

## BORRMANN'S TYPE IV GASTRIC CANCER: CLINICOPATHOLOGIC ANALYSIS

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**OBJECTIVE:** To determine whether there is a specific pattern of clinicopathological features that could distinguish Borrmann's type IV gastric cancer from other types of gastric cancer.

**DESIGN:** A retrospective study of patients with advanced gastric cancer treated between 1985 and 1995.

**SETTING:** The Department of Surgery, Sendai National Hospital, a 716-bed teaching hospital.

**PATIENTS:** The clinicopathologic features of 88 patients with Borrmann's type IV carcinoma of the stomach were reviewed from the database of gastric cancer. The results were compared with those of 309 patients with other types of gastric carcinoma.

**MAIN OUTCOME MEASURES:** Gender, age, tumour size, depth of invasion, histologic type, cancer-stromal relationship, histologic growth pattern, nodal involvement, lymphatic and vascular invasion, type of operation, cause of death and 5-year survival.

**RESULTS:** Women were afflicted as commonly as men in the Borrmann's type IV group. These patients tended to be younger and to have larger tumours involving the entire stomach than patients with other types of cancer. Histologic type was commonly diffuse and scirrhous, and serosal invasion was prominent with infiltrative growth. Nodal involvement and lymphatic invasion were more common in patients with Borrmann's type IV than in those with other types of gastric cancer. The disease was advanced in most instances and a total gastrectomy was performed in 55% of the patients. The survival rate of patients with Borrmann's type IV tumour was lower than for patients with other types of gastric cancer ( $p < 0.005$ , log-rank test).

**CONCLUSIONS:** In Borrmann's type IV gastric cancer, early detection and curative resection are crucial to extend the patient's survival. Aggressive postoperative chemotherapy is recommended when a noncurative resection is performed.

**OBJECTIF :** Déterminer s'il existe des caractéristiques clinicopathologiques particulières qui permettraient de distinguer le cancer de l'estomac de Borrmann de type IV de tout autre cancer de l'estomac.

**CONCEPTION :** Étude rétrospective des patients atteints d'un cancer avancé de l'estomac traité entre 1985 et 1995.

**CONTEXTE :** Département de chirurgie de l'hôpital Sendai National, hôpital d'enseignement de 716 lits.

**PATIENTS :** On a étudié les caractéristiques clinicopathologiques de 88 patients atteints d'un cancer de l'estomac de Borrmann de type IV, tirées de la base de données sur les cancers de l'estomac. On a comparé les résultats à ceux de 309 patients atteints d'autres types de cancer de l'estomac.

**PRINCIPALES MESURES DE RÉSULTATS :** Sexe, âge, grosseur de la tumeur, profondeur de l'envahissement, type histologique, relation entre le cancer et le stroma, évolution histologique, atteinte des ganglions, envahissement lymphatique et vasculaire, type d'intervention, cause du décès et survie à cinq ans.

**RÉSULTATS :** Les femmes étaient atteintes aussi souvent que les hommes dans le groupe des cancers de Borrmann de type IV. Ces patients avaient tendance à être plus jeunes et à avoir des tumeurs plus grosses, qui atteignaient l'estomac au complet, que les patients atteints d'autres types de cancer. Le type histologique était habituellement diffus et squirrhoux et l'envahissement de la séreuse était évident avec crois-

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sance par infiltration. L'atteinte des ganglions et l'envahissement lymphatique étaient plus fréquents chez les patients atteints du cancer de Borrmann de type IV que chez ceux qui avaient d'autres types de cancer de l'estomac. La maladie était au stade avancé dans la plupart des cas et l'on a pratiqué une gastrectomie totale chez 55 % des patients. Le taux de survie des patients atteints d'une tumeur de Borrmann de type IV était plus bas que celui des patients atteints d'autres types de cancer de l'estomac ( $p < 0,005$ , test de Mantel-Haenszel).

