

## Signet Ring Cell Carcinoma of the Stomach: A Clinicopathological Comparison with the Other Histological Types

TAKASHI YOKOTA, YASUO KUNII, SHIN TESHIMA, YASUO  
YAMADA, TOSHIHIRO SAITO, SHU KIKUCHI and HIDEMI  
YAMAUCHI

*Department of Surgery, Sendai National Hospital, Sendai  
983-8520*

YOKOTA, T., KUNII, Y., TESHIMA, S., YAMADA, Y., SAITO, T., KIKUCHI, S. and YAMAUCHI, H. *Signet Ring Cell Carcinoma of the Stomach: A Clinicopathological Comparison with the Other Histological Types.* Tohoku J. Exp. Med., 1998, 186 (2), 121-130 — A retrospective analysis was carried out on 93 patients with signet ring cell carcinoma of the stomach operated on between 1985 and 1995, to review the clinicopathologic characteristics from the database of gastric cancer at Sendai National Hospital. The results were compared with those for 590 patients with other types of gastric carcinoma. Women were afflicted as commonly as men in the signet ring cell carcinoma group. These patients tended to be younger and to have larger tumors. The histological type was commonly scirrhous and infiltrative. The survival of patients with signet ring cell carcinoma was worse than that of patients with other types of gastric cancer but the difference was not statistically significant. Patients with early signet ring cell carcinoma had a good prognosis, similar to that of the other groups. However, prognosis of patients with advanced signet ring cell carcinoma was poor compared with patients with other types of this disease. In multivariate analysis, the statistical significant prognostic factors were vascular microinvasion and tumor location. These findings suggest that signet ring cell carcinoma of the stomach should be regarded as a distinct type of gastric cancer. ———— signet ring cell carcinoma; gastric cancer © 1998 Tohoku University Medical Press

Signet ring cell carcinoma is a descriptive term used to denote a form of mucin-secreting adenocarcinoma whose component cells retain abundant intracytoplasmic mucin, pushing their nuclei to one side, thereby giving the cells their characteristic histological appearance. Ninety-nine percent of signet ring cell carcinoma occurs in the stomach, with the rest arising in several other organs, including the breast, gallbladder, pancreas, urinary bladder and colon. Gastric cancer can be divided into two major histologic types; intestinal and diffuse types. The intestinal type of gastric cancer is thought to arise from the metaplastic

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Address for reprints: Takashi Yokota, M.D., Department of Surgery, Sendai National Hospital, Miyagino-ku, Sendai 983-8520, Japan.

e-mail: yokoyoko@jun.nvc.go.jp

epithelium (Lauren 1965), whereas signet ring cell carcinoma in the diffuse type is thought to arise from the mucosa that is not metaplastic and is confined to the glandular neck region in a proliferating zone (Carneiro et al. 1992; Kitamura et al. 1996).

It has been reported that 3.4% to 29% of patients with gastric cancer had a signet ring cell type histology (Antonioli and Goldman 1982; Otsuji et al. 1998; Maehara et al. 1992). Maehara et al. (1992) reported that patients with signet ring cell carcinoma can expect a longer survival than those with other types of gastric cancer. That report was supported by Otsuji et al. (1998), who reported that survival of patients with early signet ring cell carcinoma was improved, but patients with advanced disease had a poor prognosis, similar to that of other types of gastric cancer. In contrast, Kim et al. (1994) reported that there was no significant difference in the 5-year survival rates between patients with early signet ring cell type and those with other gastric cancer types. They demonstrated that the prognosis for patients with advanced signet ring cell carcinoma was significantly worse than that for patients with other types of advanced cancer. The clinicopathological features of this type of malignancy are therefore still controversial.

The aim of the present investigation is to review the experience of patients treated for signet ring cell carcinoma, in order to determine whether there is a specific pattern of clinical, endoscopic, or pathological features that could distinguish these patients from patients with other types gastric cancer.

