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Poorly Differentiated, Solid-type Adenocarcinoma of the Stomach

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ABSTRACT

Data of 58 cases of poorly differentiated, solid-type adenocarcinoma of the stomach treated at our hospital between 1985 and 1995 were reviewed and compared to data of 146 cases of non-solid-type carcinoma in order to determine whether there are distinguishable clinicopathological features between these two types of carcinoma. Significant differences were observed with respect to tumor size, stage, macroscopic appearance, depth of invasion, histologic growth pattern, lymph node metastasis, microscopical lymphatic invasion and vascular permeation. Patients in the solid-type cancer group tended to have smaller tumors; the disease was in the early stage in 48% of the patients, and total gastrectomy was performed in only 20 of the 58 patients. Nodal involvement, lymphatic invasion and vascular permeation were also less common in patients with solid-type cancer. The overall survival rate of patients with solid-type carcinoma was higher than that of patients with non-solid-type carcinoma, though no significant differences were observed when corrected for stage. Our results suggest that poorly differentiated solid-type carcinoma of the stomach should be regarded as a distinct type of adenocarcinoma that has a good prognosis. The significant prognostic factors for this type of gastric cancer are lymphatic invasion and tumor location.

INTRODUCTION

Gastric cancer can be divided into two major histologic types: intestinal and diffuse (5). The intestinal type of adenocarcinoma is thought to arise from a metaplastic epithelium. The diffuse type of gastric cancer is best represented by the tumor type classically known as linitis plastica (2, 3, 6, 11, 12). Microscopically, this type shows a diffuse growth of malignant cells, associated with extensive fibrosis and inflammation. In the intestinal type, the degree of differentiation ranges widely. In the more differentiated tumors, most of the cells are columnar and mucin-secreting, whereas poorly differentiated variants have a predominantly solid pattern. Among poorly differentiated adenocarcinomas of the stomach, the solid-type is characterized by closely

packed tumor cells and a well-defined boundary, but little is known about the clinicopathological features of this type of cancer (1, 13).

In the present study, we reviewed cases of poorly differentiated, solid-type gastric cancer in order to determine whether there is a specific pattern of clinical, endoscopic, or pathological features that could distinguish these patients from patients with non-solid-type carcinoma. The prognostic factors in solid-type carcinoma and variables associated with these factors were investigated by univariate and multivariate analyses.

PATIENTS AND METHODS

Between January 1985 and December 1995, 923 patients with gastric adenocarcinoma underwent surgery in the Department of Surgery, Sendai National Hospital. The macroscopic and histologic classifications of gastric cancer were based on the General Rules for Gastric Cancer Study in Japan (4). Fifty-eight cases of gastric adenocarcinoma of an almost entirely solid growth pattern were selected from 204 cases of poorly differentiated adenocarcinoma. Signet-ring cell carcinomas and carcinomas with lymphoid stroma were excluded from the study, because the former is certainly of glandular origin and the latter is a distinctive entity that usually has an excellent prognosis. One hundred and forty-six cases of ordinary poorly differentiated adenocarcinoma, classified as non-solid-type poorly differentiated adenocarcinoma, were studied as controls. The tumors in the control group were composed of cells in either cords or nests, occasionally forming small glandular spaces and fibrous stroma of various degrees. Early gastric cancer specimens were cut into serial step sections, and specimens of advanced cancer were sliced at their center and embedded in paraffin for histologic examination. Paraffin sections were routinely stained with hematoxylin and eosin.

All data from both groups were analyzed by the chi-square test. The survival curves of patients with solid carcinoma and ordinary poorly differentiated adenocarcinoma were drawn in relation to the stage of disease and were calculated by the Kaplan-Meir method. Survival was calculated from the date of operation to the date of the most recent follow-up examination or to the date of death. The differences between survival curves were measured using the logrank 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 univariate analysis: gender, age, tumor size, tumor location, lymph node metastasis, lymphatic invasion, vascular invasion, cancer-stromal relationship, histological growth pattern, depth of invasion, type of operation and stage. Independent variables that showed statistical significance in the univariate analysis were then entered in the multivariate analysis.

