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Clinical Significance of *PLA2G2A* Expression in Gastric Cancer Patients who Receive Gastrectomy and Adjuvant S-1

SHINSUKE HATORI[1,2], KENTARO SAKAMAKI[3], TAKEHIKO YOKOHORI[4], YAYOI KIMURA[5], YUKIHIKO HIROSHIMA[6], ITARU HASHIMOTO[1], KEISUKE KOMORI[1], HAYATO WATANABE[1], KAZUKI KANO[1], HIROHITO FUJIKAWA[1], TORU AOYAMA[2], MASAKATSU NUMATA[2], TAKANOBU YAMADA[1], HIROSHI TAMAGAWA[2], NAOTO YAMAMOTO[1], TAKASHI OGATA[1], MANABU SHIZAWA[1], NORIO YUKAWA[2], SOICHIRO MORINAGA[2], YASUSHI RINO[2], MUNETAKA MASUDA[2], HIROSHI SAEKI[4], YOHEI MIYAGI[6] and TAKASHI OSHIMA[1]

[1]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan;*
[2]*Department of Surgery, Yokohama City University, Yokohama, Japan;*
[3]*Department of Data Science, Yokohama City University, Yokohama, Japan;*
[4]*Department of Gastroenterological Surgery, Gunma University, Maebashi, Japan;*
[5]*Advanced Medical Research Center, Yokohama City University, Yokohama, Japan;*
[6]*Kanagawa Cancer Center Research Institute, Yokohama, Japan*

Abstract. *Background/Aim: This study aimed to evaluate the prognostic significance of PLA2G2A expression in patients with locally advanced gastric cancer (GC). Patients and Methods: PLA2G2A expression levels in cancerous tissue specimens and adjacent normal mucosa obtained from 134 patients with stage II/III GC who received adjuvant chemotherapy with S-1 after curative resection were measured using real-time quantitative polymerase chain reaction. Subsequently, the associations of PLA2G2A expression with clinicopathological features and survival were evaluated. Results: No association was observed between clinicopathological features and PLA2G2A expression levels. Overall survival was significantly longer in patients with high PLA2G2A expression levels (p=0.022). Multivariate analysis revealed that PLA2G2A expression was a significant, independent prognostic factor (hazard ratio=0.136; 95% confidence interval=0.0185-0.992; p=0.049). Conclusion: PLA2G2A mRNA expression may serve as a useful prognostic marker in patients with locally advanced GC who receive curative surgery and adjuvant chemotherapy with S-1.*

The number of new gastric cancer (GC) cases worldwide in 2020 was 1,089,103, the fifth highest, accounting for 5.6% of all cancers. In addition, there were 768,793 deaths, the fourth highest, accounting for 7.7% of all cancer-related deaths (1). The standard therapy for pathological stage II/III GC is curative surgery and postoperative adjuvant chemotherapy (2-6). However, despite these standard therapies, a considerable number of patients die; therefore, personalised treatment based on biomarkers is expected to improve treatment outcomes (7-12).

Phospholipase A2 group IIA (*PLA2G2A*) mRNA encodes a member of the phospholipase A2 family (PLA2). It catalyses the hydrolysis of the sn-2 fatty acyl ester bond of phosphoglycerates, releasing free fatty acids and lysophospholipids, and participates in the regulation of phospholipid metabolism in bio-membranes (13). PLA2G2A has been reported to be expressed in many human cancers (13-16). Moreover, some studies have reported that PLA2G2A expression in cancer tissue is associated with survival in several different cancers (17, 18). However, the clinical significance of *PLA2G2A* mRNA expression in the GC tissue of patients with locally advanced GC who undergo curative surgery and adjuvant chemotherapy has not yet been reported.

In this study, we examined the relationship between *PLA2G2A* mRNA expression in GC tissue and the clinicopathological factors and survival of patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1.

Patients and Methods

Patients and samples. Approval was received from the Ethics Committees of Yokohama City University and Yokohama City Medical Center (approval number: 18-7A-4) as well as Kanagawa Cancer Center (approval number: epidemiological study-29) before

Correspondence to: Dr. Takashi Oshima, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2-3-2 Nakano Asahi, Yokohama, Kanagawa 241-8515, Japan. Tel: +81 455202222, Fax: +81 455202202, e-mail: oshimat@kcch.jp

Key Words: Gastric cancer, S-1, prognostic factor, PLA2G2A.

