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The Clinical Implication of PTEN and FAK Expression in Gastric Cancer Patients

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Objective: The tumor suppressor gene *phosphatase and tensin homolog* (*PTEN*) was reported to inhibit the growth and invasion of gastric cancer (GC) via the downregulation of focal adhesion kinase (FAK). To date, the clinical implication of PTEN and FAK expression in GC has not been well addressed.

Methods: A total of 200 GC patients receiving curative surgery were enrolled. The clinicopathologic features according to the expression of PTEN and FAK protein using immunohistochemical staining were compared among patients.

Results: Patients with high PTEN expression were more likely to have smaller tumor size, more well- and moderately differentiated tumors, a more superficial gross appearance, less scirrhous stromal reactions, more likely to have high FAK expression, and have less advanced pathologic tumor (T) category, node (N) category, and tumor, node, metastasis (TNM) stage and more distant metastases than patients with low PTEN expression. Multivariate analysis showed that PTEN/FAK expression status is an independent prognostic factor affecting overall survival (OS) and disease-free survival (DFS). Patients with PTEN(high)/FAK(low) had better OS and DFS, followed by those with PTEN(high)/

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FAK(high), those with PTEN(low)/FAK(low), and those with PTEN(low)/FAK(high) (OS: 83.3% versus 58.0% versus 46.2% versus 26.5%, respectively, $P < 0.001$; DFS: 83.3% versus 55.8% versus 30.8% versus 24.4%, respectively, $P < 0.001$).

Conclusions: GC patients with high PTEN expression were more likely to have fewer tumor recurrences and a better prognosis than those with low PTEN expression. PTEN and FAK may have opposing effects on GC patient survival. Our results may have clinical impact on treatment of GC patients.

Key words: PTEN – FAK – Gastric cancer – Curative surgery – Survival

Despite the declining incidence of gastric cancer (GC), this disease remains the sixth most common cancer and the second most common cause of cancer-related death.[1] Surgical resection and lymph node dissection are the main treatments for curing GC, and the pathologic tumor stage was associated with patient prognosis.

Tumor suppressor phosphatase and tensin homolog (PTEN) expression was reported to be associated with good prognosis in GC.[2] The clinical implications of focal adhesion kinase (FAK) expression on cancer patient prognosis are controversial. Overexpression of FAK was associated with a poor prognosis in colon cancer,[3] pancreatic cancer,[4] breast cancer, and GC,[5] whereas low FAK expression was associated with a poor prognosis in cholangiocarcinoma.[6]

Overexpression of PTEN has been reported to lead to the downregulation of FAK expression and inhibited GC cell invasion.[7] Furthermore, downregulation of Notch1 could inhibit the invasion and metastasis of GC through PTEN activation and dephosphorylation of AKT (a serine/threonine protein kinase, also known as protein kinase B) and FAK.[8] However, there are no reports regarding the correlations between PTEN and FAK expression and their impact on GC patient prognosis.

The aim of the present study was to analyze the correlation between PTEN and FAK expression, the clinicopathologic characteristics, initial recurrence pattern, and patient prognosis of GC after curative surgery.

Materials and Methods

A total of 200 GC patients receiving curative resection were enrolled. The present study was approved by the Institutional Review Board at our hospital (number: 2017-10-009AC) and in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in The Declaration of Helsinki. The exclusion criteria included a history of gastric surgery or a pathologic diagnosis other than adenocarcinoma. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in *The Declaration of Helsinki*.

The pathologic staging of GC was performed after surgery according to the 8th American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) classification.[9] The data were prospectively collected and regularly updated. Before surgery, chest radiography, abdominal sonography, or abdominal computed tomography (CT) scan were performed. A total or subtotal gastrectomy was performed according to the tumor location.

After surgery, follow-up studies including image studies and tumor markers were arranged every 3 months for the first 3 years, followed by a follow-up every 6 months until the patient's death. In our hospital, adjuvant chemotherapy was not routinely performed before 2008. Since 2008, adjuvant chemotherapy such as TS-1 was performed for stage II and III GC patients. However, none of the patients enrolled in this study received adjuvant chemotherapy.

Recurrence was classified as locoregional, hematogenous, distant lymphatic, or peritoneal. Patients who experienced recurrence of GC after surgery could receive 5-fluouracil–based chemotherapy.

