Clinical Significance of coexisting histological diffuse type in stage II/III gastric cancer: A retrospective study

Hiroaki Tanaka (hiroakitan@med.osaka-cu.ac.jp)
Osaka Shiritsu Daigaku https://orcid.org/0000-0001-7301-1112
Mami Yoshii
Osaka Shiritsu Daigaku
Yuichiro Miki
Osaka Shiritsu Daigaku
Tatsuro Tamura
Osaka Shiritsu Daigaku
Takahiro Toyokawa
Osaka Shiritsu Daigaku
Masatsune Shibutani
Osaka Shiritsu Daigaku
Hisashi Nagahara
Osaka Shiritsu Daigaku
Masakazu Yashiro
Osaka Shiritsu Daigaku
Kazuya Muguruma
Osaka Shiritsu Daigaku
Kosei Hirakawa
Osaka Shiritsu Daigaku
Masaichi Ohira
Osaka Shiritsu Daigaku

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Abstract

Background: Since 1965, the Laurén classification has been used most commonly for gastric adenocarcinoma, with two types, intestinal type and diffuse type. Signet ring cell carcinoma (Sig) and non-solid poorly differentiated adenocarcinoma (Por2) are the histological forms of diffuse type and are often found in advanced tumors, and they seem to be associated with a poor prognosis. S-1 based adjuvant chemotherapy for patients with stage II/III gastric cancer has generally been accepted in Japan, but histological type does not alter treatment strategy. The aim of the present study was to investigate the prognostic impact of the histopathologic mixture of Sig and Por2 in patients with stage II/III gastric cancer treated with S-1 adjuvant chemotherapy.

Methods: The clinicopathological data of 968 gastric carcinoma patients who underwent gastrectomy between 2007 and 2016 at our department were retrospectively analyzed. In this study, tumors containing Sig or Por2 were classified as Diffuse type, and those not containing them were classified as Intestinal type.

Results: There were 307 cases of Diffuse type and 661 of Intestinal type. Diffuse type included 189 cases with Sig. Pathological diagnosis of Sig was an independent risk factor for peritoneal recurrence in patients with stage II/III. Patients with Diffuse type had worse overall survival than those with Intestinal type in Stage III. Of the patients who received S-1 adjuvant chemotherapy, the prognosis of Stage III patients with Sig but not Por2 was Significantly worse compared to patients with Intestinal type.

Conclusions: The coexistence of Signet ring cell carcinoma in the primary tumor was associated with a poor prognosis in patients with stage III gastric cancer. These findings suggest that, because mixed Sig gastric cancer had a high risk of peritoneal recurrence even if adjuvant chemotherapy were performed, the pathological diagnosis should be considered when determining the therapeutic strategy for adjuvant chemotherapy in stage III gastric cancer.

Background

Gastric cancer is a highly heterogeneous disease. According to Laurén's classification, gastric cancer is categorized as Intestinal type and Diffuse type [1]. Diffuse type exhibits single cells or poorly cohesive cells infiltrating the gastric wall, such as Signet ring cell carcinoma (Sig) and non-solid poorly differentiated adenocarcinoma (Por2) according to the Japanese Classification, and they are included in the poorly cohesive carcinoma subtype in the World Health Organization (WHO) classification of 2010[2, 3]. Sig and Por2 tumors tend to infiltrate diffusely and preferentially develop peritoneal metastases [4]. Gastric carcinomas often consist of a mixture of histological patterns [5]. In the Japanese Classification of Gastric Cancer, the predominant histologic type is used even if mixed with undifferentiated components, so it may be defined as differentiated type [2]. Sig and Por2 often coexist with other histologies, but their clinical Significance is unclear. Furthermore, the clinical difference between Sig and Por2 in advanced gastric cancer remains unclear.

