Association between FGF10 expression and gland-forming differentiation pattern in gastric adenocarcinoma: An immunohistochemical analysis

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Abstract. The histological classification of gastric adenocarcinoma influences its prognostic outcomes and therapeutic strategies. Although fibroblast growth factor (FGF)10 is important for gastric morphogenesis, its use as a molecular marker of gland-forming differentiation pattern remains undefined. The present study examined 117 surgically resected gastric adenocarcinoma specimens using immunohistochemical analysis to evaluate the expression of FGF10 and FGF receptor 2 (FGFR2). Expression patterns in tumor cells and the surrounding stroma were assessed using a four-tier scale. Associations between marker expression and histological differentiation were analyzed by multivariable ordinal logistic regression, adjusting for age, human epidermal growth factor receptor 2 and epidermal growth factor receptor status. Elevated FGF10 expression was significantly associated with well-differentiated, gland-forming histological subtypes, particularly in moderately differentiated tubular adenocarcinoma [adjusted odds ratio (OR) in tumor cells: 1.749, 95% confidence interval (CI) 1.231-2.487, P=0.002; adjusted OR in stroma: 2.418, 95% CI 1.123-5.206, P=0.024]. Conversely, FGFR2 expression showed no association with differentiation pattern (adjusted OR: 0.908, 95% CI 0.452-1.824, P=0.788). Survival analysis revealed no significant relationship between FGF10 or FGFR2 expression level and overall patient survival [hazard ratio (HR) for FGF10 in tumor cells: 0.823, 95% CI 0.640-1.057, P=0.127; HR for FGF10 in stroma: 0.675, 95% CI 0.385-1.183, P=0.170; HR for FGFR2 in tumor cells: 1.080, 95% CI 0.559-2.085, P=0.819]. FGF10 may thus be a promising molecular marker of gland-forming differentiation pattern in gastric adenocarcinoma, offering valuable insights for refining its histopathological classification. These findings may contribute to the development of stratification biomarkers for personalized therapeutic approaches, particularly for the selection of molecular-targeted therapies. The absence of an association with overall survival, however, highlights the need for further investigations into the underlying mechanisms and their broader clinical significance.

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Abbreviations: FGF10, fibroblast growth factor 10; FGFR2, fibroblast growth factor receptor 2; CI, confidence interval; HER2, human epidermal growth factor receptor 2; pap, papillary adenocarcinoma; tub, tubular adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; por1, solid-type poorly differentiated adenocarcinoma; por2, non-solid-type poorly differentiated adenocarcinoma; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor; OS, overall survival; VIF, variance inflation factors; OR, odds ratio; HR, hazard ratio

Key words: gastric adenocarcinoma, FGF10, FGFR2, gland-forming differentiation pattern, IHC

Introduction

Gastric adenocarcinoma constitutes a significant global health burden, ranking fifth in terms of both incidence and mortality among malignancies worldwide (1). Despite established

treatment modalities, advanced gastric cancer maintains dismal prognostic outcomes (2), necessitating personalized therapeutic strategies based on molecular characterization.

The molecular landscape of gastric cancer includes established biomarkers, such as programmed death-ligand 1, human epidermal growth factor receptor 2 (HER2), and claudin 18.2, which are now utilized in clinical practice (3-6). Emerging markers, including mesenchymal-epithelial transition factor amplification, Dickkopf-related protein 1, and fibroblast growth factor (FGF) receptor 2 (FGFR2) amplification, can also expand the available therapeutic targets (7-9). Liquid biopsy via circulating tumor DNA and tumor-infiltrating T lymphocytes offer diagnostic and prognostic insights, supporting personalized treatment strategies (10,11).

Histopathologically, gastric adenocarcinoma is dichotomized into differentiated and undifferentiated subtypes with established prognostic implications (12-14). Differentiated adenocarcinomas encompass papillary adenocarcinoma (pap) and tubular adenocarcinoma (tub), and the latter is further subclassified into well-differentiated (tub1) and moderately differentiated (tub2) variants (15). Tub1 exhibits regular glandular structures with a favorable prognosis (14,15), whereas pap demonstrates papillary architecture with occasionally unfavorable outcomes (16,17).