Immunohistochemical staining for PTEN and FAK protein

The procedures of immunohistochemical (IHC) staining were the same as a previous study.[10] The monoclonal antibodies against PTEN (#9188; Cell Signaling Technology, Danvers, MA, USA) and FAK (#3285; Cell Signaling Technology) were used.[11,12] The slides were incubated with the antibody at a final dilution of 1:150 in phosphate-buffered saline

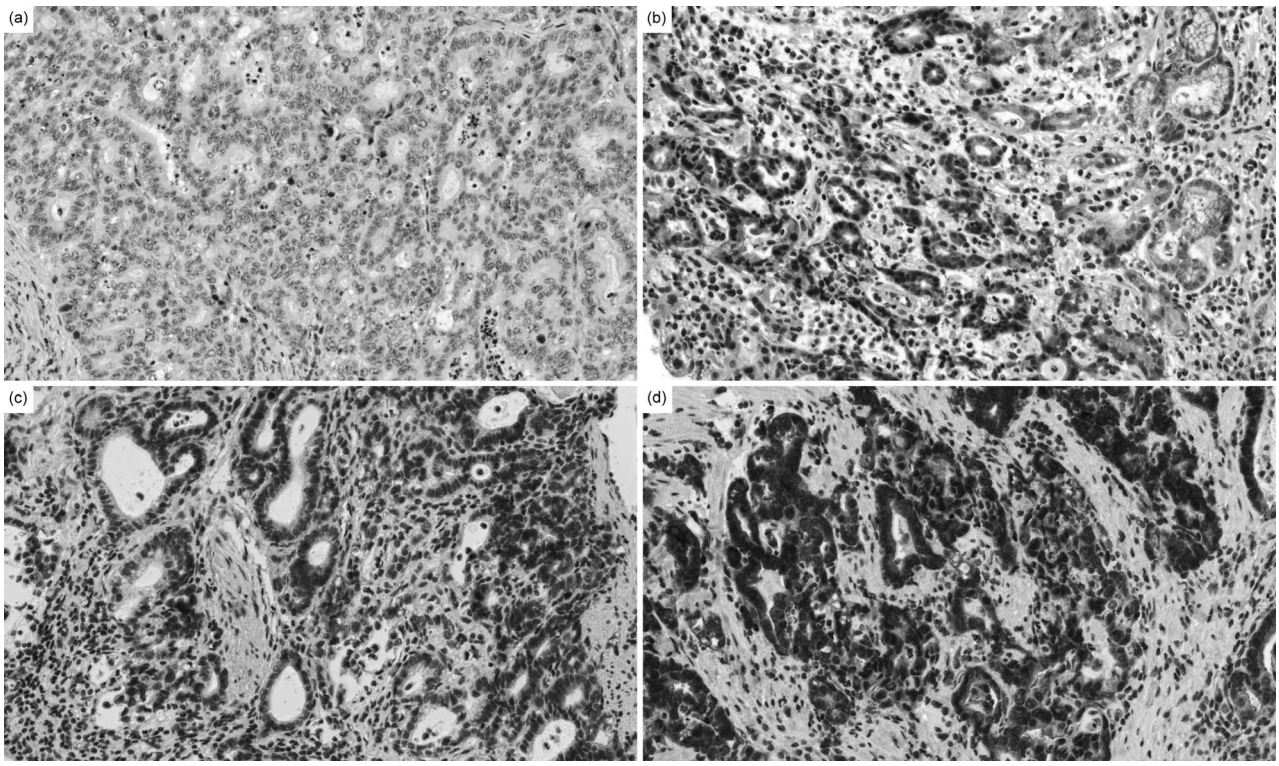

Fig. 1 Immunohistochemical stains for PTEN and FAK. (a) High expression of PTEN. (b) Low expression of PTEN. (c) High expression of FAK. (d) Low expression of FAK.

overnight at 4°C. The reaction was visualized with AEC(RED) substrate Kit (cat. 00-2007, Invitrogen). Subsequently, the slides were briefly counterstained with hematoxylin. PTEN expression was evaluated in normal mucosa and adenocarcinomas. PTEN expression was observed in the cytoplasm of GC tissue. As in a previous report,[10] the results of IHC staining for PTEN were scored as 0 (<5% positive cells), 1+ (5–25% positive cells), 2+ (26–75% positive cells), and 3+ (>75% positive cells). Low PTEN expression was defined when the IHC staining result was 0 or 1+, and high PTEN expression was defined when the IHC staining result was 2+ or 3+. The same criteria were applied in the definition of FAK expression. High and low expressions of PTEN and FAK are shown in Fig. 1.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 25.0. A χ^2 test with Yates correction or Fisher's exact test was used to compare the categorial data. Overall survival (OS) was measured from the operation date to the date of either death or the last follow-up. The definition of disease-free survival (DFS) was the length of time after GC surgery during which a patient survived without the recurrence of tumor. The Kaplan–Meier method was used to estimate the distributions of OS and DFS. Multivariate analysis with Cox proportional hazards models were used to compare the prognostic factors of OS and DFS. $P < 0.05$ was considered statistically significant.