Patients show various sensitivities to chemotherapy; therefore, tailoring individualized anti-cancer drugs for the treatment of gastric cancer is important. S-1-based chemotherapy is a standard postoperative adjuvant therapy for patients with stage II or III gastric cancer in Asia [6]. S-1, an oral fluoropyrimidine derivative, is known to be a pivotal agent for the treatment of patients with gastric cancer in Japan. The usefulness of S-1 alone or S-1 combined with cisplatin or docetaxel has been reported for peritoneal metastasis [7]. Currently, the management of patients with gastric cancer is dependent on the clinical and pathological TNM stage. As a consequence, treatment guidelines have not yet been tailored by histology. Histological type could be a surrogate marker of disease biology.

The aim of this study was to retrospectively investigate the relationship of the presence of Diffuse type in primary tumor and clinicopathological background with prognosis, including recurrence after postoperative adjuvant chemotherapy, in patients with advanced stage II and III gastric cancer.

Methods

Patients

A retrospective analysis of the gastric cancer database of the Department of Surgical Oncology, Osaka City University Graduate School of Medicine, was performed. Clinicopathological data of 968 patients with gastric carcinoma who underwent curative resection (i.e., R0 resection) without preoperative chemotherapy between 2007 and 2016 were examined. Patients with postoperative death within 30 days or incomplete follow-up were excluded. Histological diagnosis according to the 15th edition of the Japanese Gastric Cancer classification was defined to follow a quantitatively predominant histology. The Diffuse type is characterized by non-solid poorly cohesive cells (Por2) and Signet ring cell carcinoma (Sig) are characterized as Diffuse type by Laurén classification. In this study, we histologically divided the cohort into the Intestinal and Diffuse predominant types, and defined as the diffuse mixed Intestinal type when Sig or Por2 was mixed in the intestinal predominant type. Diffuse dominant type and diffuse mixed Intestinal type were defined as Diffuse type.

Adjuvant chemotherapy consisting of S-1 was basically administered orally twice daily for the first 4 weeks of a 6-week cycle. The dose of S-1 administered per day was based on the patient's body surface area as follows: $<1.25\ m^2$, 80 mg; $1.25–1.50\ m^2$, 100 mg; and $>1.5\ m^2$, 120 mg. Treatment of both groups was continued until one of the following occurred: disease progression, administration difficulty due to adverse effects, or decision to stop treatment at the discretion of the treating physician.

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) curves were drawn using the Kaplan-Meier method, and the log-rank test was used to assess the Significance of differences in survival. The day of surgery was used as the starting point for the measurement of OS. Each statistical analysis was performed using the JMP software program (SAS Institute, Cary, NC, USA). The Mann-Whitney test was used to assess the associations between histological types and clinicopathological features.

Results

Difference of background between Diffuse type and Intestinal type

The cohort in this study consisted of 218 (22%) diffuse predominant type and 750 (78%) intestinal predominant type. 89 of 750 intestinal predominant type had mixed Diffuse type histology, which was defined as a diffuse mixed Intestinal type (Table 1). Finally, 661 cases of Intestinal type and 307 cases of Diffuse type were compared and examined (Table 1). Diffuse type was more common in young women and type 4 gastric cancer than Intestinal type, while early gastric cancer was abundant in the Diffuse type, and 64% had pathological stage I. Patients with Diffuse type had peritoneal recurrence more frequently than patients with Intestinal type, whereas Intestinal type had more hepatic recurrence caused by venous infiltration than Diffuse type. The similar tendency was recognized in comparison with Diffuse mixed Intestinal type and Intestinal type (Table 1). In other words, Diffuse mixed-Intestinal type should be treated as Diffuse type. And, the pure diffuse dominant type was not observed except for the tendency in which there were many early cases.

Clinical relevance of Sig compared to Por2

Table 2 showed comparison of the background differences between Sig and Por2 in the Diffuse type. Of the 307 patients with Diffuse type, Sig was included in 189, Por2 in 177, and both Sig and Por2 in 59. There were no relevant factors in the background to include both Sig and Por2. Sig tended to be more common in early stage, whereas Por2 cases had more cases of pT3 or more, positive for lymph node metastasis, and pathological stage II/III than Sig cases. The recurrence pattern for patients with Sig was similar to that of patients with Por2.