RESULTS

Various clinicopathologic features of 58 solid and 146 non-solid carcinomas of the stomach were compared, and the results are shown in Table 1.

Table 1. Clinicopathologic features of solid type versus non-solid type of poorly differentiated adenocarcinoma of the stomach.

Variable	Solid type (%)	Non-solid type (%)	p Value
Number	58	146	
Gender			
Male	35 (60)	92 (63)	p=0.8456
Female	23 (40)	54 (37)	
Age	57.8±2.0	59.8±1.1	p=0.3744
Symptoms			p=0.1496
Present	25 (43)	81 (55)	
Not present	33 (57)	65 (45)	
Tumor size (cm, diameter)	5.0±0.4	6.4±0.3	p=0.0187
Stage I	23 (56)	41 (29)	P=0.0013
II	9 (16)	20 (14)	
III	7 (12)	39 (27)	
IV	9 (16)	43 (30)	
Macroscopic appearance			p<0.0001
Early cancer			
II a + II c	7 (12)	5 (4)	
II b	6 (10)	1 (1)	
II c	15 (26)	23 (16)	
Advanced cancer			
Borrmann I	1 (2)	0 (0)	
Borrmann II	10 (17)	19 (13)	
Borrmann III	17 (30)	54 (38)	
Borrmann IV	2 (3)	33 (23)	
Borrmann V	0 (0)	7 (5)	
Unknown	0	3	
Depth of invasion*			p<0.0001
m	17 (29)	12 (8)	
sm	11 (19)	16 (11)	
mp	5 (9)	19 (13)	
ss	8 (14)	32 (23)	
se	15 (26)	55 (39)	
si	2 (3)	9 (6)	
Unknown	0	4	
Histologic growth pattern			
Expansive	17 (30)	2 (2)	p<0.0001
Intermediate	34 (61)	32 (24)	
Infiltrative	5 (9)	98 (74)	
Unknown	2	14	

(Continued)

Variable	Solid type (%)	Non-solid type (%)	p Value
Lymph node metastasis			
Positive	23 (40)	104 (73)	p<0.0001
Negative	35 (60)	38 (27)	
Unknown	0	4	
Lymphatic invasion			
Positive	17 (29)	100 (70)	p<0.000001
Negative	41 (71)	42 (30)	
Unknown	0	4	
Vascular permeation			
Positive	5 (9)	40 (28)	p=0.0045
Negative	53 (91)	101 (72)	
Unknown	0	5	
Operation			
Total gastrectomy	20 (34)	61 (42)	p=0.6240
Distal gastrectomy	36 (63)	80 (55)	
Others	2 (3)	5 (3)	
Causes of death			
Peritonitis carcinomatosis	4	31	
Liver metastasis	2	4	
Undefined recurrence	1	7	
Other disease	3	6	

**) Tumor extends into the mucosa (m), submucosa (sm), muscularis propria (mp) or subserosa (ss). Tumor penetrates the serosa (se). Tumor penetrates through the serosa with direct invasion of continuous structures (si).*

The gender ratios were 1.5 and 1.7 for solid-type and non-solid-type groups, respectively. The tumors frequently occurred in the antrum and body of the stomach, but 23% of the solid-type and 26% of the non-solid-type tumors occurred proximally (Fig 1).

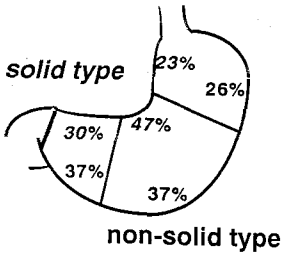

Figure 1. Anatomic location of poorly differentiated, solid-type (upper) and non-solid-type (lower) gastric cancer.

The tumor size of the non-solid cancers was larger than that of the solid-type cancers (p=0.0187). Twenty-three cases in the solid-type cancer group were diagnosed as stage I, whereas more than half of the cases in the non-solid-type cancer group was diagnosed as stage III or IV. A significant difference was observed in the gross tumor appearance between the two groups; early cancers were more common in the solid-type cancer group (p<0.0001). Tumors penetrating the

serosa with direct invasion to continuous structures were found more frequently in the non-solid-type group than in the solid-type group. With respect to the pattern of tumor infiltration in surrounding tissues, the incidence of expansive growth was higher in the solid-type group than in the non-solid type group ($p<0.0001$). The patients with non-solid cancer showed a higher tendency to have nodal involvement, lymphatic invasion and vascular invasion. The surgical procedure used 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 non-solid cancer group; it was observed in 31 patients.