Undifferentiated adenocarcinomas comprise poorly differentiated adenocarcinoma (por), signet-ring cell carcinoma (sig), and mucinous adenocarcinoma (muc) (15). Por is subdivided into solid (por1) and non-solid (por2) types, with por2 showing diffuse infiltration and a poorer prognosis compared with por1 (15,18). Sig exhibits characteristic intracytoplasmic mucin with peripheral nuclear displacement, whereas muc demonstrates abundant extracellular mucin production (15). The gland-forming differentiation pattern is generally associated with prognosis (14), although it can be modulated by invasion depth and metastatic parameters (19,20).

FGFR2 has emerged as a significant prognostic biomarker for gastric adenocarcinoma (9,21-24), with established therapeutic relevance (25-28). FGFR2 exists in two predominant isoforms, IIIb and IIIc, with FGFR2-IIIb reported to be more frequently overexpressed than FGFR2-IIIc in gastric adenocarcinoma (24). These isoforms have differential binding affinities for various FGFs, with FGF10 selectively activating FGFR2-IIIb (29-31).

FGF10 is a secreted FGF that mediates tissue homeostasis, repair, and morphogenesis throughout development and adult physiology (31). Notably, FGF10 contributes to gastric development and morphogenesis (32). In murine models, Fgf10 expression was localized to mesenchymal compartments subjacent to gastric glands, participating in mesenchymal-epithelial signaling (33). In addition, adult transgenic mice overexpressing Fgf10 demonstrated epithelial proliferation, mucus-secreting cell expansion, and parietal/chief cell reduction, suggesting that FGF10 may influence gastric epithelial differentiation beyond the embryonic stages (33). Notably, FGF10 amplification has been reported in human gastric cancer (34), and its expression level has been associated with a poor prognosis (35).

These findings suggest that the FGF10-FGFR2 axis may be involved in the differentiation of gastric adenocarcinoma, although its clinicopathological significance remains unclear. This study aimed to elucidate the association between FGF10-FGFR2 axis activation and the gland-forming differentiation pattern in human gastric adenocarcinoma. We analyzed FGF10 and FGFR2 expression in surgically resected specimens using immunohistochemistry (IHC), and evaluated the associations with clinicopathological parameters to identify the potential therapeutic and prognostic implications.

Materials and methods

Human samples. This retrospective, single-institution study utilized surgically resected gastric tumor specimens collected at Gifu University Hospital (Gifu, Japan) between June 1, 2000, and December 31, 2008. Clinical records were reviewed to collect information on patient background, treatment, and postoperative course. Cases with histological diagnoses other than adenocarcinoma (e.g., small cell carcinoma, undifferentiated carcinoma, or neuroendocrine tumor) were excluded from the analysis. Patients were also excluded if they were under 20 years old, had incomplete clinical data, exhibited inadequate immunohistochemical staining, or were deemed unsuitable for the study by the attending physician. Histological classification was primarily performed according to the 15th edition of the Japanese Classification of Gastric Carcinoma (15). In addition, tumors were further categorized into intestinal/indeterminate and diffuse types based on the WHO Classification of Digestive System Tumours, 5th edition (36), to facilitate international comparison. Tumor staging was based on the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control Tumor-Node-Metastasis classification of malignant tumors (37). This study was approved by the Institutional Review Board of Gifu University (approval no. 2024-253; approved on December 4, 2024) and conducted in accordance with the Declaration of Helsinki (2013 version). The study was publicly disclosed on the institution's website, and patients were given the opportunity to opt out of participation. The study design, data collection, analysis, and reporting were performed in accordance with the Reporting Recommendations for Tumor Marker Prognostic Studies guidelines (38).