Of the 189 cases of Sig, 79 were cases in which Sig was histologically dominant, and 110 cases with histologically infrequent (Table 3). A total of 139 (78%) had histological predominance of Por2. There was no clinically Significant difference between Por2-dominant and Por2-infrequent type. Sig-dominant tumors were more frequent in early stage cancers, and peritoneal dissemination was more frequent in patients with Sig-infrequent cancers. Table 4 showed risk factor for peritoneal recurrence. Multivariate analysis revealed that total gastrectomy and coexistence of Sig were independent risk factors associated with peritoneal metastases after curative surgery.

Impact of Sig on overall survival and relapse free survival after S-1 adjuvant chemotherapy

The median length of follow-up was 36 months. Kaplan-Meier curves according to pathological stage are shown in Figure 1. OS analysis by pathological stage showed that there was no difference between

Diffuse type and non-Diffuse type in stage II (Fig.1A). However, patients with Diffuse type had a Significantly worse prognosis in pathological stage III (five-year OS 42%) compared to non-Diffuse type (five-year OS 59%) (Fig.1B). Recurrence for peritoneal dissemination was seen in 14 (24%) of 24 mixed Sig patients and 16 (36%) of 45 mixed Por2 patients. There was no Significant difference in prognosis between Sig and Por2 or histologically infrequent tumors (data not shown). Of the cases with pathological stage II or III, the proportion of patients who received postoperative adjuvant chemotherapy was 61% in Sig, 67% in Por2, and 49% in Intestinal type. Although there was no Significant difference among all patients who received adjuvant chemotherapy with S-1, the 5-year survival rate was marginally lower for the Diffuse type than for the non-Diffuse type in stage III (Fig. 2A, B). Regarding recurrence-free survival (RFS), there were few survival differences (Fig. 2C, D). Comparing Por2 and Sig in pathological stage III, the prognosis of patients with Sig was Significantly worse than that of patients with non-Diffuse type (Fig. 3A, B). There was little effect on RFS in patients with Por2, but patients with Sig had Significantly worse RFS (Fig.3C, D). In other words, patients with Sig are more likely to experience an early relapse while taking S-1.

Discussion

In this study, the prognosis of patients with diffuse mixed type gastric cancer was worse than that of patients with Intestinal type in pathological stage III. Moreover, in stage 3 patients who received postoperative adjuvant chemotherapy with S-1, patients with Signet ring cell carcinoma had a Significantly worse prognosis than patients with non-solid type poorly gastric carcinoma.

The Diffuse type was more common in women and younger patients, and it was associated with type 4 cancer and peritoneal metastases as the site of initial recurrence after surgery. A meta-analysis of 73 studies showed that patients with Diffuse type had the worst prognosis [8]. They found that the risk of death was increased by 23% regardless of race, stage, and chemotherapy. Microsatellite instability (MSI) of four genomic subtypes classified by the TCGA study of gastric cancer was mainly present in non-diffuse distal cancer, whereas chromosomal instability was seen in Diffuse type cancers [9]. In the molecular classification of the Asian Cancer Research Group (ACRG), Diffuse type corresponds to microsatellite stable and the epithelial-to-mesenchymal transition (MSS/EMT) phenotype [10]. The MSS/EMT was often observed in stage III/IV advanced gastric cancer and had the worst prognosis due to frequent peritoneal metastases. The EMT was also observed in younger patients and corresponded to Laurén's Diffuse type [11]. Thus, diffuse gastric cancer cells appear to possess the capacity of epithelial-mesenchymal transition, which promotes peritoneal metastasis [12]. Mixed type was seen in 15% of patients, and they showed a metastatic, as well as a prognostic, pattern like predominant Sig and Por2 tumors. Chen et al examined 3071 patients with gastric cancer and divided them into three groups according to the Lauren classification: Intestinal type 46%, Diffuse type 32%, and mixed type 21%. They demonstrated that the clinical appearance and outcome of mixed type in the Lauren classification was similar to Diffuse type gastric cancer [5].