Results

Clinicopathologic features

Among the 200 GC patients, 144 exhibited high PTEN expression, and 56 had low PTEN expression. Patients with high PTEN expression were more likely to have smaller tumor size, more well- and moderately differentiated tumors, a more superficial gross appearance, less scirrhous stromal reactions, more likely to have high FAK expression, and have less advanced pathologic T category, N category, and TNM stage than patients with low PTEN expression (Table 1).

Among the 200 GC patients, 175 had high FAK expression, and 25 had low FAK expression. However, there was no significant difference in the

Table 1 Clinical profile in 200 gastric cancer patients with high or low PTEN expression

Clinical profiles	*PTEN*, low expression (n = 56)	*PTEN*, high expression (n = 144)	*P*
Age, yr			0.615
<65	16 (28.6)	47 (32.6)	
≥65	40 (71.4)	97 (67.4)	
Sex			0.293
Male	44 (78.6)	102 (70.8)	
Female	12 (21.4)	42 (29.2)	
Tumor size, cm			0.040
<5	18 (32.1)	70 (48.6)	
≥5	38 (67.9)	74 (51.4)	
Tumor location			0.074
Upper stomach	15 (26.8)	27 (18.8)	
Middle stomach	12 (21.4)	44 (30.6)	
Lower stomach	26 (46.4)	72 (50)	
Whole stomach	3 (5.4)	1 (0.7)	
Cell differentiation			0.022
Poor	35 (62.5)	65 (45.1)	
Moderate	21 (37.5)	77 (53.5)	
Well	0	2 (1.4)	
Gross appearance			0.023
Superficial type	8 (14.3)	48 (33.3)	
Borrmann type 1 and 2	15 (26.8)	34 (23.6)	
Borrmann type 3 and 4	33 (58.9)	62 (43.1)	
Stromal reaction type			0.011
Medullary type	6 (10.7)	42 (29.2)	
Intermediate type	35 (62.5)	80 (55.6)	
Scirrhous type	15 (26.8)	22 (15.3)	
Lauren's histology			0.108
Intestinal type	30 (53.6)	95 (66)	
Diffuse type	26 (46.4)	49 (34)	
MSI status			0.268
MSI-L/S	44 (78.6)	102 (70.8)	
MSI-H	12 (21.4)	42 (29.2)	
FAK expression			0.017
Low	12 (21.4)	13 (9.0)	
High	44 (78.6)	131 (91.0)	
Pathologic T stage			0.032
T1	8 (14.3)	47 (32.6)	
T2	12 (21.4)	26 (18.1)	
T3	11 (19.6)	31 (21.5)	
T4	25 (44.6)	40 (27.8)	
Pathologic N stage			0.032
N0	17 (30.4)	75 (52.1)	
N1	7 (12.5)	18 (12.5)	
N2	11 (19.6)	19 (13.2)	
N3	21 (37.5)	32 (22.2)	
Pathologic TNM stage			0.008
I	12 (21.4)	62 (43.1)	
II	12 (21.4)	31 (21.5)	
III	32 (57.2)	51 (35.4)	

MSI, microsatellite instability; MSI-L/S, microsatellite instability-low/stable; MSI-H, microsatellite instability-high; FAK, focal adhesion kinase; T, tumor; N, node; TNM, tumor, node, metastasis.

clinicopathologic characteristics between patients with high FAK expression and low FAK expression (Supplemental Table 1).

