: i) intraperitoneal administration at a dose of 8 mg to 10 mg after surgical resection in 9 patients, ii) intravenous administration at a dose of 8 mg to 30 mg after surgical resection and / or on postoperative days in 26 patients. Four patients received a continuous infusion of fluorouracil with CDDP. Continuous hyperthermic peritoneal perfusion (CHPP) with physiologic saline that contained either 10 µg/mL MMC or 125 to 150 mg CDDP was used in 3 patients. Multivariate analysis identified gross appearance and curability, but not chemotherapy, as independent prognostic indicators in P1 gastric cancer patients (Table 2). Based on the results of the multivariate analysis, P1 gastric cancer patients were classified in 3 groups as follows: group A, patients in whom an R0/1 resection had been performed and with tumors having a gross appearance of other than type 4; group B, patients in whom an R0/1 resection had been performed and with a type 4 tumor; and group C, patients in whom an R0/1 resection had not been performed. The 5-year survival rates and median survival times (MSTs) were 40% (29 months), 10% (11 months), and 0% (8 months) in groups A, B, and C, respectively. The prognosis for group A was significantly better than the prognosis for group B ( $P = 0.045$ ) and group C ( $P = 0.0003$ ) (Fig. 2).

In P2/3 patients, multivariate analysis identified the presence of other incurable factors to be an independent



**Fig. 2.** Group A, patients in whom an R0/1 resection had been performed and with tumors having a gross appearance of other than type 4; Group B, patients in whom an R0/1 resection had been performed and with type 4 tumors; and Group C, patients in whom an R0/1 resection had not been performed. The 5-year survival rates and median survival times were 40% (29 months), 10% (11 months), and 0% (8 months) in groups A, B, and C, respectively. The prognosis for group A was significantly better than the prognosis for group B ( $P = 0.045$ ) and group C ( $P = 0.0003$ ).

prognostic indicator. The MSTs for patients with and without other incurable factors were 5 months and 8 months, respectively, and this difference was statistically significant ( $P = 0.0035$ ).

## DISCUSSION

Gastric cancer is one of the most common malignancies. Although the prognosis for patients with gastric carcinoma has improved because of the availability of diagnostic techniques and better intraoperative and postoperative care, death from gastric cancer still ranks second among all cancer deaths worldwide.<sup>15</sup> The most common site of gastric cancer metastasis is the peritoneum. Peritoneal carcinomatosis is a common manifestation of digestive tract cancer and is generally regarded as a terminal condition with a short median survival. In fact, the prognosis for P2 or P3 patients is extremely poor; we found no 5-year survivors in the current study. Because of this extremely poor prognosis, systemic chemotherapy is the main therapeutic option for gastric cancer patients with peritoneal metastasis. The issue of whether or not gastrectomy achieves a survival benefit for those patients is controversial. In the current study, we identified a 5-year survival rate of 16.5% in P1 gastric cancer patients. Although this survival rate was not favorable, it is true that systemic chemotherapy alone could not have achieved this survival rate. Thus, it appears that there is a certain population in which gastrectomy provided a significant survival benefit compared with systemic

chemotherapy alone in P1 gastric cancer patients. From clinical point of view, it is extremely important to identify that population. However, there is little information on this regard thus far. Therefore, we then applied a multivariate analysis to determine predictive factors of improved survival after gastrectomy in gastric cancer patients with P1 peritoneal metastasis and found gross appearance and curability to be independent prognostic indicators. In fact, these two factors were very effective in predicting the prognosis of P1 gastric cancer patients, and the 5-year survival rate and MST were 40% and 29 months, respectively, in patients in whom an R0/1 resection had been performed and with tumors having a gross appearance of other than type 4. Hioki et al. reported that gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors were likely to have an improved survival after gastrectomy, with a median survival of 25 months, a 3-year survival of 45.5%, and a 5-year survival of 27.3%. Therefore, these authors emphasized that patients with a good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates instead of treating them with palliative systemic chemotherapy alone.<sup>16</sup> It is well known that predominant histology of type 4 tumor was signet-ring cell carcinoma and poorly differentiated carcinoma. Therefore, our results are almost consistent with their results. Therefore, surgery should primarily be considered in patients in whom an R0/1 resection can be performed and with tumors having a gross appearance of other than type 4. Because the prognosis was extremely poor for the rest of the P1 patients, chemotherapy should be the primary treatment considered in these patients. On the other hand, the presence of other incurable factors was an independent prognostic indicator in P2/3 gastric cancer patients in the current study. However, even in P2/3 patients, the MST was 8 months for patients without other incurable factors. Therefore, chemotherapy should also be considered in P2/P3 patients.