In the Diffuse type, the two histotypes of Sig and Por2 differ in their clinical and molecular features to the point of representing distinct entities [13]. Poorly differentiated carcinoma cells have the potential to convert into the EMT phenotype. On the other hand, Sig is also common in early stage cancers, and the overall prognostic impact of the presence or absence of Sig is equivocal [14–16]. Pure Sig is usually present in the intramucosal layer, while its morphology is often lost during tumor growth and transformation into poorly cohesive carcinoma [17]. Sig can easily transform into poorly cohesive carcinoma in invasive areas and is most frequent in advanced gastric cancer [18]. Piessen et al demonstrated that Sig often developed peritoneal metastasis and lymph node invasion and would often fail R0 resection, and Sig was associated with a worse prognosis than non-Sig in a group matched-controlled study [19]. Possible reasons for a poor prognosis are unsuspected peritoneal carcinomatosis and lymph node involvement, which are frequent. We previously reported that Signet ring cells themselves had the capacity to produce immune suppressive enzymes, which increased metastasis [20]. Therefore, Sig in advanced gastric cancer is associated with a poorer prognosis than the poorly differentiated type.

The predictive effect of each histological subtype on the efficacy of chemotherapy has not been definitively elucidated. A decrease in the objective response rate was found in the presence of a diffuse component of advanced gastric cancer. The Laurén Diffuse type of gastric cancer is frequently highly infiltrative and resistant to chemotherapy [21]. Yoon et al demonstrated that RhoA activity plays a critical role in maintaining cancer stem cell phenotype, and direct RhoA inhibition was effective with chemotherapy [22]. The survival rate was better in Intestinal type than in Diffuse type with regimens containing docetaxel. Subgroup analysis of JCOG9912 indicated that S-1 was more effective than 5-FU alone in the treatment of Diffuse type [23]. S-1 combined with docetaxel therapy was superior to S-1 monotherapy in patients with Diffuse type in the START trial [24]. It has recently, been reported that S-1 plus docetaxel improved efficacy in patients with stage III gastric cancer [7]. If effective intraperitoneal treatment is developed, it should be directed at patients with a high risk of peritoneal recurrence. More effective adjuvant therapy is needed, perhaps with immunotherapy or new target agents.

The limitations of this study are that it was a retrospective study in a single-institution setting. However, the subjects of this study accumulated over a period of approximately 12 years, indicating an adequate investigation. Furthermore, the impact of histology on second-line chemotherapy, which could affect OS, was not examined.

Conclusions

Signet ring cell carcinoma, when observed in advanced cancer tissue, is associated with a high rate of peritoneal recurrence even after radical resection. The present results suggest that early recurrence during postoperative adjuvant chemotherapy should be considered in patients with stage III gastric cancer showing histological coexistence of Signet ring cell carcinoma.

Abbreviations

TNM: Tumor, Node and Metastasis

WHO: World Health Organization

OS: overall survival

DFS: disease free survival

Declarations

Ethics approval and consent to participate

The ethics committee of Osaka City University approved this study as a retrospective observational study #4423 that uses only medical record information without patient invasion or intervention and therefore does not need to go through the procedure of obtaining direct consent by disclosing information on the study through opt-out.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests

Funding

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Authors' contribution

HT, KH and MO contributed to study conception and design and preparation of the manuscript. MY, TT1 and TT2 contributed data analysis and interpretation NS, HN, YM, and KM participated in data collection and analysis. All authors read and approved the final manuscript.