Table I. *Polymerase chain reaction primers and conditions.*

Gene			Annealing temperature (˚C)	Product size (bp)
PLA2G2A	Sense	5'-CCATGAAGACCCTCCTACTG-3'	59	108
	Antisense	5'-CCTTTCCTGTCGTCAACTTG-3'		
β-actin	Sense	5'AGTTGCGTTACACCCTTTCTTGAC-3'	60	171
	Antisense	5'-GCTCGCTCCAACCGACTGC-3'		

this study commenced. In this study, we assessed samples of GC tissues and adjacent normal mucosa from 134 patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1 at the Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Department of Surgery, Yokohama City University or the Yokohama City University Medical Center, Gastroenterological Center between January 2002 and December 2012. All participants provided informed consent. Each GC tissue and adjacent normal mucosa specimen was immediately embedded in optimum cutting temperature compound (Sakura FineTechnical Co. Ltd., Tokyo, Japan) and stored at –80˚C until use. Each specimen was stained with haematoxylin and eosin for histopathological evaluation. Specimens comprising more than 80% cancer cells were used for the preparation of total RNA extracts.

RNA extraction and complementary DNA (cDNA) synthesis. Total RNA was extracted from GC tissue and adjacent normal mucosa using TRIzol Reagent (Gibco; Life Technologies, Gaithersburg, MD, USA). cDNA was synthesised from total RNA using an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA, USA).

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). qRT-PCR was performed using iQ SYBR Green Supermix (Bio-Rad Laboratories). PCR reactions were performed in a total volume of 15 μl, including cDNA derived from 0.75 mg of RNA; 27 nM of each primer; and 7.5 μl of iQ SYBR Green Supermix, which contained 50 units/ml of iTag DNA polymerase; and 0.4 mM each of dCTP, dTTP, dGTP, and dATP. The PCR conditions were as follows: 3 min at 95˚C, followed by 35 cycles of cDNA denaturation for 15 s at 95˚C, annealing for 15 s at 60˚C for both *PLA2G2A* and *β-actin*, a primer extension for 30 s at 72˚C, and 72˚C for 10 min. The PCR primer sequences of *PLA2G2A* and *β-actin*, which was used as an internal control, are shown in Table I.

Statistical analysis. The expression levels of *PLA2G2A* mRNA in GC tissues and adjacent normal mucosa were compared using the Wilcoxon signed-rank test. *PLA2G2A* mRNA expression was categorised into a low expression group (n=17) and a high expression group (n=117) based on the expression level of *PLA2G2A* mRNA in GC tissue. A two-fold cross-validation approach was used to obtain the optimal cut-off point. The relationship between the expression levels of *PLA2G2A* mRNA and potential explanatory variables were evaluated using the chi-square test. The association between the expression levels of *PLA2G2A* mRNA and postoperative survival was assessed using the Kaplan–Meier method, and the differences in outcomes between the *PLA2G2A* mRNA high and low expression groups were analysed using the log-rank test. Univariate and multivariate analyses were performed to determine prognostic factors using a Cox proportional hazards regression model. All statistical analyses were performed using IBM SPSS Statistics 20 software (SPSS Inc., Chicago, IL, USA). Two-tailed *p*-values were calculated, and differences were considered significant at *p*-value <0.05.

Results

Comparison of PLA2G2A mRNA expression levels between GC tissue and normal adjacent mucosa. PLA2G2A mRNA expression in GC tissue was significantly higher than that in normal adjacent mucosa (p=0.003; Wilcoxon test; Figure 1).

Relationship between PLA2G2A mRNA expression level and clinicopathological features. The study specimens were divided into two groups according to a two-fold cross-validation approach [high *PLA2G2A* expression group (n=117) and low *PLA2G2A* expression group (n=17)] based on the level of *PLA2G2A* mRNA expression. *PLA2G2A* mRNA expression was not significantly correlated with any clinicopathological factor (Table II).

Relationship between PLA2G2A expression level in GC tissue and survival in patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1. The 5-year overall survival (OS) in the high *PLA2G2A* mRNA expression group was significantly better than that in the low *PLA2G2A* mRNA expression group (94.2% *vs.* 61.1%, respectively; p=0.022; Figure 2). The median follow-up period was 1,107 days. In stage II patients, there was no significant difference in OS between the low and high expression groups of *PL2AG2A* mRNA in GC tissue (Figure 3A). In stage III patients, the OS of patients with high *PL2AG2A* mRNA expression in GC tissue was significantly better than that of patients with low expression (Figure 3B).