Postoperative survival curves for patients with solid-type and non-solid type stomach cancers are shown in Fig 2. The overall 5-year survival rate for patients with solid-type cancer (66%) was significantly ($p<0.05$) better than that for patients with non-solid type (29%) (Fig 2a). Within each stage, there were no survival differences, but in all stages except stage I, survival was better for patients with solid-type cancer (Fig 2b).

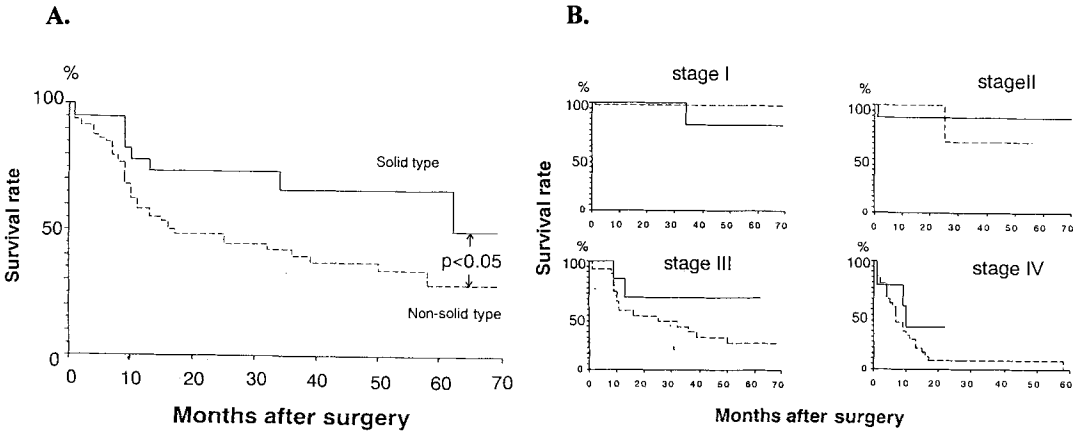

Figure 2. A) Overall survival of patients with solid-type versus those with non-solid-type gastric cancer patients. Overall survival of patients with solid-type cancer was significantly better than that of patients with non-solid-type cancer ($p<0.05$ by the logrank test). B) Survival corrected for stage. The survival curves of the two groups did not differ significantly.

Univariate analysis was performed to evaluate significant relationships between clinicopathologic features and patient survival. Table 2 summarizes the results of the analysis. Unfavourable prognostic factors included tumors located throughout the entire stomach, presence of capillary microinvasion, infiltrative and scirrhous histologic pattern, cancer invasion beyond the subserosal layer, lymph node metastasis and advanced stage. Multivariate analysis using Cox's proportional hazards regression model showed lymphatic invasion and tumor location to be significantly correlated with 5-year survival (Table 3).

Table 2. Prognostic significance by univariate analysis of various variables for patients with solid-type poorly differentiated adenocarcinoma of the stomach.

Variable	5-year survival (%)	Logrank p value
Age (yr)		0.4327
≥65	62.7	
≤64	69.8	
Gender		0.8968
Male	66.7	
Female	66.1	
Size, diameter (cm)		Eliminated
≤1.9	100	
2-4.9	75.0	
≥5	51.9	
Location		<0.0001
Upper third	77.8	
Middle third	79.4	
Distal third	69.6	
Whole	0	
Lymph node metastasis		Eliminated
Negative	100	
Positive	38.3	
Lymphatic invasion		0.0004
Negative	95.7	
Positive	49.1	
Vascular invasion		0.8775
Negative	72.9	
Positive	80.0	
Histologic growth pattern		Eliminated
Expansive	100	
Intermediate	78.0	
Infiltrative	50.0	
Cancer-stromal relationship		0.1524
Medullary	85.7	
Intermediate	69.3	
Scirrhous	40.0	
Depth of invasion		Eliminated
m	100	
sm	100	
mp	60.0	
ss	78.8	
se	22.2	
si	0	
Gastrectomy		<0.0001
Total	76.6	
Subtotal	54.5	
Stage		Eliminated
I	100	
II	80.0	
III	45.5	
IV	0	

Table 3. Multivariate analysis of significant prognostic factors for survival in patients with solid-type poorly differentiated adenocarcinoma of the stomach using Cox's proportional hazards regression model.