Even when an R0 resection can be achieved in patients with peritoneal metastasis, there is a high possibility of residual micrometastases, which can induce recurrence postoperatively. Because chemotherapy can eliminate micrometastases that surgery cannot, chemotherapy plays an extremely important role in improving the prognosis of gastric cancer patients with peritoneal metastasis. A recent study showed perioperative chemotherapy to significantly improve progression-free and overall survival in patients with operable gastric and lower esophageal adenocarcinomas.<sup>17</sup> Preoperative chemotherapy has the potential benefit of eliminating micrometastases prior to surgery. Therefore, preoperative

chemotherapy might be useful in improving the prognosis for patients with peritoneal metastasis in whom an R0 resection can be performed. Moreover, intraperitoneal chemotherapy using paclitaxel in combination with general chemotherapy was recently shown to significantly improve survival in ovarian cancer patients with peritoneal metastasis.<sup>18</sup> This therapy might also be effective in the previously mentioned patient population.

Accurate clinical staging is extremely important in formulating the treatment strategy for patients with peritoneal metastasis. Conventional imaging techniques often underestimate the extent of the intra-abdominal spread of advanced gastric cancer. Clinical staging can be improved by laparoscopy, as this modality enables the identification of intra-abdominal tumor deposits on peritoneal surfaces, which may not be detected by noninvasive preoperative imaging. Therefore, staging laparoscopies should be performed in advanced gastric cancer patients with possible peritoneal metastasis to better guide treatment strategies.

There are a few limitations in the present study. First, because this was a retrospective study covering a long period, there is some bias. Especially, chemotherapy regimens underwent significant changes during the course of the study and patients received a variety of chemotherapy regimens. This is likely to have affected the study results although chemotherapy was not an independent prognostic factor. Second, the number of patients included in the current study was small; therefore a large-scale, prospective, randomized, controlled trial is needed to confirm the results.

In conclusion, our data indicated a good prognosis for P1 patients in whom an R0/1 resection could be performed and with tumors having a gross appearance of other than type 4. Therefore, radical surgery and adequate adjuvant chemotherapy should be performed in patients meeting these criteria.

*The authors declare no conflict of interest.*

*Human rights statement and informed consent:* All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

## REFERENCES

- 1 Okajima K, Yamada S. [Surgical treatment of far-advanced gastric cancer]. *Gan No Rinsho*. 1986;32:1203-9. PMID: 2431172.
- 2 Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J*

- Surg. 1999;178:256-62. PMID: 10527450.
- 3 Boku T, Nakane Y, Minoura T, Takada H, Yamamura M, Hioki K, et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. *Br J Surg.* 1990;77:436-9. PMID: 2340396.
  - 4 Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer.* 1989;63:364-7. PMID: 2910444.
  - 5 Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer.* 2000;88:358-63. PMID: 10640968.
  - 6 Gretschel S, Siegel R, Estevez-Schwarz L, Hunerbein M, Schneider U, Schlag PM. Surgical strategies for gastric cancer with synchronous peritoneal carcinomatosis. *Br J Surg.* 2006;93:1530-5. PMID: 17051604.
  - 7 Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJ. Tumor load and surgical palliation in gastric cancer. *Hepatogastroenterology.* 2001;48:1219-21. PMID: 11677934.
  - 8 Ouchi K, Sugawara T, Ono H, Fujiya T, Kamiyama Y, Kakugawa Y, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. *J Surg Oncol.* 1998;69:41-4. PMID: 9762890.
  - 9 Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ. Value of palliative resection in gastric cancer. *Br J Surg.* 2002;89:1438-43. PMID: 12390389.
  - 10 Haugstvedt T, Viste A, Eide GE, Soreide O. The survival benefit of resection in patients with advanced stomach cancer: the Norwegian multicenter experience. *Norwegian Stomach Cancer Trial.* *World J Surg.* 1989;13:617-21; discussion 21-2. PMID: 2479177.
  - 11 Maeta M, Sugawara A, Ikeguchi M, Tsujitani S, Yamashiro H, Shibata S, et al. Does the extent of lymph node dissection affect the postoperative survival of patients with gastric cancer and disseminating peritoneal metastasis? *Surg Today.* 1994;24:40-3. PMID: 7519911.
  - 12 Kikuchi S, Arai Y, Morise M, Kobayashi N, Tsukamoto H, Shimao H, et al. Gastric cancer with metastases to the distant peritoneum: a 20-year surgical experience. *Hepatogastroenterology.* 1998;45:1183-8. PMID: 9756030.
  - 13 Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011;14:101-12. PMID: 21573743.
  - 14 Japanese Research Society for Gastric Cancer. *Japanese Classification of Gastric Carcinoma.* Tokyo: Kanehara; 1995.
  - 15 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69-90. PMID: 21296855.
  - 16 Hioki M, Gotohda N, Konishi M, Nakagohri T, Takahashi S, Kinoshita T. Predictive factors improving survival after gastrectomy in gastric cancer patients with peritoneal carcinomatosis. *World J Surg.* 2010;34:555-62. PMID: 20082194.
  - 17 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376:687-97. PMID: 20728210.
  - 18 Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354:34-43. PMID: 16394300.