CONCLUSIONS : Dans le cas du cancer de l'estomac de Borrmann de type IV, la détection précoce et la résection curative jouent un rôle crucial dans le prolongement de la survie du patient. On recommande une chimiothérapie postopératoire agressive après une résection non curative.

**B**orrmann's type IV gastric cancer is clinically characterized by a diffuse thickening and sclerosis of the gastric wall, marked hypertrophy of the mucosal folds and erosions or ulcers. The infiltrative carcinoma may grow either superficially over the surface of the mucosa or permeate the entire thickness of the wall, producing a characteristic tumour pattern known as linitis plastica.<sup>1,2</sup> Linitis plastica is thought to originate in glands in the deepest layers of the mucosa or in heterotopic glands in the muscularis mucosae or submucosa. This type of carcinoma has often spread to both the cardia and the pylorus by the time of surgical exploration. The mucosal lining is often only slightly affected, making it difficult to detect the presence of carcinoma on endoscopic inspection. Ten percent to 20% of all gastric carci-

nomas are thought to be Borrmann's type IV.<sup>3</sup> The prognosis for this type of cancer remains poor, and the 5-year survival rates after gastric resection range from 10% to 20%.<sup>4-6</sup> Because of the difficulty in diagnosing linitis plastica, we present our experience with this neoplasm and compare it to other types of gastric cancer.

#### PATIENTS AND METHODS

In the 10-year period 1985 to 1995, 923 patients with histologically proven carcinoma of the stomach were treated in the Department of Surgery, Sendai National Hospital. Of these, 397 had histologically advanced gastric cancer, 88 being found to have Borrmann's type IV gastric tumours.

Fig. 1 shows the 4 types of Borrmann's cancer: type I, polypoid or

fungating; type II, ulcerating lesions surrounded by elevated borders; type III, ulcerating lesions with invasion of the gastric wall; and type IV, advanced carcinoma without any craters or elevated lesions that is macroscopically widespread.

Our patients' medical records were reviewed for the following: clinical, laboratory, radiographic and endoscopic findings; tumour size; depth of gastric wall invasion; histologic type and growth pattern; lymphatic and vascular invasion; and follow-up information, including recurrence and survival. The macroscopic and microscopic classifications of gastric cancer were based on the general rules for gastric cancer study in Japan.<sup>7</sup> Histopathologic examination was performed on the primary lesions with step sections to determine the depth of cancer invasion and on resected lymph nodes by using 3 central sections to confirm the presence of metastasis. All data were analysed by the *t*-test for unpaired data and by the  $\chi^2$  test. Survival curves were calculated by Kaplan-Meier analysis, and comparisons were made with use of the log-rank test. Survival was calculated from the date of operation to the most recent follow-up date or to the date of death and included all patients in the study. A probability value of less than 0.05 was considered significant.

#### RESULTS

From our total study group of 923 patients with gastric cancer, the incidence of Borrmann's type IV cancer was 9.5% (88 patients) and the inci-