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Tables

Table 1 Difference of clinicopathological features between Diffuse type and Intestinal type

	Intestinal predominat type (n=750)		Diffuse predominant type (n=218)		
	Intestinal type (n=661)	Diffuse mixed intestinal type (n=89)		p value	p value
	Intestinal type (n=661)	Diffuse type (n=307)		Intestinal vs Diffuse	Diffuse mix vs predominant
Age (Median)	70	65	64	0.0001	0.414
Sex					
Male	175	57	121	0.0001	0.1668
Female	486	32	97		
Macroscopic type					
Type 0	357	48	112	0.0001	0.113
Type 1,2,3	296	38	87		
Type 4	8	3	19		
Surgery					
DG	471	70	158	0.1533	0.397
PG	10	0	1		
TG	180	19	59		
pT					
1/2	476	54	107	0.0001	0.0487
3/4	185	35	111		
pN					
0/1	532	64	167	0.015	0.321
2/3	129	25	51		
pStage					
I	419	46	115	0.0008	0.931
II/III	242	43	103		
Lymphatic invasion					
negative	368	51	118	0.07	0.126
positive	293	38	100		
Venous invasion					
negative	546	73	201	0.033	0.698
positive	115	16	17		
Recurrence					
Peritoneum	30	11	38	0.001	0.261
Liver	32	2	2	0.0031	0.376
LN	30	3	9	0.651	0.752
other	18	3	7	0.6478	0.943

Table 2 Comparison of patients' background characteristics between Sig and Por2

	n=189	n=177	
	Sig	Por 2	p value
Age	62 ± 12	64 ± 12	0.664
Sex			
Male	101	111	0.083
Female	88	66	
Macroscopic type			
Type 0	117	67	0.001
Type 1,2,3	62	90	
Type 4	10	20	
pT			
1/2	134	73	0.000
3/4	55	104	
pN			
0/1	154	115	0.025
2/3	35	62	
pStage			
I	122	60	0.000
II/III	67	111	
Lymphatic invasion			
negative	115	72	0.005
positive	74	105	
Venous invasion			
negative	170	151	0.049
positive	19	26	
Recurrence			
Peritoneum	29	37	0.708
Liver	1	4	0.199
LN	5	9	0.160
other	3	8	0.030

Table 3 Impact of histological occupancy in Diffuse type

	sig-dominant (n=79)	sig-infrequent (n=110)	p value	por2-dominant (n=139)	por2-infrequent (n=38)	p value
Age	60 ± 13	64 ± 12	0.069	63 ± 13	66 ± 11	0.638
Sex						
Male	35	66	0.032	86	25	0.658
Female	44	44		53	13	
Macroscopic type						
Type 0	58	59	0.067	54	13	0.700
Type 1,2,3	19	43		68	22	
Type 4	2	10		17	3	
pT						
1/2	67	67	0.001	60	13	0.112
3/4	12	43		79	25	
pN						
0/1	72	82	0.001	95	20	0.146
2/3	7	28		44	18	
pStage						
I	64	58	0.001	51	9	0.310
II/III	15	52		88	29	
Lymphatic invasion						
negative	59	62	0.013	59	14	0.461
positive	20	48		80	24	
Venous invasion						
negative	74	102	0.752	127	25	0.001
positive	5	8		12	13	
Recurrence						
Peritoneum	6	23	0.012	32	5	0.181
Liver	0	1	0.395	2	2	0.159
LN	2	3	0.934	7	2	0.954
other	1	2	0.761	6	2	0.803