#### PATIENTS AND METHODS

A total of 923 patients with histologically proven carcinoma of the stomach were treated in the Department of Surgery, Sendai National Hospital over an 11-year period, from 1985 to 1995. Of the 923 patients, 93 were diagnosed histologically as having signet ring cell carcinoma (10.1% of all cases). The clinicopathological features of these patients with signet ring cell carcinoma were compared with those of 590 of the 923 patients with other types of gastric cancer whose prognosis could be determined. The macroscopic and histologic classifications of gastric cancer were based on the General Rules for Gastric Cancer Study in Japan (1981). Histopathologic examination of the primary lesions was performed using step sections in order to determine the depth of cancer invasion, and histological examination of resected lymph nodes was performed to confirm the presence of metastasis.

All data from both groups were analyzed by the *t*-test for unpaired data and the chi-square test. The survival curves of patients with signet ring cell carcinoma and other types of gastric cancer were drawn in relation to the stage in months (early or advanced cancer) and were calculated by the Kaplan-Meier method. Survival was defined as the period calculated in months from the time of operation to the most recent of follow-up examination or to the death the

patient. The differences between survival curves were measured using the log-rank test. A probability of less than 0.05 was considered statistically significant. Multivariate Cox's proportional hazards regression analysis was then performed to determine which variables were independent prognostic factors. The following independent variables were entered in the multivariate analysis: gender, age, tumor size, tumor location, lymph node metastasis, lymphatic invasion, vascular invasion, cancer-stromal relationship, histological growth pattern.

## RESULTS

Tumors were identified in the antrum and gastric body in 39% and 24% of signet ring cell carcinoma patients, respectively, compared with 39% and 30% in the corresponding sites in patients with other types of gastric cancer. Various clinicopathologic features of 93 signet ring cell carcinoma and 590 other type gastric cancers were compared, and the results are shown in Table 1. Significant differences were observed with respect to the gender, age, gross tumor size, histologic growth pattern and cancer-stromal relationship. The gender ratios were 0.98 and 2.16 for signet ring cell carcinoma and other types of carcinoma, respectively ( $p < 0.001$ ). Patients with signet ring cell carcinoma tended to be younger ( $p < 0.0001$ ) and they had larger tumors ( $p < 0.01$ ). The mean diameter of the lesions was 6.2 cm in signet ring cell carcinoma and 5.0 cm in other types of carcinoma. Regarding the microscopic growth pattern and cancer-stromal relationship, an infiltrative pattern and scirrhous type were more common in patients with signet ring cell carcinoma than in those with other types of carcinoma. No significant differences were observed in the macroscopic appearance, depth of cancer invasion, nodal involvement, lymphatic invasion, vascular permeation and stages. With respect to the macroscopic appearance, 34 cases (37%) and 9 cases (10%) of signet ring cell carcinoma patients were diagnosed as Borrmann type IV and III, respectively, whereas only 55 cases (9%) and 189 cases (32%) of other types were diagnosed as type IV and type III, respectively, but the difference in the macroscopic type did not reach statistically significant. The surgical procedure performed was based on the location and extent of the lesion in all instances. There was no difference between the two groups in the type of operation. With respect to cancer recurrence, peritoneal dissemination was common in the signet ring cell carcinoma group.

Postoperative survival curves for patients with signet ring cell carcinoma and other types of cancer are shown in Fig. 1. The overall survival for patients with signet ring cell carcinoma was worse than that for patients with other types of gastric cancer, but the difference was not statistically significant. Postoperative survival was also examined separately for early and advanced cases. The cumulative 5-year survival for patients with early signet ring cell carcinoma was similar to that for patients with other types of gastric carcinoma in the early stage (Fig. 2a). The cumulative 5-year survival for patients with advanced signet ring cell

TABLE I. *Clinicopathologic features of signet ring cell carcinoma versus other types of gastric cancer*