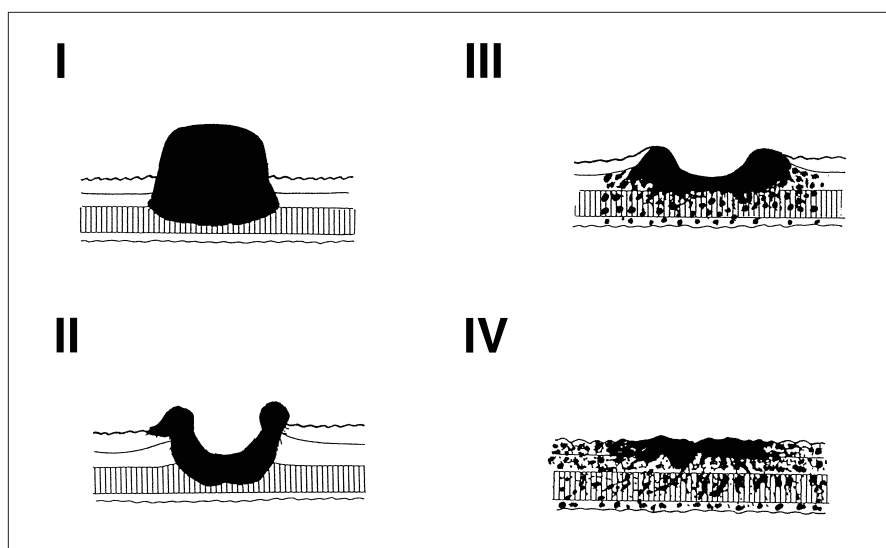


FIG. 1. Borrmann's 4 types of gastric cancer. I — polypoid or fungating, II — ulcerating lesions surrounded by elevated borders, III — ulcerating lesions with invasion of the gastric wall, IV — diffusely infiltrating (linitis plastica).

dences of Borrmann's types I, II and III were 2.8% (26 patients), 9.3% (86 patients) and 21.3% (197 patients), respectively.

When the clinicopathologic data from the 88 patients with Borrmann's type IV gastric cancer were compared with those from patients with other types of cancer (Table I), significant differences were noted with respect to age, gender, tumour size, depth of invasion, histologic type, cancer-stromal relationship, histologic growth pattern, lymph-node metastasis, lymphatic invasion and vascular invasion. Patients with Borrmann's type IV gastric cancer tended to be younger and female, and they had larger tumours that involved the entire stomach wall. Of the 88 patients, 44 were men and 44 were women. The mean diameters of the lesions were 10.5 cm for Borrmann's type IV tumours and 4.8 to 6.6 cm for other types. Microscopically, Borrmann's type IV tumours were made up of diffuse type of carcinoma cells that had penetrated deeply into the subserosa with infiltrative growth; the cancer cells had penetrated the serosal (visceral peritoneum) layer in 66 (75%) of the 88 resected specimens. An infiltrative growth pattern was seen in 72 (82%) patients. These patients were more likely to have nodal involvement and lymphatic invasion but were less likely to have liver metastasis. With respect to cancer recurrence, peritoneal dissemination was common in the Borrmann's type IV group; 35 (40.0%) patients had peritoneal recurrence but no hepatic metastasis whereas 6 (7.0%) patients with Borrmann's type II and 15 (7.6%) patients with Borrmann's type III tumours had hepatic metastases. In 48 (55%) of the 88 patients, a total gastrectomy was performed.

Postoperative survival is illustrated in Fig. 2. The 5-year survival rates were 6.7% for patients with Borrmann's type IV and 63%, 58.1% and 29.7% for types I, II and III, respectively ( $p < 0.005$ ).