We then divided GC patients into 4 groups according to PTEN and FAK expression: PTEN (low)/FAK(low), PTEN(low)/FAK(high), PTEN (high)/FAK(low), and PTEN(high)/FAK(high). Compared with GC patients with PTEN(low)/FAK(low) and PTEN(low)/FAK(high), GC with PTEN(high)/FAK(low) and PTEN(high)/FAK(high) had more well and moderate differentiation, a more superficial gross appearance, less scirrhous reactiv-

Table 2 Clinical profile in 200 gastric cancer patients according to PTEN/FAK expression

Clinical profiles	*PTEN/FAK* (low/low) (n = 13)	*PTEN/FAK* (low/high) (n = 43)	*PTEN/FAK* (high/low) (n = 12)	*PTEN/FAK* (high/high) (n = 132)	*P*
Age, yr					0.950
<65	4 (30.8)	12 (27.9)	4 (33.3)	43 (32.6)	
≥65	9 (69.2)	31 (72.1)	8 (66.7)	89 (67.4)	
Sex					0.647
Male	11 (84.6)	33 (76.7)	8 (66.7)	94 (71.2)	
Female	2 (15.4)	10 (23.3)	4 (33.3)	38 (28.8)	
Tumor size, cm					0.095
<5	2 (15.4)	16 (37.2)	6 (50)	64 (48.5)	
≥5	11 (84.6)	27 (62.8)	6 (50)	68 (51.5)	
Tumor location					0.106
Upper stomach	1 (7.7)	14 (32.6)	2 (16.7)	25 (18.9)	
Middle stomach	5 (38.5)	7 (16.3)	6 (50)	38 (28.8)	
Lower stomach	6 (46.2)	20 (46.5)	4 (33.3)	68 (51.5)	
Whole stomach	1 (7.7)	2 (4.7)	0	1 (0.8)	
Cell differentiation					0.047
Poor	9 (69.2)	26 (60.5)	4 (33.3)	61 (46.2)	
Moderate	4 (30.8)	17 (39.5)	7 (58.3)	70 (53)	
Well	0	0	1 (8.3)	1 (0.8)	
Gross appearance					0.008
Superficial type	1 (7.7)	7 (16.3)	4 (33.3)	44 (33.3)	
Borrmann type 1 and 2	5 (38.5)	10 (23.3)	1 (8.3)	33 (25)	
Borrmann type 3 and 4	7 (53.8)	26 (60.5)	7 (58.3)	55 (41.7)	
Stromal reaction type					0.005
Medullary type	3 (23.1)	3 (6.8)	2 (16.7)	40 (30.3)	
Intermediate type	6 (46.2)	30 (68.2)	8 (66.7)	72 (54.5)	
Scirrhous type	4 (30.8)	11 (25)	2 (16.7)	20 (15.2)	
Lauren's histology					0.228
Intestinal type	7 (53.8)	23 (53.5)	10 (83.3)	85 (64.6)	
Diffuse type	6 (46.2)	20 (46.5)	2 (16.7)	47 (35.6)	
Pathologic T stage					0.184
T1	1 (7.7)	7 (16.3)	5 (41.7)	42 (31.8)	
T2	3 (23.1)	9 (20.9)	1 (8.3)	25 (18.9)	
T3	2 (15.4)	9 (20.9)	1 (8.3)	30 (21.4)	
T4	7 (53.8)	18 (41.9)	5 (41.7)	35 (32.3)	
Pathologic N stage					0.015
N0	3 (23.1)	14 (32.6)	8 (66.7)	67 (50.8)	
N1	4 (30.8)	3 (7.0)	2 (16.7)	16 (12.1)	
N2	2 (15.4)	9 (20.9)	0	19 (14.4)	
N3	4 (30.8)	17 (39.5)	2 (16.7)	30 (22.7)	
Pathologic TNM stage					0.004
I	2 (15.4)	10 (23.3)	5 (41.7)	57 (43.2)	
II	5 (38.5)	7 (16.3)	3 (25)	28 (21.2)	
III	6 (46.2)	26 (60.5)	4 (33.3)	47 (35.6)	

PTEN, tumor suppressor phosphatase and tensin homolog; FAK, focal adhesion kinase; T, tumor; N, node; TNM, tumor, node, metastasis.

ity, and less advanced pathologic N category and TNM stage (Table 2).

Initial recurrence pattern

Patients with high PTEN expression had less tumor recurrence than those with low PTEN expression (25.0% versus 50.0%, $P = 0.001$). With regard to the initial recurrence pattern, patients with low PTEN expression were more likely to have anastomosis recurrence and distant metastasis (especially peritoneal recurrence and bone metastasis) than those with high PTEN expression (Supplemental Table 2).

