

Clinicopathological Properties of Poorly-differentiated Adenocarcinoma of the Stomach: Comparison of Solid- and Non-solid-types

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Abstract. *Background:* The purpose of this study was to clarify the clinicopathological and biological properties of the poorly-differentiated types of gastric carcinoma (solid-type and non-solid-type). *Patients and Methods:* A total of 1,558 patients with primary gastric adenocarcinomas were enrolled in this study. The surgical results were compared. *Results:* Patients with non-solid-type tumors tended to be younger females with peritoneal or lymph node metastases and lymphatic invasion, and with tumors that were ill-defined, of larger diameter and deeper. Those patients with differentiated tumors tended to have the opposite characteristics of those patients with non-solid-type tumors. Patients with solid-type tumors had intermediate characteristics. The survival in patients with non-solid-type tumors was poor compared to those with differentiated or solid-type tumors. There was a significant difference in the survival of stage III tumors with either solid- or non-solid-type tumors ($p=0.0480$). *Conclusion:* Therapeutic strategies should be based on the histological type of the tumor in patients with poorly-differentiated gastric adenocarcinoma.

Gastric carcinomas are generally classified into 2 main categories according to a number of official classifications. The Japanese classification of gastric carcinoma (1) categorizes gastric carcinomas as either differentiated or undifferentiated, the Lauren classification (2) categorizes them as intestinal or diffuse, and the Ming classification (3) categorizes them as expanding or infiltrative. The Japanese

classification further subdivides undifferentiated carcinomas into 3 categories, poorly-differentiated, signet-ring cell and mucinous carcinoma, while poorly-differentiated adenocarcinomas are defined as tumors with few glandular structures. Furthermore, poorly-differentiated carcinomas are subdivided into either solid- or non-solid-types. Solid-type tumors display a solid sheet-like proliferation with an alveolar pattern and indistinct tubular differentiation. Non-solid-type tumors are acinar, trabecular or consist of separate cells or clusters of a few cells; they also display diffuse infiltration, usually with abundant fibrous stroma.

In addition, the Lauren classification mentions that diffuse carcinomas lack glandular structure, are always classified as one of the most malignant grades and have a poor prognosis compared with the intestinal type. However, the prognostic significance of the histological appearance of these carcinomas has been the subject of controversy in recent studies (4-6). In our previous study, the histological appearance (differentiated *versus* undifferentiated) was not identified as an independent prognostic factor (7). However, it is commonly supposed that poorly-differentiated carcinomas have a worse prognosis. Therefore, in the present study, the clinicopathological characteristics and the results of surgery were compared for solid- and non-solid-type carcinomas. Moreover, the characteristics of differentiated tumors (well-differentiated, moderately-differentiated and papillary) were compared with those of both types of poorly-differentiated adenocarcinoma.

Patients and Methods

Between April 1992 and March 2000, a consecutive series of 1,558 patients with gastric cancer, who underwent gastrectomy in the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Japan, and its associated institutions, were enrolled in this study. A total of 440 patients

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were histopathologically diagnosed with poorly-differentiated tumors (138 solid-type and 302 non-solid-type) and 1,118 patients were diagnosed with differentiated tumors (well-differentiated, moderately-differentiated or papillary). The most poorly-differentiated adenocarcinomas in the Japanese classification correspond to the diffuse type in the Lauren classification and the infiltrative type in the Ming classification. Patients with other undifferentiated types of gastric cancer, such as signet-ring cell carcinoma and mucinous carcinoma, were excluded from this study in order to clarify the properties of the poorly-differentiated type of gastric cancer. Experienced pathologists in each institution classified these tumors according to the Japanese classification of gastric carcinoma on the basis of their pathology. Of the registered patients, 1,333 were curatively resected (117 solid-type, 226 non-solid-type and 990 differentiated). A total of 15.2% (21/138) of the patients with solid-type tumors received palliative gastrectomies, compared with 25.2% (76/302) of those with non-solid-type tumors and 11.4% (128/1118) of those with differentiated tumors. The proportion of palliative gastrectomies in patients with non-solid-type tumors was significantly higher than in patients with the other two types ($p < 0.0001$).