**Table I**

**Clinicopathologic Features of Borrmann's Type IV Gastric Cancer Versus Other Types of Cancer\***

Variable	Type				p value
	IV	I	II	III	
Number	88	26	86	197	
Gender					< 0.01
Male	44 (50)	19 (73)	64 (74)	136 (69)	
Female	44 (50)	7 (27)	22 (26)	61 (31)	
Age, yr	57.3	68.1	63.9	64.4	< 0.0005
Tumour size, cm	10.5	4.8	4.9	6.6	< 0.0001
Depth of invasion					< 0.001
TI (m, sm)	1 (1)	8 (32)	5 (6)	3 (2)	
TII (mp, ss)	20 (24)	15 (60)	55 (65)	85 (43)	
TIII (se)	44 (52)	2 (8)	21 (25)	71 (40)	
TIV (si)	19 (23)	0	3 (4)	29 (15)	
Unknown	4	1	2	9	
Histologic type					< 0.001
Intestinal	13 (16)	19 (73)	47 (56)	99 (53)	
Diffuse	69 (84)	7 (27)	37 (44)	89 (47)	
Unknown	6	0	2	9	
Cancer-stromal relationship					< 0.001
Scirrhus	60 (80)	4 (18)	14 (18)	46 (26)	
Intermediate	10 (13)	6 (27)	40 (50)	82 (46)	
Medullary	5 (7)	12 (55)	26 (32)	50 (28)	
Unknown	13	4	6	19	
Histologic growth pattern					< 0.001
Expansive	2 (3)	7 (32)	12 (15)	16 (9)	
Intermediate	11 (15)	12 (55)	49 (62)	101 (56)	
Infiltrative	58 (82)	3 (13)	18 (23)	62 (35)	
Unknown	17	4	7	18	
Nodal involvement					< 0.001
Positive	77 (92)	8 (33)	55 (65)	158 (83)	
Negative	7 (8)	16 (67)	29 (35)	32 (17)	
Unknown	4	2	2	7	
Lymphatic invasion					< 0.001
Positive	68 (87)	10 (42)	55 (66)	145 (79)	
Negative	10 (13)	14 (58)	28 (34)	38 (21)	
Unknown	10	2	3	14	
Vascular invasion					< 0.01
Positive	27 (35)	2 (8)	13 (16)	55 (30)	
Negative	50 (65)	22 (92)	69 (84)	128 (70)	
Unknown	11	2	4	14	
Operation					
Total gastrectomy	48 (55)	8 (31)	22 (26)	78 (40)	
Distal gastrectomy	31 (35)	16 (62)	59 (68)	105 (53)	
Gastrojejunostomy	2 (2)	0	0	4 (2)	
Exploratory laparotomy	5 (6)	0	0	4 (2)	
Others	2 (2)	2 (7)	5 (6)	6 (3)	
Cause of death					
Peritonitis carcinomatosa	35	0	5	23	
Liver metastasis	0	2	6	15	
Other recurrence	22	0	5	18	
Other disease	2	0	1	1	

\*Numbers in parentheses are percentages.  
m = mucosa, sm = submucosa, mp = muscularis propria, ss = subserosa, se = tumour penetration of serosa, si = tumour invasion of adjacent structures.

## DISCUSSION

The classification of advanced gastric cancer by Borrmann in 1926<sup>8</sup> into 4 types is still accepted worldwide by endoscopists, radiologists and surgeons.<sup>9</sup> According to this classification, Borrmann's type IV gastric cancer shows a special morphology both macroscopically and microscopically. Early detection of Borrmann's type IV cancer is difficult because in its early stage the cancer cells individually invade the mucosa propria without either ulceration or elevation on the mucosal surface. In addition, the high incidence of peritoneal dissemination was reported to lower the survival rate for patients with Borrmann's type IV cancer.<sup>10</sup>

The purpose of our study was to review the experience with patients having Borrmann's type IV gastric cancer, including linitis plastica or scirrhus-type gastric cancer, to determine whether there is a specific pattern of clinicopathological features that could distinguish their cancers from other types of gastric cancer. The prognostic value of tumour configuration remains controversial because numerous smaller studies have failed to demon-

strate independent prognostic significance.<sup>11</sup> In our series, 84% of the Borrmann's type IV lesions were classified as diffuse-type adenocarcinoma, and the carcinoma cells had deeply penetrated the serosa with an infiltrative growth pattern in 82% of resected specimens. Total gastrectomy was the procedure most frequently performed for Borrmann's type IV cancer (55%), compared with other types of cancer, mainly because of the large maximum diameter of the lesion. Tumour size and depth of invasion are significant predictors of the spread of this type of gastric cancer. These observations are consistent with those reported by others.<sup>5,12</sup> The 5-year survival for patients with Borrmann's type IV gastric cancer was significantly worse than for patients with other Borrmann types of gastric cancer (6.7% versus 29.7% to 63%, Fig. 2).