Univariate and multivariate analyses of survival in patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1. In the univariate Cox proportional hazards model, only high

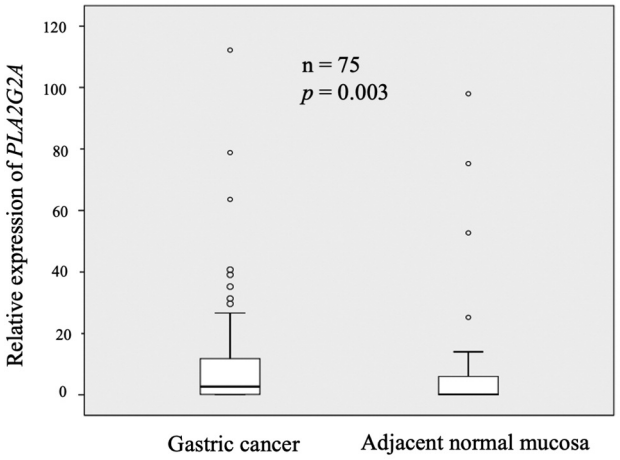

Figure 1. *Comparison of PLA2G2A mRNA expression levels between gastric cancer (GC) tissue and adjacent normal mucosa. The relative expression of PLA2G2A mRNA in GC tissue was significantly higher than that in the adjacent normal mucosa (p=0.003; Wilcoxon's signed-rank test).*

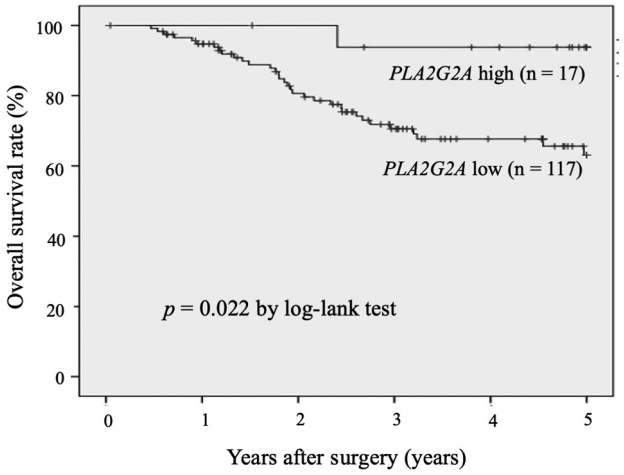

Figure 2. *Overall survival (OS) of patients with stage II/III gastric cancer (GC) who underwent curative resection and postoperative adjuvant chemotherapy with S-1 (n=134) according to PL2AG2A mRNA expression levels. The OS of patients with high PL2AG2A mRNA expression was better than that of patients with low expression.*

Table II. *Relationship between PLA2G2A gene expression and clinicopathological features.*

Variable/category	PLA2G2A expression		*p*-Value
	Low (n=17)	High (n=117)	
Age			
≤65	8	55	0.997
>65	9	62	
Gender			
Male	12	80	0.854
Female	5	37	
Tumour size			
≤6 cm	6	54	0.400
>6 cm	11	63	
Histological type			
Differentiated	49	49	0.148
Undifferentiated	68	68	
T factor			
1-3	5	48	0.360
4	12	69	
Lymph node metastasis			
Absent	4	12	0.115
Present	13	105	
Lymphatic invasion			
Absent	3	27	0.616
Present	14	90	
Venous invasion			
Absent	7	26	0.090
Present	10	91	
TNM stage			
II	5	35	0.966
III	12	82	

PLA2G2A mRNA expression in GC tissue was a significant prognostic factor. In the multivariate Cox regression analyses, high *PLA2G2A* mRNA expression was confirmed to be an independent prognostic factor in patients with stage II/III GC (hazard ratio: 0.136; 95% confidence interval=0.0185-0.992; *p*=0.049; Table III).

Discussion

In the present study, we examined the clinical significance of *PLA2G2A* mRNA expression in patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1.