Patient demographics (age and gender), tumor characteristics (tumor location, tumor diameter, macroscopic appearance, histological classification, lymph node metastasis, depth of invasion, venous invasion and lymphatic invasion) and survival data were prospectively recorded according to the Japanese classification of gastric carcinoma. The 1,333 curatively-resected patients consisted of 943 males and 390 females, with a mean age of 64.8 ± 10.8 years (age range, 21–93 years). The pre-operative evaluation was performed by oral barium-meal examination, gastrofiberscopy with biopsy and computed tomography (CT). Clinical lymph node metastases were diagnosed by CT; irregular shape and a diameter greater than 10 mm were strong positive indications of lymph node metastases.

A macroscopically superficial type of carcinoma was observed in 855 patients, the well-defined type was observed in 206 patients and the ill-defined type was observed in 272 patients. The mean tumor diameter was 49.2 ± 26.6 mm. A total of 763 of the patients (57.2%) had T1 tumors, 352 (26.4%) had T2 tumors and 218 (16.4%) had T3,4 tumors. At least 15 lymph nodes were dissected in each patient and lymph node involvement was detected in 440 cases: pN1 in 247, pN2 in 142 and pN3 in 51, according to the Japanese classification. Lymph node dissection was performed according to the routine procedure used in Japanese institutions. Partial gastrectomy was employed in 932 patients and total gastrectomy in 401. D2 gastrectomy was adopted in 661 patients, while 529 had D1 gastrectomies together with removal of the left gastric artery lymph node and lymph nodes along the common hepatic artery, and, in some instances, the lymph node at the root of the celiac artery. A total of 143 patients had D3 gastrectomies.

All patients were followed-up according to our standard protocol (at least every 12 weeks for 5 years) which included tumor marker studies, gastrofiberscopy, abdominal ultrasonography, CT and chest radiography. Patients in whom peritoneal dissemination was indicated by physical examination or imaging modalities were further investigated through aspiration biopsy. The mean follow-up was 60.4 ± 36.8 months.

Statistical analysis. Statistical analyses were performed using the SPSS software version 10.0 for Windows (SPSS Inc., Chicago, IL,

USA). Statistical significance was defined as $p < 0.05$. Disease-specific survival was calculated using the Kaplan-Meier method and group differences were assessed using the log-rank test. To evaluate the impact of clinicopathological factors on long-term survival, potential prognostic factors were analyzed with a forward condition Cox proportional-hazards regression model. The following variables were included: age, gender, location of tumor, macroscopic appearance, tumor diameter, histological type, depth of invasion, lymph node metastasis, lymphatic invasion and venous invasion. Tumors were classified histologically as either differentiated or poorly-differentiated (solid- and non-solid-types). The clinicopathological features were analyzed by means of two-tailed Chi-square tests.

Results

Comparison of clinicopathological characteristics. There were significant differences in age, gender, peritoneal metastasis, location of tumor, macroscopic appearance, tumor diameter, depth of invasion, lymph node metastasis, lymphatic invasion and venous invasion, but not of hematogenous metastasis, between the 3 groups of registered patients. Patients with differentiated tumors tended to be older males; their tumors were located in the lower third of the stomach, were smaller and were generally of the macroscopically superficial type. In contrast, patients with tumors of the non-solid type tended to be younger females with peritoneal metastasis; their tumors were larger and deeper with lymph node metastasis and lymphatic invasion, tended to occupy the entire stomach and were macroscopically ill-defined. Patients with tumors of the solid-type had characteristics intermediate between the 2 types described above (Table I).

A similar tendency was seen when only the curatively-resected patients were considered. In patients with solid-type tumors, venous invasion was more frequent than in the other histological types, and patients with non-solid-type tumors were generally younger females. These tumors also tended to occupy the entire stomach, were larger and deeper, and were macroscopically ill-defined with lymph node metastasis and lymphatic invasion (Table II).