Patients with high FAK expression had more tumor recurrence (52.8% versus 22.2%, $P = 0.021$) and distant metastasis (39.8% versus 11.1%, $P = 0.018$) than those with low FAK expression, especially for stage II and III GC. There was no

Table 3 Patterns of initial recurrence of gastric cancer after curative surgery according to PTEN/FAK expression

Initial recurrence patterns	*PTEN/FAK* (low/low) (n = 13)	*PTEN/FAK* (low/high) (n = 43)	*PTEN/FAK* (high/low) (n = 12)	*PTEN/FAK* (high/high) (n = 132)	*P*
Total recurrence	4 (30.8)	24 (55.8)	2 (16.7)	34 (25.8)	0.007
Locoregional recurrence	2 (15.4)	11 (25.6)	0	18 (13.6)	0.195
Hepatoduodenal ligament	1 (7.7)	2 (4.7)	0	12 (9.1)	0.389
Abdominal wall	0	5 (11.6)	0	7 (5.3)	0.603
Perigastric area	0	2 (4.7)	0	1 (0.8)	0.267
Remnant stomach	0	2 (4.7)	0	1 (0.8)	0.267
Anastomosis	1 (7.7)	5 (11.6)	0	1 (0.8)	0.002
Distant metastasis	2 (15.4)	20 (46.5)	2 (16.7)	23 (17.4)	0.010
Peritoneal dissemination	0	13 (30.2)	1 (8.3)	12 (9.1)	0.058
Hematogenous metastasis	2 (15.4)	7 (16.3)	2 (16.7)	11 (8.3)	0.125
Liver	1 (7.7)	1 (2.3)	1 (8.3)	9 (6.8)	0.517
Lung	0	2 (4.7)	0	1 (0.8)	0.267
Bone	1 (7.7)	3 (7)	1 (8.3)	0	0.004
Adrenal gland	0	0	0	1 (0.8)	0.501
Brain	0	1 (0.7)	0	0	0.196
Distant lymphatic recurrence	0	3 (7.0)	1 (8.3)	9 (6.8)	0.592
Virchow's node	0	0	1 (8.3)	0	0.757
Para-aortic lymph node	0	3 (7.0)	0	9 (6.8)	0.517

Some patients had more than one initial recurrence pattern.

PTEN, tumor suppressor phosphatase and tensin homolog; FAK, focal adhesion kinase.

significant difference in the initial recurrence pattern between patients with high FAK expression and patients with low FAK expression in stage I GC.

Patients with PTEN(high)/FAK(low) had the lowest tumor recurrence rate, followed by those with PTEN(high)/FAK(low), PTEN(low)/FAK(low), and PTEN(low)/FAK(high). Patients with PTEN(low)/FAK(high) had the most distant metastasis compared with that of the other three groups ($P = 0.010$). Patients with PTEN(high)/FAK(high) had no bone metastasis, which was the least compared with that of the other three groups (Table 3).

OS

As shown in Fig. 2a, the 5-year OS (60.2% versus 31.2%, $P < 0.001$) was significantly better in patients with high PTEN expression than low PTEN expression.

As shown in Fig. 2c, the 5-year OS was similar between patients with high FAK expression and low FAK expression (50.4% versus 64.0%, $P = 0.150$). Regarding TNM stage, the 5-year OS was similar between patients with high FAK expression and low FAK expression in stage I GC (77.2% versus 71.4%, $P = 0.692$); however, the 5-year OS was higher in patients with low FAK expression than high FAK expression in stage II and III GC (61.1% versus 33.9%, $P = 0.020$).

In Fig. 3a, the 5-year OS was the highest in GC patients with PTEN(high)/FAK(low), followed by those with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high) (83.3% versus 58.0% versus 46.2% versus 26.5%, respectively, $P < 0.001$).

Multivariate analysis demonstrated that age, sex, lymphovascular invasion, pathologic TNM stage, and PTEN/FAK expression status were independent prognostic factors for OS (Table 4).

DFS

As shown in Fig. 2b, the 5-year DFS (58.1% versus 25.9%, $P < 0.001$) was significantly higher in patients with high PTEN expression than those with low PTEN expression. In Fig. 2d, the 5-year DFS was similar between patients with high FAK expression and low FAK expression (47.6% versus 60.0%, $P = 0.187$). Regarding TNM stage, the 5-year DFS was similar between patients with low FAK expression and high FAK expression (71.4% versus 77.2%, $P = 0.682$) with stage I GC; however, the 5-year DFS was better in patients with low FAK expression than those with high FAK expression in stage II and III GC (55.6% versus 29.3%, $P = 0.021$).

In Fig. 3b, The 5-year DFS was the highest in GC patients with PTEN(high)/FAK(low), followed by those with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high) (83.3% versus 55.8% versus 30.8% versus 24.4%, respectively, $P < 0.001$).