Variable	Signet ring cell carcinoma (%)	Other types (%)	<i>p</i> Value
	( <i>n</i> = 93)	( <i>n</i> = 590)	
Gender			
Male	46 (49)	403 (68)	<i>p</i> < 0.001
Female	47 (51)	187 (32)	
Age	55.9 ± 1.2	62.9 ± 0.4	<i>p</i> < 0.0001
Tumor size (cm, diameter)	6.2 ± 0.5	5.0 ± 0.1	<i>p</i> < 0.01
Macroscopic appearance			
Early cancer	41 (44)	212 (36)	n.s.
Advanced cancer			
Borrmann I	3 ( 3)	23 ( 4)	
Borrmann II	2 ( 2)	84 (14)	
Borrmann III	9 (10)	189 (32)	
Borrmann IV	34 (37)	55 ( 9)	
Borrmann V	4 ( 4)	27 ( 5)	
Depth of invasion			n.s.
m	27 (28)	125 (21)	
sm	14 (15)	101 (17)	
mp	9 (10)	75 (13)	
ss	10 (11)	116 (20)	
se	23 (25)	121 (21)	
si	10 (11)	52 ( 9)	
Histologic growth pattern			
Expansive	8 ( 9)	83 (16)	<i>p</i> < 0.001
Intermediate	23 (26)	308 (58)	
Infiltrative	59 (65)	138 (26)	
Unknown	3	61	
Cancer-stromal relationship			
Medullary	27 (30)	193 (36)	<i>p</i> < 0.001
Intermediate	14 (15)	230 (43)	
Scirrhou	50 (55)	111 (21)	
Unknown	2	56	
Lymph node metastasis			
Positive	39 (43)	305 (52)	n.s.
Negative	52 (57)	285 (48)	
Unknown	2	0	

TABLE 1. *Continued*

Variable	Signet ring cell carcinoma (%)	Other types (%)	<i>p</i> Value
Lymphatic invasion			
Positive	46 (49)	289 (51)	n.s.
Negative	47 (51)	275 (49)	
Unknown	0	26	
Vascular permeation			
Positive	18 (20)	96 (17)	n.s.
Negative	70 (80)	464 (83)	
Unknown	5	30	
Stage I	44 (47)	255 (43)	n.s.
II	11 (12)	74 (13)	
III	11 (12)	96 (16)	
IV	27 (29)	165 (28)	
Operation			
Total gastrectomy	32 (34)	194 (33)	n.s.
Distal gastrectomy	59 (64)	381 (64)	
Others	2 ( 2)	15 ( 3)	
Causes of death			
Peritonitis carcinomatosa	21	71	
Liver metastasis	2	31	
Undefined recurrence	7	68	
Other disease	3	25	

n.s., not significant.

carcinoma was worse than that for patients with other types of gastric cancer in the advanced stage, but the difference was not significant (Fig. 2b). To account for the interrelationships among variables of 5-year survival, multivariate analysis was performed on several variables, including age and gender. Using Cox's proportional hazards regression model, vascular invasion and tumor location were demonstrated to be significantly correlated with 5-year survival (Table 2).

## DISCUSSION

Signet ring cell carcinoma of the stomach accounted for 10.1% of cases of gastric carcinoma experienced at Sendai National Hospital during the 11 years from 1985 to 1995. This incidence does not much differ from several other large series (Kim et al. 1994; Otsuji et al. 1998). The present study demonstrated several unique features in patients with signet ring cell carcinoma of the stomach. Statistically significant differences were observed in 1) gender, 2) age, 3) tumor size, 4) histologic growth pattern, and 5) cancer-stromal relationship. The ten-



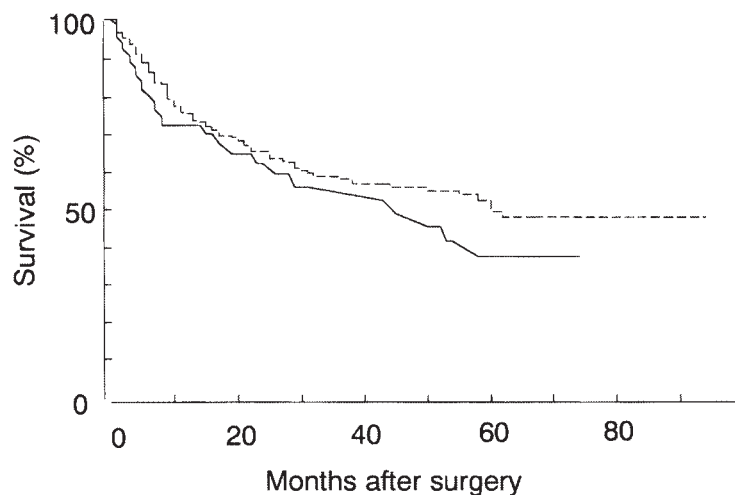


Fig. 1. The postoperative survival of patients who underwent gastrectomy for gastric cancer. (—), signet ring cell carcinoma; (-----), other types of cancer. The overall survival of patients with signet ring cell carcinoma was worse than that of patients with other types of gastric carcinoma, but the difference was not statistically significant.