Survival time. There was no significant difference in disease-specific survival between the patients with differentiated and solid-type tumors ($n=1,558$) (5-year survival rate, 79.7% versus 78.6%, $p=0.6285$). However, there were significant differences in survival rates between patients with differentiated and non-solid-type tumors (5-year survival rate, 79.7% versus 55.4%, $p < 0.0001$), and also between those with solid- and non-solid-type tumors ($p < 0.0001$) (Figure 1). Furthermore, among the curatively-resected patients, there were significant differences in disease-specific survival between patients with differentiated and solid-type tumors (5-year survival rate, 87.0% versus 88.4%, $p=0.6305$), between those with differentiated and non-solid-type tumors (5-year survival rate, 87.0% versus 67.5%,

Table I. The clinicopathological characteristics of all registered patients (n=1,558).

Variables	Differentiated-type (n=1118)	Solid-type (n=138)	Non-solid-type (n=302)	p-value
Age				<0.0001
≥70/<70	446/672	39/99	73/229	
Gender				<0.0001
Male/Female	829/289	94/44	171/131	
Peritoneal metastasis				<0.0001
Presence/Absence	54/1064	10/128	41/261	
Hematogenous metastasis				0.0626
Presence/Absence	45/1073	8/130	5/297	
Location of tumor				<0.0001
Lower third	470	38	85	
Middle third	405	61	107	
Upper third	218	28	64	
Entire	25	11	46	
Macroscopic appearance				<0.0001
Superficial	704	59	106	
Well-defined	195	30	42	
Ill-defined	219	49	154	
Tumor diameter (mm)				<0.0001
<50	726	66	110	
≥50, <100	331	52	123	
≥100	61	20	69	
Depth of invasion				<0.0001
T1	652	54	65	
T2	263	42	80	
T3,4	203	42	157	
Lymph node metastasis				<0.0001
Presence/Absence	375/743	68/70	202/100	
Lymphatic invasion				<0.0001
Presence/Absence	546/572	80/58	232/70	
Venous invasion				<0.0001
Presence/Absence	372/746	66/72	133/169	

$p < 0.0001$), and between those with solid- and non-solid-type tumors ($p = 0.0001$) (Figure 2). Among the patients with curatively-resected early gastric cancer (T1 tumors), there was no significant difference in disease-specific survival between those with solid-type ($n = 54$) and non-solid-type ($n = 63$) tumors (5-year survival rate, 100% versus 95.9%, $p = 0.1990$) (Figure 3). However, there was a significant difference in survival between the advanced gastric cancer patients (T2 or deeper) with solid-type ($n = 63$) and non-solid-type ($n = 163$) tumors (5-year survival rate, 78.2% versus 55.7%, $p = 0.0048$) (Figure 4). There was also a significant difference in stage III (IIIA and IIIB) survival between solid- and non-solid-type adenocarcinomas in the advanced gastric cancer patients ($p = 0.0480$) (Table III).

Prognostic factors. A Cox proportional-hazards regression model in patients with curative resection revealed that age, tumor diameter, depth of invasion, lymph node metastasis and venous invasion had independent effects on prognosis

when the tumors were classified histologically as either differentiated or undifferentiated (solid- and non-solid-types) (Table IV).

Cause of death in patients with curative resection. Of the 1,333 patients who underwent curative resection, 265 (19.9%) died. Of these, 181 died of gastric cancer, 40 died of comorbid diseases and 21 died of other cancers. Death was more frequent in patients with non-solid-type tumors than in those with differentiated or solid-type tumors. However, there was no significant difference in the distribution of causes of death between the groups (Table V).

Pattern of recurrence. The types of recurrence were assessed using the imaging modalities. In patients with non-solid-type tumors, peritoneal metastasis was the most frequent type of recurrence, whereas in those with solid- or differentiated-type tumors, hematogenous metastases predominated ($p = 0.0020$) (Table VI).