Table 4 Risk factors for peritoneal recurrence

	HR (95% CI)	p value	HR (95% CI)	p value
Age	0.61 (0.07-4.27)	0.6312		
Macroscopic type				
Type 0 vs type 4	5.60 (1.24-30.78)	0.025	2.19 (0.23-50.1)	0.71
Surgery				
TG vs DG	4.18 (1.95-9.60)	0.0002	3.70 (1.59-9.16)	0.002
Histology				
Por2 or non-por2	3.27 (1.58-6.92)	0.0015	2.23 (0.90-5.58)	0.081
Sig or non-sig	4.23 (1.92-9.26)	0.0004	3.34 (1.37-8.16)	0.0081
pT				
pT3 vs pt4a	2.39 (1.10-5.57)	0.0272	1.61 (0.63-4.27)	0.135
pN				
pN1 vs pN3	2.65 (0.92-8.82)	0.0713		
Lymph node dissection				
D1, D1+ vs D2	0.84 (0.47-3.34)	0.738		
Lymphatic invasion				
negative vs positive	1.38 (0.47-4.60)	0.569		
Venous invasion				
negative vs positive	0.39 (0.06-2.85)	0.728		

Figures

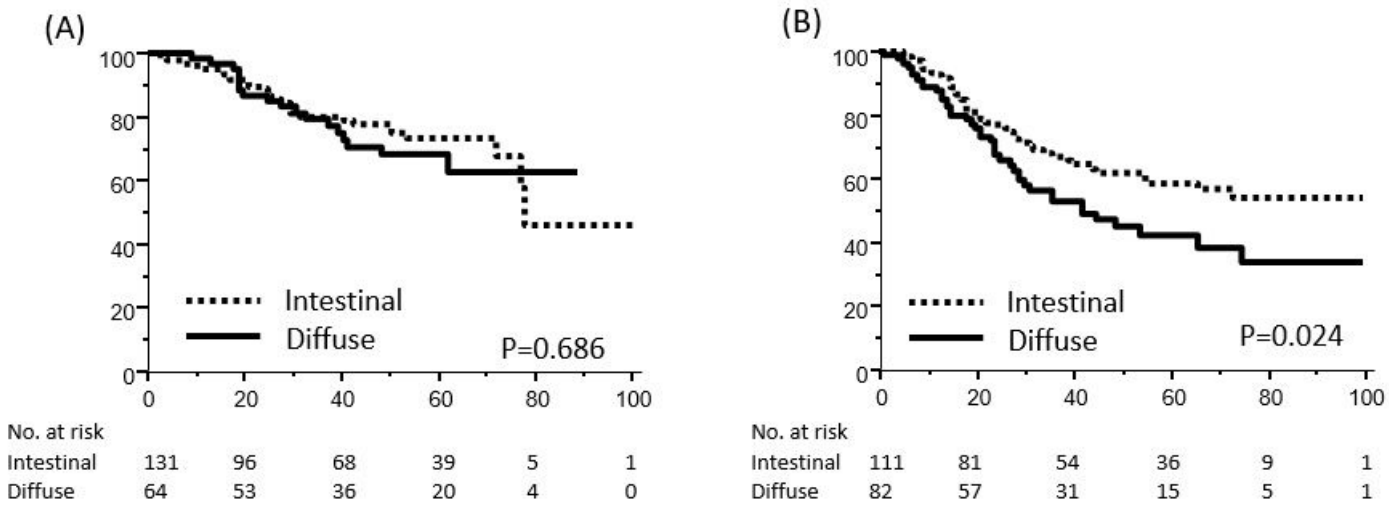

Figure 1

Kaplan-Meier curves comparing months of overall survival in Diffuse type (solid line) and Intestinal type (dotted line) are shown for pathological stage II (A) and stage III (B).