Although there have been substantial advances in the diagnosis of cancers of the gastrointestinal tract, a large number of lesions of type IV gastric cancer are still detected at the advanced stage, and the survival rates remain poor.<sup>4-6</sup> This type of cancer is especially difficult to detect at an early stage because of its specific morphol-

ogy. Borrmann's type IV cancer cells grow typically in the submucosal layer, and the mucosal lining of the stomach is usually only slightly affected.<sup>13</sup> Thus, cancer cells are often not present in mucosal biopsies for Borrmann's type IV cancer because they are in the submucosal plane, and biopsies are random or non-targeted because of the absence of mucosal lesions. Nakamura and colleagues<sup>14</sup> proposed that slightly depressed lesions located in the fundus without convergence of the mucosal folds represented an early stage feature of Borrmann's type IV cancer. They also suggested that Borrmann's type IV cancer originating from the pyloric gland has the same morphology in its early development. In this type of carcinoma, cancer cells with less differentiation grow in the plane of the submucosa beneath an otherwise normal mucosa and then individually invade the whole stomach wall with an indistinct border line. These microscopic findings are expressed by either linitis plastica or a scirrhus pattern. Kohli and associates<sup>15</sup> demonstrated that an early feature of scirrhus gastric cancer might be type IIC (depressed type) or types III and IIC (excavated and depressed type)-like depression in the body of the stomach, mainly in the fundus. They stressed that physicians should focus their attention on shallow, ulcerative lesions in the body and fundus of the stomach, and they emphasized the usefulness of double-contrast radiography and the dye-spraying method in endoscopy for early detection of this type of cancer.

Marginal tumour involvement is reported to be significantly more frequent in patients with Borrmann's type IV tumours than in patients with other types of gastric cancer.<sup>16</sup> According to Kitamura and associates,<sup>12</sup> the positive rate of cancer cells in the resection margin was 24.7% in Borrmann's type IV tumours, compared with only 2.2% in other types of can-

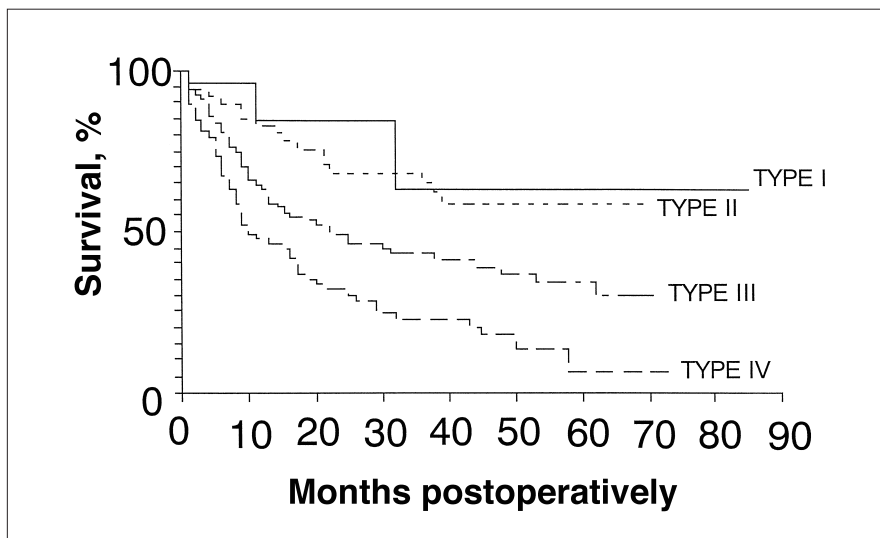


FIG. 2. Survival curve for patients with Borrmann's type IV and other types of Borrmann's cancer of the stomach. There is a statistical difference in survival rates by the log-rank test ( $p < 0.005$ ).