First, we compared the expression level of *PLA2G2A* mRNA in GC tissues and paired adjacent normal mucosa. A previous study reported that an immunohistochemical analysis of 866 paired GC and normal tissue samples found that *PLA2G2A* was not expressed in normal gastric mucosa but exhibited a significantly increased expression in the cytoplasm of GC cells (19). Similarly, our results showed that the expression level of *PLA2G2A* mRNA in GC tissue was significantly higher than that in normal adjacent mucosa.

Next, we examined the association between the expression level of *PLA2G2A* mRNA in GC tissues and clinicopathological features. A previous study reported that the expression level of *PLA2G2A* mRNA in cancer tissue was significantly associated with tumour size, tumour differentiation, tumour depth, lymph node metastasis, and tumour–node–metastasis stage in patients with GC (19).

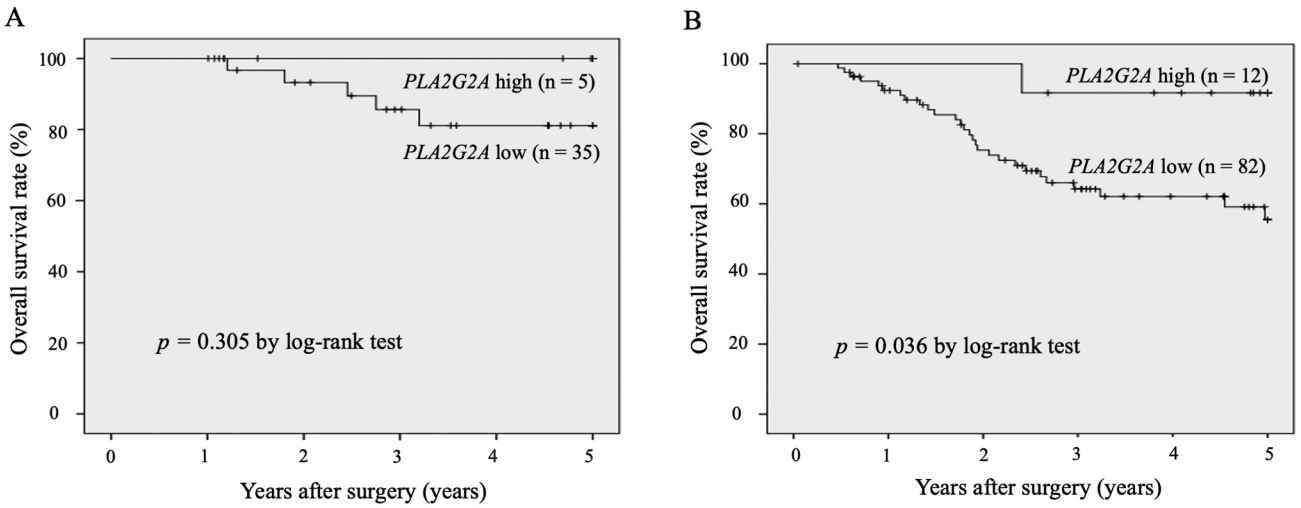

Figure 3. *Overall survival (OS) of patients with stage II (A) and III (B) gastric cancer (GC) who underwent curative resection and postoperative adjuvant chemotherapy with S-1 according to PL2AG2A mRNA expression levels. In stage II patients, there was no significant difference in OS between the low and high expression groups of PL2AG2A mRNA in GC tissue. In stage III patients, the OS of patients with high PL2AG2A mRNA expression was significantly better than that of patients with low expression.*

Table III. *Univariate and multivariate analyses of clinicopathological features associated with overall survival.*

Variable/category	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age						
≤65	1					
>65	0.787	0.408-1.519	0.475			
Gender						
Male	1					
Female	1.479	0.695-3.147	0.310			
Tumour size						
≤6 cm	1					
>6 cm	1.067	0.553-2.060	0.847			
Histological type						
Differentiated	1					
Undifferentiated	0.973	0.497-1.907	0.937			
T factor						
T1-3	1					
T4	0.973	0.497-1.907	0.937			
Lymph node metastasis						
Absent	1					
Present	2.726	0.655-11.356	0.168	1.098	0.499-2.417	0.816
Lymphatic invasion						
Absent	1					
Present	1.002	0.456-2.201	0.997			
Venous invasion						
Absent	1					
Present	1.566	0.685-3.580	0.288			
PLA2G2A expression level						
Low	1					
High	0.132	0.0194-0.990	**0.048**	0.136	0.0185-0.992	**0.049**

HR: Hazard ratio; CI: confidence interval. Bold values indicate statistical significance ($p<0.05$).