Immunohistochemistry. All paraffin-embedded tissues were cut into 4-μm-thick serial sections, deparaffinized, and stained with hematoxylin and eosin or used for IHC. For IHC, the sections were placed in citrate buffer (10 mmol/l, pH 6.0) and autoclaved in a pressure chamber at 121˚C for 20 min to retrieve the antigens, followed by rinsing and blocking in 3% hydrogen peroxide in methanol for 10 min at room temperature to remove endogenous peroxidase. Non-specific binding sites were blocked in 0.01 M phosphate-buffered saline (pH 7.4) containing 2% bovine serum albumin (Wako Pure Chemical, Osaka, Japan) for 40 min at room temperature. The sections were then incubated overnight (16 h) at 4˚C in a humidified chamber with the following primary antibodies: FGF10 (rabbit polyclonal IgG, 1:500; Abcam, Cambridge, UK, #ab80064), FGFR2 (rabbit polyclonal IgG, 1:500; Abcam #ab10648), HER2 (rabbit monoclonal IgG, 1:400, Clone 4B5; Roche Diagnostics, Basel, Switzerland, #790-2991), epidermal growth factor receptor (EGFR) (rabbit monoclonal IgG, 1:200, Clone D38B1; Cell Signaling Technology, Danvers, MA, USA; #4267), CD44 (mouse monoclonal IgG, 1:50, Clone G44-26; BD Pharmingen, San Diego, CA, USA; #550392), and Ki67 (mouse monoclonal