dency of signet ring cell carcinoma to appear in younger patients has been stressed in previous reports (Maehara et al. 1992; Kim et al. 1994; Otsuji et al. 1998). This is borne out in our study, in which the average age of patients at diagnosis (55.9 years) was significantly younger than that of patients with other types of gastric cancer. No explanation for this younger age at presentation has been put forward, but it seems likely to be related to higher-than-expected proportion of patients disposed to risk factors for early gastric cancer. Regarding the microscopic appearance, the proportion of early cases in signet ring cell cancer was higher than in other types of gastric cancer (Maehara et al. 1992; Kim et al. 1994; Otsuji et al. 1998). In the present study, early cancer was more common in the patients with signet ring cell carcinoma (44%) than in the patients with other types of cancer (36%), but this difference was not statistically significant.

We found nearly even distribution of tumors in the stomach between the two groups. Other studies have reported up to a 50% middle-lesion predominance (Maehara et al. 1992). There is, however, no reason to expect a site specificity based on our current understanding of signet ring cell carcinoma.

In our study, 55% of the signet ring cell carcinomas were scirrhous type and 65% of those were infiltrative cancer. The microscopic spread of scirrhous carcinoma cells in Borrmann type-4 tumors can be either continuous with the primary lesion or discontinuous from it, forming skip submucosal foci. The histologic techniques for diagnosis still consist of methods using dyes such as hematoxylin and eosin. In most cases, cells stained with hematoxylin and eosin can be identified as malignant by standard cytologic criteria. In cases of scirrhous carcinoma, however, the malignant cells are dispersed and resemble reactive inflammatory cells. Signet ring cell carcinoma is one of the few malignant tumors

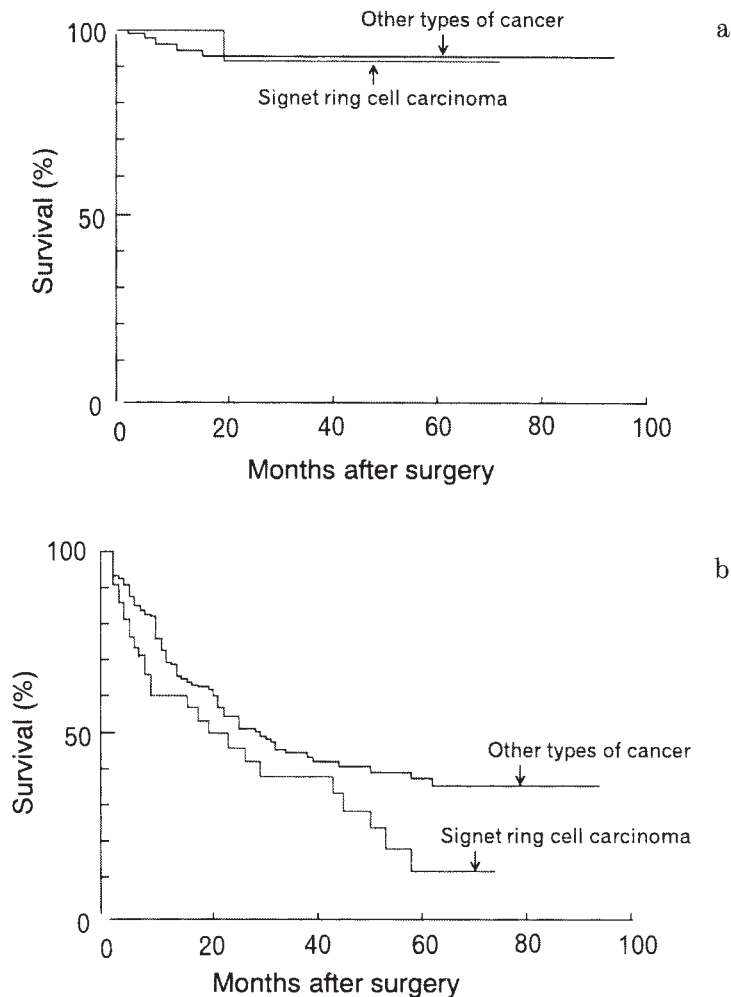


Fig. 2 a) The cumulative 5-year survival for patients with early gastric carcinoma, comparing signet ring cell type with the other types. The survival of the patients with the former was similar to the other types of gastric cancer in the early stage. b) The cumulative 5-year survival for patients with advanced signet ring cell carcinoma. The survival of the patients with advanced signet ring cell carcinoma was worse than that of patients with other types of gastric cancer in the advanced stage.