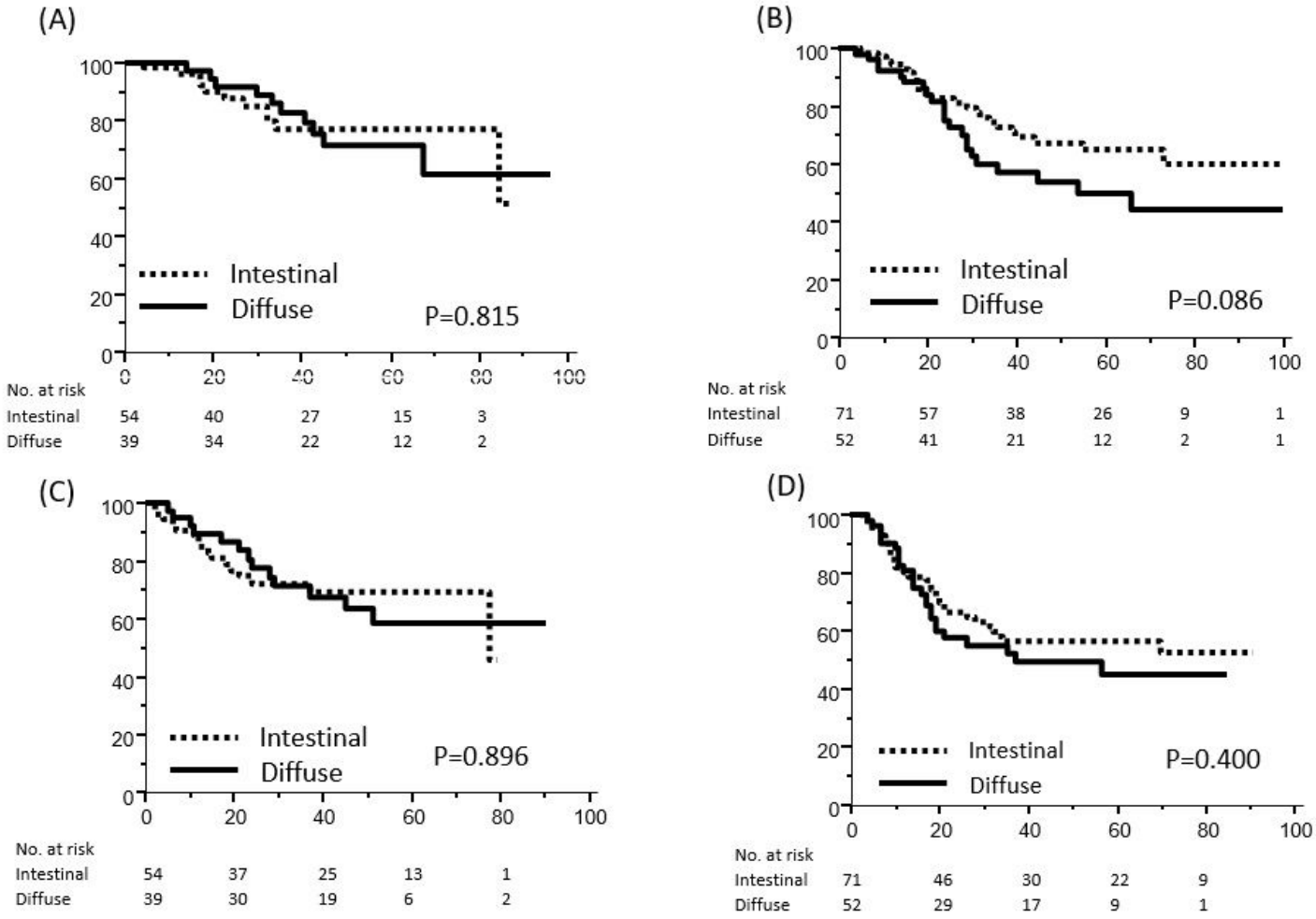

Figure 2

Kaplan-Meier curves comparing months of overall survival (A, B) and relapse-free survival (C, D) in Diffuse type (solid line) and Intestinal type (dotted line) are shown for pathological stage II (A, C) and stage III (B, D) treated with S-1 adjuvant chemotherapy.