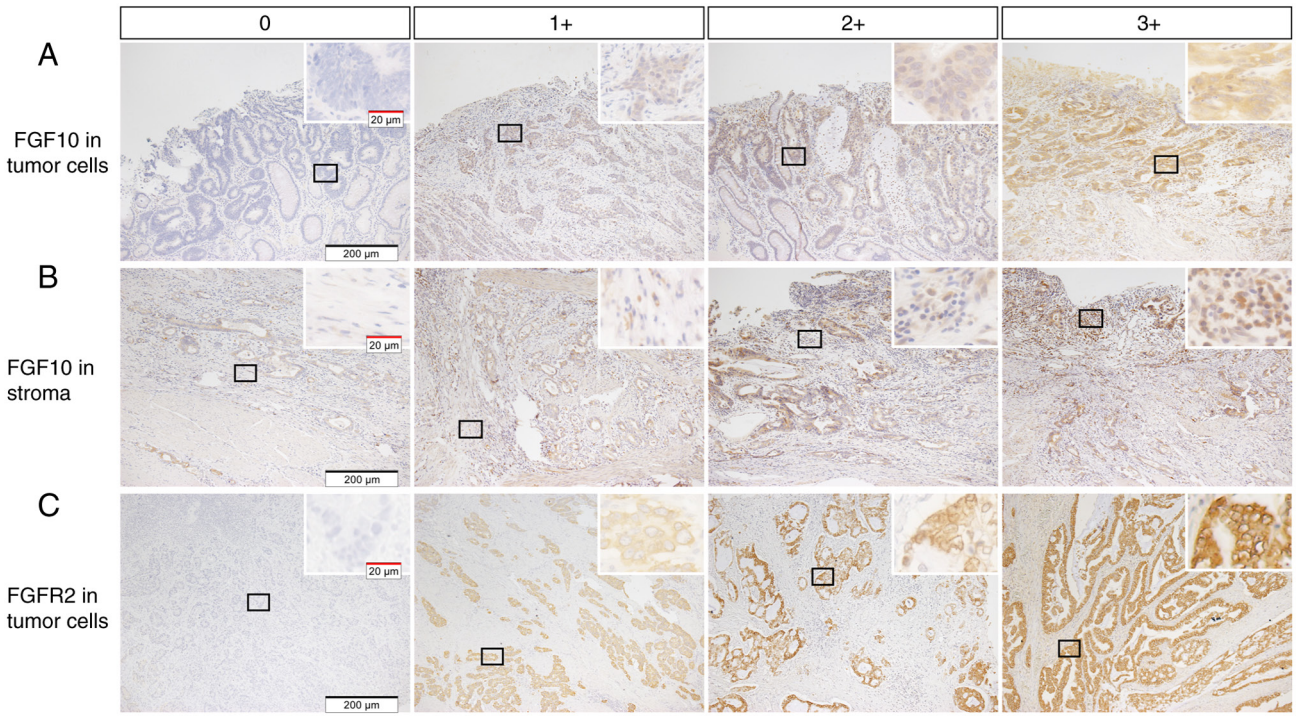

Figure 1. Expression of FGF10 and FGFR2 in gastric cancer tissues. Representative immunohistochemical images demonstrating the differential expression patterns of FGF10 and FGFR2 in gastric adenocarcinoma tissues. (A) FGF10 immunoreactivity in tumor cells (boxes), demonstrating heterogeneous cytoplasmic expression patterns graded as negative (0), weakly positive (1+), moderately positive (2+), and strongly positive (3+). (B) FGF10 expression in stromal compartments (boxes), exhibiting variable immunopositivity across the four-tier intensity scale. (C) FGFR2 immunolocalization in tumor cells (boxes), showing differential membrane and cytoplasmic staining intensities categorized according to the standardized four-tier grading system. (A) Tumor cells stained for FGF10, (C) tumor cells stained for FGFR2 and (B) stroma including immune cells stained for FGF10 are shown in the insets as higher magnification views of the boxed areas. Scale bars: black, 200 μm; red (insets), 20 μm. Tumor cells were identified as malignant epithelial cells, distinguished by their characteristic morphological features such as formation of abnormal glandular structures, nuclear atypia (enlargement, irregular contours, hyperchromasia), and cytoplasmic changes typical of gastric adenocarcinoma. Stromal cells were identified as the non-neoplastic cells within the connective tissue surrounding the tumor glands, including fibroblasts, inflammatory cells (such as lymphocytes and plasma cells), and vascular endothelial cells. FGF10, fibroblast growth factor 10; FGFR2, fibroblast growth factor receptor 2.

IgG, 1:100, Clone MIB-1; DAKO, Agilent Technologies, Santa Clara, CA, USA; #M7240). The next day, the sections were exposed to biotinylated goat anti-rabbit IgG (1:200; Vectastain Elite ABC kit; Vector Laboratories, Newark, CA, USA) for 60 min at room temperature, followed by incubation with avidin-biotin peroxidase complex (Vectastain Elite ABC kit; Vector Laboratories) to activate immunoreactivity. The bound complex was visualized using 3,3'-diaminobenzidine (Sigma, St. Louis, MO, USA) for 3-5 min under a microscope, to prevent overstaining. Finally, the sections were counterstained with hematoxylin for 2 min and dehydrated through graded alcohols. The specificity of the antibodies for IHC was validated using positive and negative controls. FGF10 expression was confirmed in plasma cells and FGFR2 expression in the glandular epithelium in normal intestinal tissue (positive control), and negative controls showed no notable immunoreactivity (Fig. S1). The normal intestinal tissue used for positive and negative controls was obtained from the archival tissue bank of Gifu University Hospital. These samples were non-neoplastic tissues sourced from surgical resections and were processed and paraffin-embedded in the same manner as the study specimens.

Histological assessment of tumor and stromal cells. The distinction between tumor and stromal cells was performed by two board-certified pathologists (K.K. and H.T.) based on standard histopathological assessment of cellular morphology in hematoxylin and eosin-stained sections. Tumor cells were identified as malignant epithelial cells characterized by features such as nuclear pleomorphism and the formation of abnormal glandular structures. Stromal cells were identified as the surrounding non-neoplastic connective tissue components, including fibroblasts, inflammatory cells, and vascular elements.

Immunohistochemical evaluation. The four-tier score was determined based on the visual assessment of staining intensity by two independent pathologists. The categories were defined as follows: 0 (negative) for no discernible immunoreactivity; 1+ (weakly positive) for faint, hard-to-see staining; 2+ (moderately positive) for clear, intermediate-intensity staining; and 3+ (strongly positive) for intense staining. Representative images illustrating these four tiers of staining intensity for FGF10 and FGFR2 are provided in Fig. 1.

For example, expression levels of FGF10 and FGFR2 in tumor cells and FGF10 in the stroma were scored using a four-tier scale: 0 (negative), 1+ (weakly positive), 2+ (moderately positive), and 3+ (strongly positive) (Fig. 1). HER2 expression was classified as negative (0 or 1+) or positive (2+ or 3+), EGFR was classified as negative (0) or positive (1+ to 3+), and CD44 was classified as negative (0), weakly positive (1+), or

strongly positive (2+). Immunohistochemical evaluations were independently performed by two board-certified pathologists (K.K. and H.T.) who were blinded to clinical outcomes and patient characteristics. Inter-observer agreement was assessed using weighted Cohen's κ coefficients, demonstrating substantial agreement for FGF10 tumor expression (κ=0.78), FGF10 stromal expression (κ=0.74), and FGFR2 tumor expression (κ=0.82). Discrepancies (6.8%) were resolved through collaborative microscopic review and consensus.