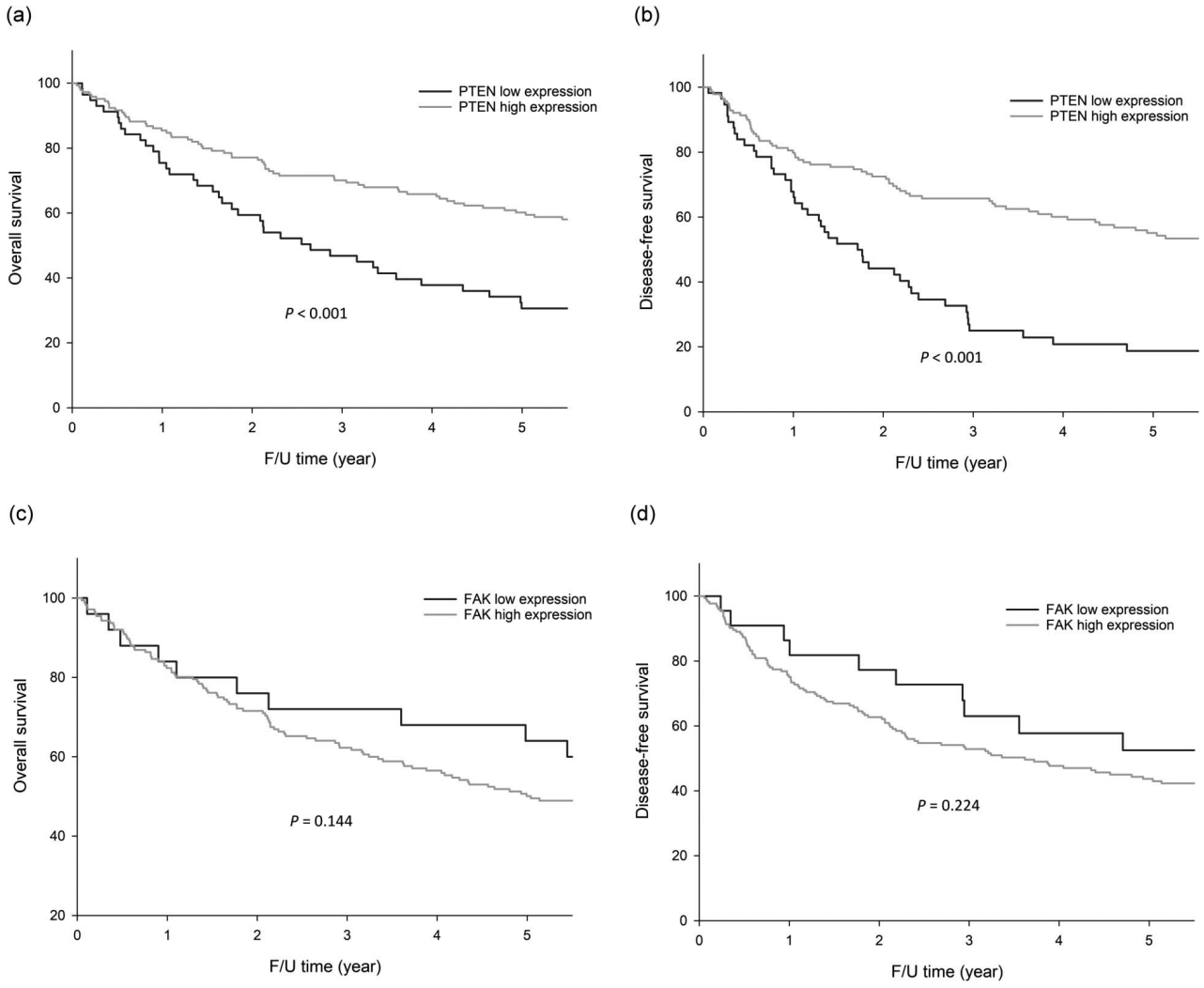

Fig. 2 (a) The 5-year OS rates were significantly higher for GC patients with high PTEN expression than those with low PTEN expression (60.2% versus 31.2%, $P < 0.001$). (b) The 5-year DFS rates were significantly higher for GC patients with high PTEN expression than those with low PTEN expression (58.1% versus 25.9%, $P < 0.001$). (c) The 5-year OS rates were not significantly different between GC patients with high FAK expression and low FAK expression (50.4% versus 64.0%, $P = 0.150$). (d) The 5-year DFS rates were not significantly different between GC patients with high FAK expression and low FAK expression (47.6% versus 60.0%, $P = 0.187$).