Conversely, a study of 116 patients with colorectal cancer found no significant correlation between the expression level of *PLA2G2A* mRNA in cancer tissue and any clinicopathological factors, including age, sex, depth of invasion, and lymph node status (18). Our results also showed no significant association between the expression level of *PLA2G2A* mRNA in cancer tissue and clinicopathological factors.

In addition, we examined the association between *PLA2G2A* mRNA expression level in cancerous tissue and survival in patients with stage II/III GC who underwent curative surgery and postoperative adjuvant chemotherapy with S-1. Previous studies reported that the reduced expression of *PLA2G2A* may result in poor survival after resection of primary oesophageal squamous cell carcinoma. It has been reported that GC patients with positive *PLA2G2A* expression showed higher 5-year OS than those with negative expression. Furthermore, another study reported that patients with higher expression levels of *PLA2G2A* had a significantly extended survival and an almost 3-fold higher 5-year survival rate. Our results corroborate these findings, as the 5-year OS was significantly better in patients with high expression levels of *PLA2G2A* mRNA in GC tissue.

Moreover, we performed univariate and multivariate analyses of clinicopathological factors and *PLA2G2A* mRNA expression to identify independent prognostic factors. The expression level of *PLA2G2A* had previously been shown to be an independent predictor of survival in patients with GC and a useful protective factor (hazard ratio=1.423; 95% confidence interval=1.047-1.935*;* p=0.024) in a study involving 866 patients (16). Our univariate and multivariate Cox regression analyses identified high *PLA2G2A* mRNA expression in cancerous tissue as the only factor independently associated with survival in patients with stage II/III GC who underwent curative gastrectomy and postoperative adjuvant chemotherapy with S-1.

The mechanism of the association between high *PLA2G2A* expression and improved survival in patients with stage II/III GC who received postoperative adjuvant chemotherapy with S-1 after curative surgery remains unclear. PLA2G2A expression has been reported to be positively correlated with Wnt pathway activation in GC cells, and β-catenin and the TCF/LEF transcription factor TCF4, which are both major components of the signalling pathway, are highly expressed in all PLA2G2A-expressing cells. Furthermore, PLA2G2A inhibits tumour invasion by negatively regulating S100A4 and NEDD9 expression in GC cells (20). In addition, it has been reported that knockdown of PLA2G2A in GC cells leads to high 5-FU sensitivity, and transfection of PLA2G2A cDNA into 5-FU sensitive cells increased sensitivity to treatment (21). In that study, GC cells with elevated PLA2G2A levels were sensitive to 5-FU treatment, whereas those with lower PLA2G2A levels exhibited treatment resistance. While only a hypothesis, it is possible that the aforementioned mechanism is involved in the positive prognosis after adjuvant chemotherapy with S-1 and radical resection for locally advanced GC in patients with high PLA2G2A expression.

Our study has several limitations. First, we only investigated *PLA2G2A* mRNA expression in cancer tissue and adjacent normal mucosa of GC specimens. While we believe that PLA2G2A protein expression is associated with *PLA2G2A* mRNA expression, PLA2G2A protein expression should be determined using immunohistochemical analysis of the same specimens. Second, the heterogeneity of GC specimens poses a challenge. The specimens used for mRNA extraction were 5 mm^2 GC specimens; although these specimens were consistent with tissues collected from the maximum depth, they do not faithfully represent the entire tumour. To better elucidate the role of *PLA2G2A* mRNA expression as a prognostic factor in GC, we intend to address these issues in future studies. Further, we believe that conducting the study in a larger cohort will help us to determine the significance of *PLA2G2A* mRNA expression with greater accuracy.

In conclusion, *PLA2G2A* mRNA expression may serve as a useful prognostic marker in patients with stage II/III GC who undergo curative resection and postoperative adjuvant chemotherapy with S-1.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

Authors' Contributions

SH and TO designed the study. Data collection and literature searches were performed by IH, KK, HW, KK, SH, and TO. Data analysis and interpretation were performed by SH, YH, YK, YM, and TO. Data interpretation was performed by all investigators. The article and figures were drafted by SH and TO. Finally, the article was revised and approved by all investigators. Thus, all of the Authors actively participated in this study.

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