Table II. *The clinicopathological characteristics of the curatively-resected patients (n=1,333).*

Variables	Differentiated-type (n=990)	Solid-type (n=117)	Non-solid-type (n=226)	p-value
Age				<0.0001
≥70/<70	389/601	31/86	49/177	
Gender				<0.0001
Male/Female	734/256	81/36	128/98	
Location of tumor				<0.0001
Lower third	413	32	60	
Middle third	377	53	93	
Upper third	188	27	50	
Entire	12	5	23	
Macroscopic appearance				<0.0001
Superficial	696	59	100	
Well-defined	157	23	26	
Ill-defined	137	35	100	
Tumor diameter (mm)				<0.0001
<50	680	64	103	
≥50, <100	264	43	84	
≥100	46	10	39	
Depth of invasion				<0.0001
T1	646	54	63	
T2	238	41	73	
T3,4	106	22	90	
Lymph node metastasis				<0.0001
Presence/Absence	260/730	47/70	133/93	
Lymphatic invasion				<0.0001
Presence/Absence	423/567	59/58	160/66	
Venous invasion				<0.0001
Presence/Absence	281/709	57/60	96/130	

Discussion

Our analysis revealed that 2 types of poorly-differentiated gastric adenocarcinoma are clearly distinguishable on the basis of their clinicopathological characteristics and biological behavior. Patients with differentiated gastric adenocarcinomas tended to be older males and their tumors generally metastasized hematogenously. In contrast, patients with poorly-differentiated non-solid-type gastric adenocarcinomas were generally younger females and their tumors had larger diameters, were deeper and more ill-defined, had frequent lymph node metastasis and tended to spread by peritoneal metastasis. The properties of the solid-type tumors were intermediate between those of the differentiated- and non-solid-types of adenocarcinoma. Thus, poorly-differentiated solid- and non-solid-type tumors have notably different properties, despite being classified together.

It is widely accepted that gastric adenocarcinomas can be classified into 2 major categories: the so-called intestinal, expanding or differentiated-type and the diffuse, infiltrative or undifferentiated-type, as described in the Lauren, Ming and Japanese classifications, respectively. Poorly-differentiated adenocarcinomas are subclassified into the

solid-type and the non-solid-type in the Japanese classification, but not in the other 2 classifications. Our results confirm the distinction between solid- and non-solid-type tumors and indicate that this classification is important for optimizing the prognosis and treatment of gastric cancer.

Peritoneal metastasis was common in all of the registered patients, including those receiving palliative gastrectomies; hematogenous metastases were less frequent in patients with non-solid-type tumors than in patients with the other 2 types. Furthermore, the carcinoma clearly progressed more rapidly in patients with non-solid-type tumors, as shown by the larger size and depth of the tumors, and the more frequent lymph node metastasis and lymphatic invasion. Similar observations have been discussed by others (8,9). Interestingly, one of these reports stated that the clinicopathological findings of patients with poorly-differentiated solid-type gastric adenocarcinomas were similar to those patients with the differentiated-type of adenocarcinoma (9), in contrast to our present findings.

It is well known that the depth of invasion and lymph node metastasis independently affect prognosis. However, there is disagreement as to whether the histological type influences prognosis after curative surgery, irrespective of