Multivariate analysis demonstrated that age, sex, pathologic TNM stage, and PTEN/FAK expression status were independent prognostic factors for DFS (Table 4).

Discussion

This study is the first to investigate the correlation between PTEN and FAK expression and the clinicopathologic characteristics of GC patients. Our results showed that high PTEN expression is associated with a favorable patient prognosis and is an independent prognostic factor that affects OS and DFS. Patients with PTEN(high)/FAK(low) tumors were associated with better OS and DFS, followed by those with PTEN(high)/FAK(low), PTEN(low)/FAK(low), and PTEN(low)/FAK(high) tumors.

It was reported that downregulation of PTEN was correlated with peritoneal recurrence in GC,[13,14] which was associated with the activation of the PI3K/AKT pathway.[13] In renal cell carcinoma,[15] patients with bone metastasis were reported to have lower PTEN expression than those without. Bone metastasis might be caused by AKT and integrin α5 signaling. Our results showed that PTEN expression

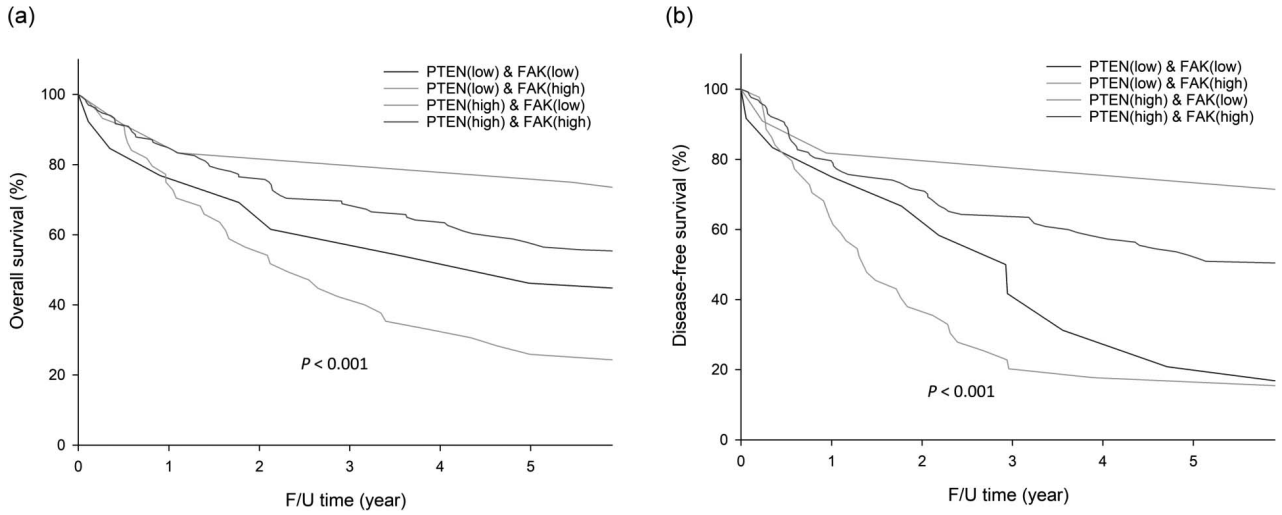

Fig. 3 (a) The 5-year OS rates were the highest in GC patients with PTEN(high)/FAK(low), followed by those with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high) (83.3% versus 58.0% versus 46.2% versus 26.5%, respectively, $P < 0.001$). (b) The 5-year DFS rates were the highest in GC patients with PTEN(high)/FAK(low), followed by those with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high) (83.3% versus 55.8% versus 30.8% versus 24.4%, respectively, $P < 0.001$).

Table 4 Multivariate Cox proportional-hazards model for the survival analysis of the gastric cancer patients after curative surgery