Variable	Relative risk	95% CI	p value
Age	0.976	0.930-1.025	0.3293
Gender (Female/Male)	1.525	0.265-8.779	0.6366
Lymphatic invasion (positive/negative)	10.276	1.217-86.775	0.0323
Tumor location			
Upper/Whole	0.013	0.001-0.256	0.0044
Middle/Whole	0.028	0.002-0.362	0.0062
Distal/Whole	0.020	0.001-0.338	0.0066

DISCUSSION

This study demonstrated several unique features for patients with poorly differentiated solid-type adenocarcinoma of the stomach. Statistically significant differences were observed between patients with solid and non-solid types of cancer in 1) tumor size, 2) stage, 3) macroscopic appearance, 4) depth of invasion, 5) histologic growth pattern, 6) lymph node metastasis, 7) lymphatic invasion, and 8) vascular permeation. Moreover, the overall survival rate of patients with solid-type cancer was significantly higher than that of patients with non-solid-type ($p<0.05$) (Fig 2a). This difference could not be explained by the late stage of non-solid-type cancers.

Although there is still some controversy regarding the prognosis of patients with solid-type of stomach cancer, it is generally believed to be poorer than that of patients with non-solid-type carcinomas. This belief is based on the fact that solid carcinomas have high incidences of venous permeation and lymph node metastasis in the early phase. From a prognostic point of view, however, little is known about poorly differentiated, solid-type adenocarcinoma of the stomach (1, 13). Matsusaka (9) reported that the 5-year survival rate of 67 patients with solid undifferentiated carcinoma of the stomach was only 37%. Ueyama et al. (13) also reported poor prognosis for 71 patients with solid-type gastric cancer. They subdivided the 71 patients into solid alveolar type and free cell type groups, and they speculated that the high incidences of venous invasion and lymph node metastasis in patients with solid carcinoma are factors leading to a poor prognosis. In our series, however, metastatic deposits in lymph nodes were histopathologically confirmed in 23 patients (40%) with solid cancer and in 104 patients (73%) with non-solid cancer, and venous invasion was less common in the patients with solid carcinoma than in those with non-solid carcinoma. Contradictory to other authors we therefore suggest that the relatively good prognosis for patients with solid-type carcinoma is thought to be due to the low incidence of lymphatic invasion.

Histologically, the amount of tumor stroma varies greatly in poorly differentiated adenocarcinoma. Poorly differentiated adenocarcinomas can include two special subtypes (solid and non-solid), depending upon the growth pattern or fibrous stroma in the carcinoma. Closely packed cells and scanty stroma are seen in the solid subtype, whereas the stroma is abundant relative to the number of tumor cells in the non-solid subtype. Solid carcinomas, including small cell carcinoma and neuroendocrine carcinoma may be undifferentiated (14). There have been several reports on the histogenesis of small cell carcinoma and neuroendocrine carcinoma (8, 10). However, the histogenesis and biological behaviour of poorly differentiated, solid-type adenocarcinoma have not been fully documented. According to Lauren (5), most poorly differentiated adenocarcinomas can be classified as diffuse type; however, the solid carcinomas have remained unclassified.

Multivariate analysis showed the significant prognostic factors to be lymphatic invasion and tumor location. Microinvasion has been reported to be a major independent risk factor for both long-term survival (15-19) and occurrence of lymph node metastasis (7). Microinvasion may represent an early sign of metastatic spread of gastrointestinal tumors, and capillary microinvasion could predispose to distant, bloodborne metastasis. The detection of microinvasion therefore has potential clinical usefulness as a marker for biologically aggressive tumors. With regard to tumor location, the prognosis for patients with cancer that had invaded the whole stomach was worse than that for patients with cancer that had invaded only the antrum, corpus or cardia of the stomach.