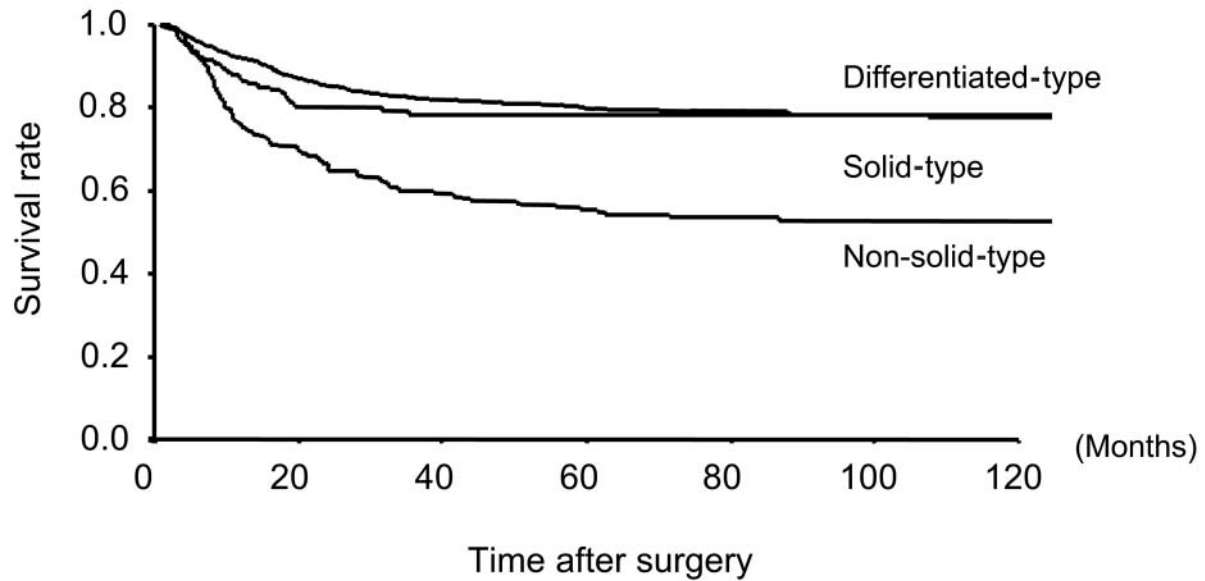


Figure 1. Disease-specific survival of registered patients ($n=1,558$). There was a significant difference in survival between patients with differentiated- ($n=1,118$) and non-solid-type tumors ($n=302$) ($p<0.0001$) and between patients with solid- ($n=138$) and non-solid-type tumors ($p<0.0001$).