	DFS			OS		
Prognostic factors	HR	95% CI	*P*	HR	95% CI	*P*
Age, yr			0.017			0.028
<65	1.00			1.00		
≥65	1.72	1.101–2.682		1.65	1.057–2.588	
Sex			0.014			0.046
Male	1.00			1.00		
Female	0.55	0.342–0.889		0.61	0.378–0.990	
Tumor size, cm			0.828			0.902
<5	1.00			1.00		
≥5	0.95	0.595–1.516		1.03	0.647–1.639	
Lauren's type			0.561			0.980
Intestinal type	1.00			1.00		
Diffuse type	0.89	0.613–1.305		1.01	0.681–1.484	
Lymphovascular invasion			0.051			0.046
Absence	1.00			1.00		
Presence	1.62	0.998–2.641		1.66	1.009–2.741	
Pathologic TNM stage			<0.001			<0.001
I	1.00			1.00		
II	1.01	0.512–1.978		1.63	0.418–1.627	
III	3.68	1.991–6.785		5.60	1.645–5.602	
PTEN/FAK expression			0.004			0.009
Low/low	1.00			1.00		
Low/high	1.13	0.546–2.325		1.90	0.866–4.181	
High/low	0.24	0.073–0.820		0.44	0.126–1.517	
High/high	0.62	0.309–1.238		1.07	0.505–2.272	

DFS, Disease-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; TNM, tumor, node, metastasis; PTEN, tumor suppressor phosphatase and tensin homolog; FAK, focal adhesion kinase.

was associated with more anastomosis recurrence, peritoneal metastasis, and bone metastasis, which is similar to the above reports. Furthermore, a higher incidence of anastomosis recurrence in patients with low PTEN expression might be due to patients with low PTEN expression presenting a more advanced T category. Although this study showed significantly more bone metastasis in patients without PTEN expression than those with, the number of patients with bone metastasis was limited. The conclusion might not be reliable, although the statistical value is considerable. However, few studies[13,14] investigated the correlation between PTEN expression and recurrence pattern in GC, and the patient number enrolled is limited; this study enrolled the largest population to date to investigate their relationship. The enrollment of more patients is required to verify our findings in the future.

Our data showed that, in comparison with GC patients with PTEN(low)/FAK(low) and PTEN (low)/FAK(high), GC with PTEN(high)/FAK(low) and PTEN(high)/FAK(high) had more well and moderate differentiation, a more superficial gross appearance, less scirrhous reactivity, and less advanced pathologic N category and TNM stage. In Supplemental Table 1, there is no significant difference in the clinicopathologic characteristics between patients with high and low expression of FAK. It seems that low expression of PTEN was associated with more favorable pathologic characteristics, regardless of the expression of FAK.

It was reported that overexpression of PTEN could lead to downregulation of FAK and inhibit GC cell invasion.[7] In this study, patients with high PTEN expression were more likely to have high FAK expression; however, whether PTEN or FAK expression would impact each other regarding patient prognosis is still unknown. Interestingly, both OS and DFS demonstrated that GC with PTEN(high)/FAK(low) were associated with the best prognosis, followed by GC with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high). Regarding tumor recurrence, GC with PTEN(high)/FAK(low) had the lowest tumor recurrence rate, followed by those with PTEN(high)/FAK(high), PTEN(low)/FAK(low), and PTEN(low)/FAK(high). In the present study, stage II and stage III GC patients with high FAK expression were associated with more tumor recurrence and a worse survival than patients with low FAK expression. It seems that PTEN expression was associated with a favorable prognosis and that FAK expression has an adverse effect on patient survival in GC. Further *in vivo* and *in vitro* studies regarding this issue are required to validate our results.

It was reported that miRNA-575 can target PTEN and regulate the development of GC.[16] miRNA-1224 can inhibit tumor metastasis by targeting FAK in intestinal-type GC.[17] Furthermore, miRNA-147 can inhibit cell proliferation and increase the chemosensitivity of GC to 5-FU by targeting PTEN.[18] It seems that the status of PTEN and FAK expression may be helpful for evaluating the response to target therapy and chemotherapy. Our study demonstrated distinguishable patient prognoses according to the PTEN/FAK expression, which may provide useful information and have clinical impact on GC treatment.

There are some limitations in the present study. First, as it is a retrospective study, some bias is likely to exist. Second, although our results showed that tumors with low PTEN expression had significantly more bone metastasis than tumors with high PTEN expression, the number of patients with bone metastasis is limited, and further study is required for validation. Third, GC is heterogeneous, and immunohistochemistry might have false-positive and false-negative staining.

Conclusions

Our results demonstrated that GC patients with low PTEN expression have more distant metastasis and a worse prognosis than those with high PTEN expression. PTEN and FAK might have opposing effects on survival in GC. For high-risk GC patients, the physicians should be aware of the possibility of tumor recurrence. Our results may have clinical impact on treatment and follow-up for GC patients.

Informed consent policy

The present study was approved by the Institutional Review Board at our hospital (number: 2017-10-009AC) and in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in The Declaration of Helsinki.

Availability of data and material

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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