In conclusion, although solid-type carcinomas have been classified as poorly differentiated adenocarcinoma, their clinicopathological features and biological behaviour, which prevent a high rate of malignancy, are similar to those of differentiated adenocarcinomas. Lymphatic invasion and tumor location are the most reliable predictors of survival for patients with this type of gastric cancer.

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REFERENCES

1. Adachi, Y., Mori, M., Maehara, Y. & Sugimachi, K.: Poorly differentiated medullary carcinoma of the stomach. Cancer 70:1462-1466, 1992.

2. Bollschweiler, E., Boettcher, K. & Hoelsher, A.H.: Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer 71:2918-2925, 1993.
3. Furukawa, H., Hiratsuka, M. & Iwanaga, T.: A rational technique for surgical operation on Borrmann type 4 gastric carcinoma. Br J Surg 75:116-119, 1988.
4. Japanese Research Society of Gastric Cancer: The general rules for gastric cancer study in surgery and pathology. Jpn J Surg 11:129-145, 1981.
5. Lauren, P.: The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 64:31-49, 1965.
6. Maehara, Y., Moriguchi, S., Orita, H., Kakeji, Y., Haraguchi, M., Korenaga, D. & Sugimachi, K.: Lower survival rate for patients with carcinoma of the stomach of Borrmann type IV after gastric resection. Surg Gynecol Obstet 171:13-16, 1992.
7. Maehara, Y., Orita, H. & Okuyama, T.: Predictors of lymph node metastasis in early gastric cancer. Br J Surg 79:245-247, 1992.
8. Matsusaka, T., Watanabe, H. & Enjoji, M.: Oat-cell carcinoma of the stomach. Fukuoka Acta Med 67:65-73, 1976.
9. Matsusaka, T.: Solid undifferentiated carcinomas of the stomach. A histological study with a supplement search for argyrophilic cells. Fukuoka Acta Med 67:163-187, 1976.
10. Murayama, H., Imai, T. & Kikuchi, M.: Solid carcinomas of the stomach: A combined histochemical, light and electron microscopic study. Cancer 51:1673-1681, 1983.
11. Nagayo, T. & Yokoyama, H.: Scirrhous carcinoma occurring in the corpus (body)of the stomach. Acta Pathol Jpn 24:797-814, 1974.
12. Saphir, O. & Parker, M.L.: Linitis plastica type of carcinoma. Surg Gynecol Obstet 76:206-213, 1943.
13. Ueyama, T. & Tsuneyoshi, M.: Poorly differentiated solid type adenocarcinomas in the stomach: A clinicopathologic study of 71 cases. J Surg Oncol 51:81-88, 1992.
14. Watanabe, H., Jass, J.R. & Sobin, L.H.: "WHO International Histological Classification of Tumors: Histological Typing of Oesophageal Gastric Tumors," 2nd Ed, Berlin: Springer-Verlag 1990.
15. Yokota, T., Takahashi, N., Yamada, Y., Saito, T., Kakizaki, K., Kikuchi, S., Kunii, Y. & Yamauchi, H.: Early gastric cancer in the young: Clinicopathological study. Aus NZ J Surg 69:321-324, 1999.
16. Yokota, T., Saito, T., Teshima, S., Kikuchi, S., Kunii, Y. & Yamauchi, H.: Lymphnode metastasis in early gastric cancer: How can surgeons perform limited surgery? Int Surg 83:287-290, 1998.

17. Yokota, T., Kunii, Y., Teshima, S., Yamada, Y., Saito, T., Kikuchi, S. & Yamauchi, H.: Gastric cancer with invasion limited to the proper muscle. Int Surg 84:7-12, 1999.
18. Yokota, T., Kunii, Y., Teshima, S., Yamada, Y., Saito, T., Kikuchi, S. & Yamauchi, H.: Signet ring cell carcinoma of the stomach. A clinicopathological comparison with the other histological types. Tohoku J Exp Med 186:121-130, 1998.
19. Yokota, T., Kunii, Y., Teshima, S., Yamada, Y., Saito, T., Takahashi, M., Kikuchi, S. & Yamauchi, H.: Significant prognostic factors in patients with node-negative gastric cancer. Int Surg, 1999, in press.

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