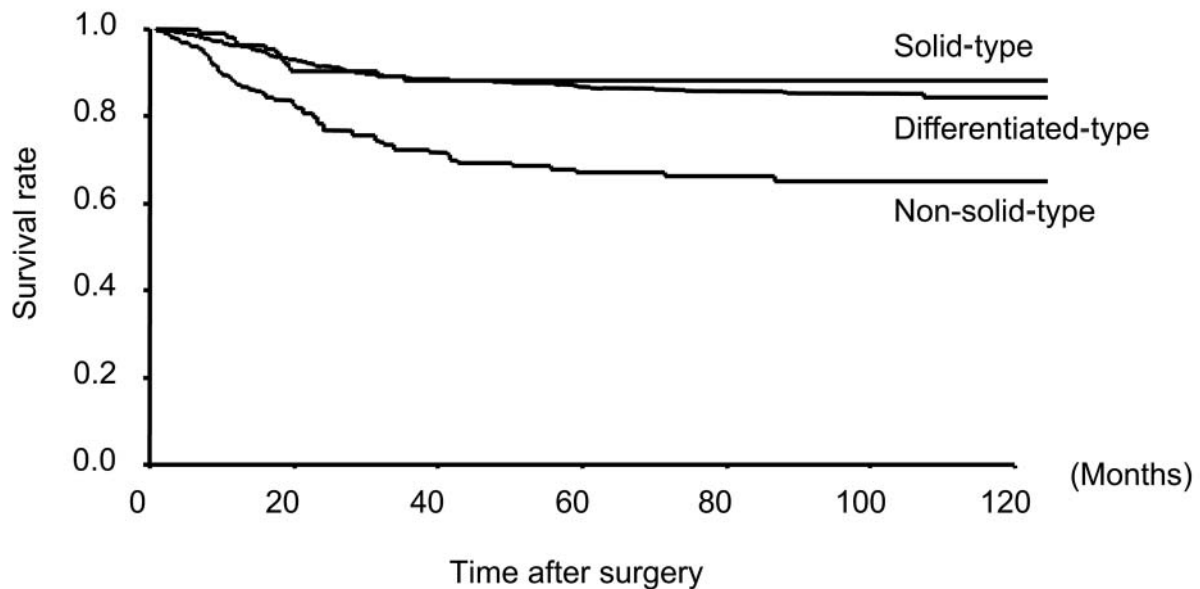


Figure 2. Disease-specific survival in patients receiving curative resection ($n=1,333$). There was a significant difference in survival between patients with differentiated ($n=990$) and non-solid tumors ($n=226$) ($p<0.0001$) and between those with solid ($n=117$) and non-solid tumors ($p=0.0001$).

cancer stage. Some authors reported that survival, estimated by univariate analysis, in patients with diffuse or infiltrative tumors was poorer than in those with intestinal or expanding-type tumors (10, 11). In our previous study (7), we did not detect a prognostic value of histological classification (differentiated *versus* undifferentiated).

However, in the current study, the survival time in patients with non-solid-type adenocarcinomas was significantly shorter than in patients with solid- or differentiated-type adenocarcinomas, whereas there was no significant difference in survival between patients with solid and differentiated adenocarcinomas. These results were observed

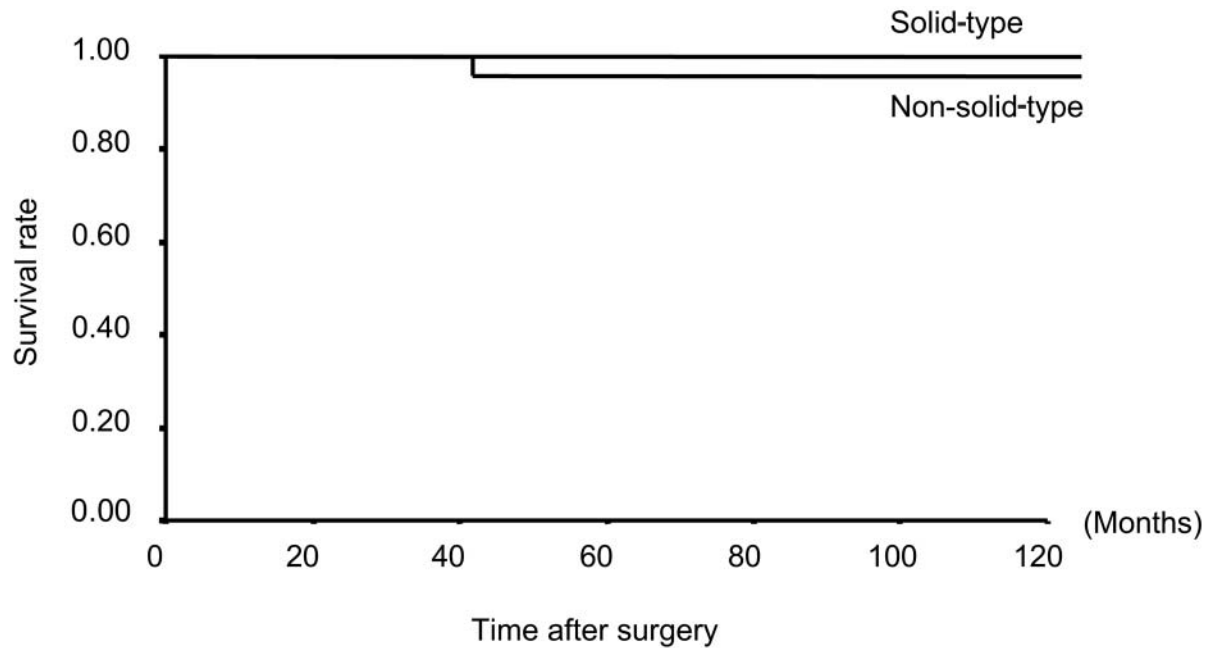


Figure 3. Disease-specific survival in patients with early gastric cancer (T1: n=117). There was no significant difference in survival between those with solid (n=54) and non-solid tumors (n=63).