cer. Borrmann's type IV gastric cancer reportedly demonstrates the ability to cause widespread intramural invasion of the esophagus as a squamous esophageal primary carcinoma.<sup>2</sup> Surgeons have traditionally palpated the esophageal margin to determine the adequacy of resection. Frozen-section examination of the esophageal margin cannot determine the adequacy of resection accurately, since the microscopic spread of scirrhous carcinoma cells in Borrmann's type IV tumours can be either continuous with the primary tumour or discontinuous from it, forming skip submucosal foci.<sup>17</sup> The histologic techniques for diagnosis during surgery still include use of dyes such as hematoxylin and eosin. In most cases, cells stained with hematoxylin and eosin could be identified as malignant by standard cytologic criteria. In the case of scirrhous carcinoma of the stomach, however, the malignant cells are dispersed and resemble reactive inflammatory cells. Our attention has been focused on the detection of antigens specific for carcinoma cells but not inflammatory cells. Such antigens were found in the cytoplasm of gastric cancer cells. A monoclonal antibody, S202, was generated by using an intact scirrhous gastric carcinoma cell line for immunization.<sup>18-20</sup> Previously, Yokota and colleagues reported on the application of immunohistochemical techniques to enhance diagnostic information obtained by conventional cytomorphologic methods: immunoperoxidase staining can be performed within 15 minutes,<sup>21</sup> and the limit of invasion of Borrmann's type IV gastric cancer at the resection margin during surgery can be determined by this method.<sup>22</sup>

It has been reported that postoperative adjuvant chemotherapy prolongs the mean survival time not only for patients who have undergone a curative operation but also for those who have undergone a noncurative operation.<sup>23-25</sup> Kurihara's group<sup>26</sup> reported

the results of questionnaires collected from 108 hospitals in Japan. The agents most frequently administered, singly or in combination, were 5-fluorouracil, mitomycin C (MMC) and tegafur. Recently, cisplatin has been used in combination with other drugs. Preusser and colleagues<sup>27</sup> reported the results of a phase II study using the combination of etoposide, doxorubicin and cisplatin for advanced gastric cancer, in which an objective response was achieved in 43 of 67 patients. Suga and colleagues<sup>28</sup> reported that the use of cisplatin produced a better response and prolonged survival in patients with scirrhous gastric cancer.

Peritoneal dissemination is the most common type of recurrence of gastric cancer. Attempts to prevent peritoneal dissemination by intraperitoneal administration of anticancer drugs postoperatively, however, have not been successful, mainly because the small water-soluble molecules of commonly used anticancer drugs are rapidly adsorbed through capillary walls in the subperitoneum, and the drugs are not retained in the peritoneal cavity. Hagiwara and associates<sup>29</sup> have developed a novel technique of administering anticancer drugs in which MMC is adsorbed to activated carbon particles.<sup>30</sup> Intraperitoneal MMC-activated carbon particles distribute a larger amount of MMC to the intraperitoneal tissues for a longer time than does MMC in aqueous solution. Perioperative intraperitoneal treatment with MMC-activated carbon particles improved survival in patients with gastric cancer and serosal infiltration after surgery by a prophylactic effect on peritoneal recurrence.<sup>31</sup>

Because we believe that resection offers the best palliation for patients with gastric cancer,<sup>32,33</sup> most of the operations were performed on patients with Borrmann's type IV, including those with nodal involvement and

peritoneal dissemination. In most of these patients, residual tumour was found in the abdomen after resection, and this would have increased the overall incidence of local recurrence and decreased the survival rate. These residual tumours usually take some time to reach a sufficient size to compress the gastrointestinal tract, by which time widespread metastases are already evident. Anticancer drugs should be given to suppress the proliferation of residual tumour cells. The outcome for patients with abdominal recurrence after gastrectomy is dismal. It is encouraging that the prognosis for patients with histologically defined scirrhous cancer was favourable if the tumour was removed before serosal encroachment occurred. It is therefore important to detect Borrmann's type IV gastric cancer at an early stage in order to achieve longer survival.

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