that is likely to be missed on microscopic examination because it is often misinterpreted initially as some type of benign process such as an aggregate of histocytes or a cohesive cluster of pyloric cells with glassy cytoplasm (Maehara et al. 1992). Early stages of the disease can be easily missed when using regular hematoxylin and eosin staining because gastric carcinoma hidden beneath the intact mucosal surface epithelium is rarely discovered. Not only is the diagnosis incidental in the early stages, but usually, it is also unexpected. A significant diagnostic delay exists in younger patients owing to the higher number of cases of diffuse carcinoma and the low level of suspicion by both the endoscopist and the pathologist. It seems reasonable to assume that if diffuse carcinoma is diagnosed in its early stages, the prognosis would be much better. Several studies have reported the application of staining techniques to supplement diagnostic informa-

TABLE 2. *Multivariate analysis of significant prognostic factor for survival in patients with signet ring cell carcinoma of the stomach using Cox's proportional hazards regression model*

Variable	Relative risk	95% CI	<i>p</i> Value
Gender (Female/Male)	0.675	0.283– 1.609	n.s.
Age	1.026	0.995– 1.058	n.s.
Lymph node metastasis (positive/negative)	0.524	0.047– 5.872	n.s.
Vascular invasion (positive/negative)	2.468	1.000– 6.087	<0.05
Lymphatic invasion (positive/negative)	4.184	0.441–39.661	n.s.
Cancer-stromal relationship			
Medullary/Scirrhou	0.434	0.040– 4.753	n.s.
Intermediate/Scirrhou	0.119	0.009– 1.651	n.s.
Histologic growth pattern			
Expansive/Infiltrative	0.972	0.049–19.163	n.s.
Intermediate/Infiltrative	0.393	0.035– 4.367	n.s.
Tumor size	1.000	0.987– 1.012	n.s.
Tumor location			
Upper/Whole	0.317	0.083– 1.220	n.s.
Middle/Whole	0.179	0.037– 0.875	<0.05
distal/Whole	0.229	0.058– 0.900	<0.05

CI, Confidence interval; n.s., not significant.

tion obtained by conventional cytomorphology; using the Genta stain (El-Zimaity et al. 1997), a monoclonal antibody reactive with signet ring cell carcinoma (Yokota et al. 1989; Otsuji et al. 1995).

Multivariate analysis showed the significant prognostic factors to be vascular invasion and tumor location. Microinvasion has been reported to be a major independent risk factor for long-term survival (Yokota et al. 1998a, b, c). Microinvasion may represent an early finding of metastatic spread of gastrointestinal tumors, and capillary microinvasion could predispose to distant metastasis. The tumor location was also an important prognostic variable, and cancer that had invaded the whole stomach was worse than that for patients with cancer that had invaded only the antrum and body of the stomach.

The pathway of fatal cancer extension in patients with signet ring cell carcinoma is striking. In 30 of the 93 cases, the disease recurred or progressed. In 21 of the 30 cases, a major component of failure was peritoneal carcinomatosis, suggesting that a predominant component of dissemination occurs via the peritoneum. Equally striking was the lack of liver metastasis; only two patients had evidence of liver involvement. The overall survival rate of patients with signet ring cell carcinoma was worse than that of patients with other types of



gastric cancer. The late stage of signet ring cell carcinoma could not explain this difference. After correcting for stage (early or advanced cancer), no significant differences in survival could be detected (Figs. 2a and b). What is clear is that surgery as the sole treatment is not curative for most patients with advanced gastric signet ring cell carcinoma. Because of the frequency of peritoneal dissemination, strong consideration should be given to evaluating the role of intraperitoneal chemotherapy in these patients (Hagiwara et al. 1992). This study also revealed that early signet ring cell carcinoma of the stomach is not lethal as was previously believed (Tso et al. 1987). We believe that an aggressive surgical approach offers the best chance of cure for patients with early gastric signet ring cell carcinoma.

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