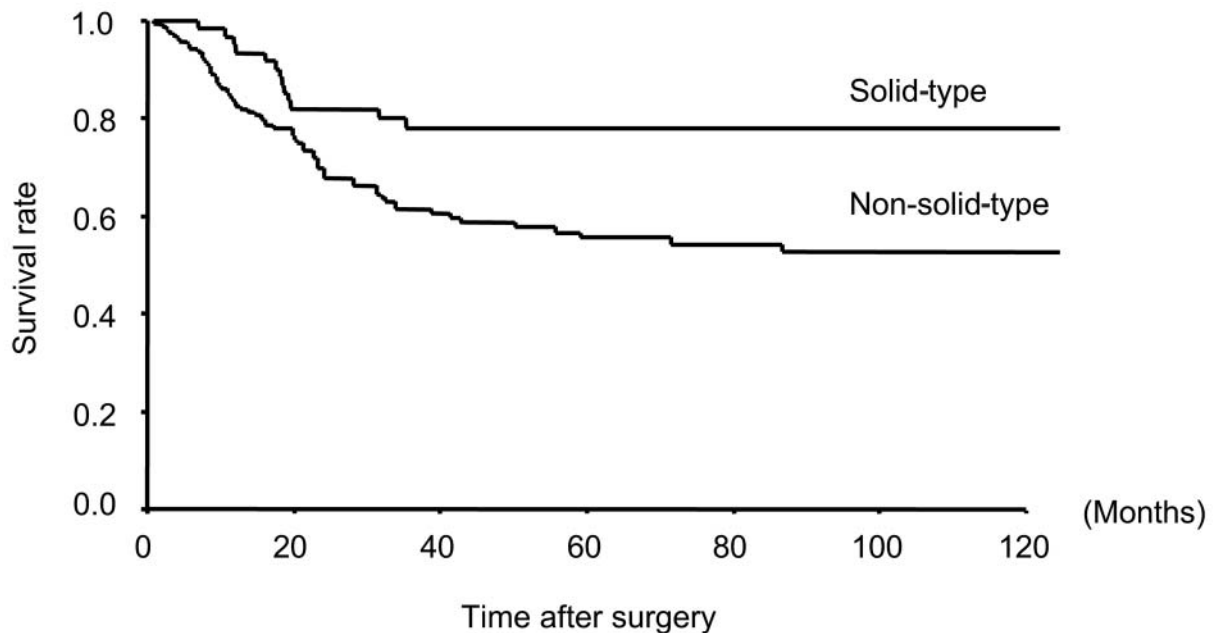


Figure 4. Disease-specific survival in patients with curatively-resected advanced gastric cancer (T2,3,4: n=226). There was a significant difference in survival between solid (n=63) and non-solid tumors (n=163) ($p=0.0048$).

both in registered patients and in those who underwent curative resection. Hence, it seems that solid-type and differentiated adenocarcinomas have similar biological behavior, in so far as this affects their prognosis. Although

the histological type of the tumor undoubtedly has some prognostic value, it is important to realize that microscopic appearance is separate from biological behavior and that histological category does not necessarily define prognosis.

Table III. The 5-year survival in advanced gastric cancer patients with solid and non-solid tumors. There was a significant difference for patients with stage III (IIIA and IIIB) tumors.

Stage	Solid-type		Non-solid-type		p-value
	(n)	5-year survival rate (%)	(n)	5-year survival rate (%)	
IB	17	93.8	24	90.8	0.8407
II	22	80.4	42	79.8	0.6925
III	21	71.9	73	36.3	0.0480
IV	3	33.3	24	14.0	0.5947

Table IV. Prognostic factors assessed by multivariate analysis in patients receiving curative resection.