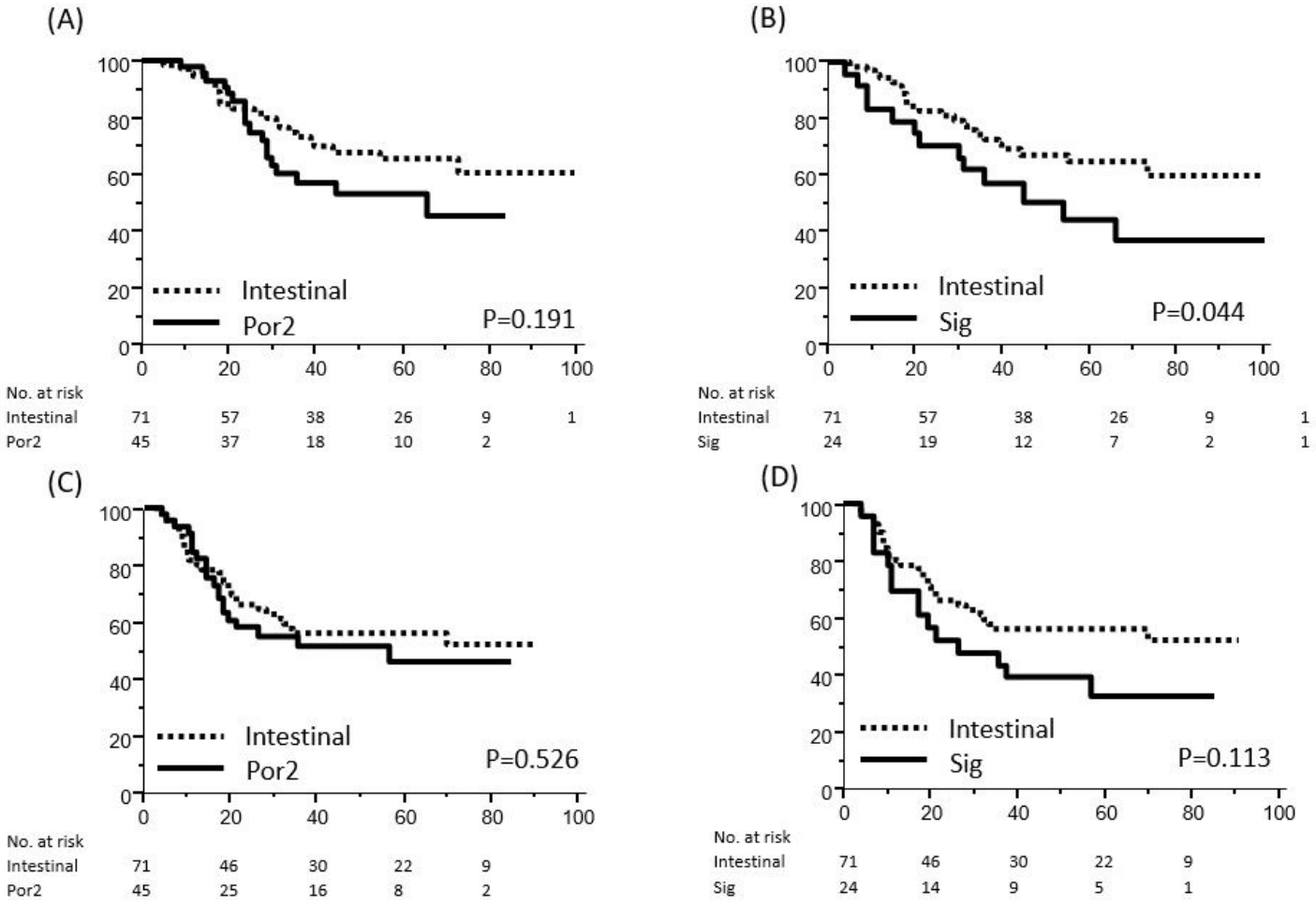

Figure 3

Kaplan-Meier curves comparing months of overall survival (A, B) and relapse-free survival (C, D) in stage III are shown for Por2 (solid line in A, C), Sig (solid line in B, D), and Intestinal type (dotted line) treated with S-1 adjuvant chemotherapy.