Variables	Coefficient	SE	Hazard ratio (95% CI)	p-value
Age (y)				
≥70/<70	0.4504	0.1522	1.5690 (1.1643-2.1143)	0.0031
Tumor diameter (mm)	0.0020			
≥50 <100/<50	0.1439	0.1794	1.1547 (0.8124-1.6413)	0.4225
≥100/<50	0.6786	0.2092	1.9711 (1.3081-2.9702)	0.0012
Depth of invasion	<0.0001			
T2/T1	1.7383	0.3246	5.6876 (3.0104-10.7457)	<0.0001
T3,4/T1	2.1763	0.3402	8.8132 (4.5244-17.1675)	<0.0001
Lymph node metastasis	<0.0001			
pN1/pN0	0.7282	0.2293	2.0714 (1.3214-3.2470)	0.0015
pN2/pN0	1.5668	0.2317	4.7912 (3.0425-7.5450)	<0.0001
pN3/pN0	2.1136	0.2653	8.2779 (4.9214-13.9237)	<0.0001
Histological type				
Non-solid/solid, differentiated	0.2218	0.1120	1.3963 (1.1161-1.2483)	0.0439
Venous invasion				
Present/Absent	0.5849	0.1731	1.7948 (1.2784-2.5196)	0.0007

In curatively-gastrectomized patients with early gastric cancer (T1 tumor), there was no significant difference in survival between patients with solid- and non-solid-type tumors, whereas in curatively-gastrectomized patients with advanced gastric cancer (T2 tumor or deeper), there was a significant difference in survival between the 2 types. This difference was particularly pronounced in the case of stage III tumors. In other words, the difference in survival between the solid- and non-solid-type was mainly due to the poor prognosis of patients with stage III non-solid adenocarcinomas. Therefore, an effective treatment, particularly against peritoneal metastasis, is urgently needed for this category.

The analysis of the pattern of recurrence after curative gastrectomy has indicated that peritoneal metastasis is frequent in patients with poorly-differentiated adenocarcinoma (12), while hematogenous metastasis is frequent in patients with differentiated adenocarcinoma (13). In the present study, hematogenous metastasis was frequent in patients with solid-type tumors and peritoneal

Table V. Causes of death in patients who underwent curative gastrectomy.

	Differentiated (n=174)	Solid (n=16)	Non-solid (n=75)
Gastric cancer	112	12	57
Co-morbid disease	27	3	10
Other cancers	18	1	2
Unknown	15	2	6

Table VI. Pattern of recurrence in patients who underwent curative gastrectomy.

	Differentiated (n=112)	Solid (n=12)	Non-solid (n=57)
Peritoneal	42	3	37
Hematogenous	58	6	13
Lymphatic	12	3	7

p=0.0020

metastasis was frequent in patients with non-solid-type tumors, although these are classified in the same category. This effect is due to the high incidence of vascular invasion of solid adenocarcinomas. Similar results have been reported in other studies (4, 9). Furthermore, it has been proposed that hematogenous metastasis in patients with poorly-differentiated solid-type adenocarcinomas depends on angiogenesis induced by vascular endothelial growth factor (VEGF) (14). In contrast, both synchronous and heterochronous peritoneal metastases were frequent in patients with poorly-differentiated non-solid-type tumors. With regard to the molecular characterization of poorly-differentiated gastric adenocarcinomas, epigenetic inactivation of E-cadherin *via* promoter hypermethylation is reportedly correlated with the development of poorly-differentiated non-solid-type tumors, but not with poorly-differentiated solid-type tumors (15). Further genetic research will be necessary to clarify the biological behavior of poorly-differentiated solid- and non-solid-type adenocarcinomas.

In conclusion, the 2 histological types of poorly-differentiated gastric adenocarcinoma (solid and non-solid) have notably different properties in terms of clinicopathological characteristics and therapeutic outcomes. Therefore, the therapeutic strategy adopted should reflect the histological type of the tumor. An optimal therapeutic strategy is urgently needed for patients with poorly-differentiated gastric adenocarcinoma and particularly for those with stage III tumors.

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