Statistical analysis. Patient characteristics were summarized using medians and ranges for continuous variables and frequencies and percentages for categorical variables. Baseline characteristics were compared between groups defined by FGF10 expression using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

The association between FGF10 expression (in tumor cells and stroma separately) or FGFR2 expression and differentiation status was evaluated using multivariable ordinal logistic regression models adjusting for patient age, HER2 status, and EGFR status, with differentiation status as an ordinal outcome (pap, tub1, tub2, por1, por2, and sig). Age is a fundamental demographic factor known to influence tumor biology and clinical outcomes, and HER2 and EGFR were included owing to their known roles as molecular markers in gastric cancer and their potential associations with histological differentiation (5,39). These variables were selected *a priori* based on biological plausibility and their relevance in previous gastric cancer studies. For the binary classification of differentiation (pap, tub1, tub2, and por1 as intestinal/indeterminate type; and por2 and sig as diffuse type), multivariable binary logistic regression models were employed with the same adjustment factors, and predicted probabilities from the multivariable models were plotted.

Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause, with data for surviving patients censored at the date of their last follow-up. OS curves were generated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Multivariable Cox proportional hazards regression models were used to assess the prognostic impacts of FGF10 and FGFR2 expression on OS, adjusting for patient age, sex, and tumor stage. Covariates included in the multivariable Cox proportional hazards regression models were selected based on their established clinical relevance and biological plausibility in relation to survival outcomes. FGF10 and FGFR2 were treated as continuous variables in all analyses.

Multicollinearity among covariates in all multivariable models was assessed using variance inflation factors (VIF). All statistical analyses were performed using R software version 4.3.2. A two-sided P-value <0.05 was considered to indicate a statistically significant difference for all analyses. A post hoc power analysis indicated that the sample size in this study provided 73% power to detect a medium effect size (Cohen's d=0.5) with a significance level of α=0.05.

In the predicted probability plots, solid lines represent the point estimate of the predicted probability and the gray shaded areas indicate the 95% confidence interval (CI), both derived from a logistic regression model. The estimates were calculated using maximum likelihood estimation. For ordinal logistic regression models, maximum likelihood estimation was used to estimate the variance of the regression coefficients under the proportional odds assumption, and the CIs for the adjusted ORs were constructed using the estimated variance. In the Cox proportional hazards model, the variance of the regression coefficients was estimated using the partial likelihood method, and the CIs for the hazard ratios were similarly constructed using the estimated variance. The CIs for Kaplan-Meier survival probabilities were calculated using Greenwood's formula.

Results

Patient characteristics and IHC analysis. A total of 120 surgically resected gastric tumor specimens were initially collected, of which 117 gastric adenocarcinoma specimens were included in the final analysis, after excluding three non-adenocarcinoma tumors (1 small cell carcinoma, 1 undifferentiated carcinoma, and 1 neuroendocrine tumor). FGF10 and FGFR2 expression levels in these 117 gastric adenocarcinoma tissues were evaluated by IHC (Fig. S2). The clinicopathological characteristics of the 117 patients are shown in Table I. The median age was 68 years (range: 31-92 years), with a male predominance (65.0%). Regarding tumor progression, most cases were T4 (66.7%) and N3 (41.0%). There were no cases of Stage I disease and Stage III was the most common (63.2%), followed by Stage II (23.1%) and Stage IV (13.7%). Notably, lymphatic invasion was present in 95.7% of cases and vascular invasion was observed in 82.1% of cases.

The expression patterns of FGF10 and FGFR2 in gastric adenocarcinoma tissues are shown in Fig. 1. FGF10 expression was observed in tumor cells in 72 of 117 cases (61.5%) and in the stroma in 75 cases (64.1%). Among the FGF10-positive cases in tumor cells, 44 cases (37.6%) showed weak expression (1+) and 28 cases (23.9%) showed high expression (≥2+; 13 cases 2+, 15 cases 3+). In the stromal component, 43 cases (36.8%) showed weak expression (1+) and 32 cases (27.4%) demonstrated high expression (≥2+; 25 cases 2+, 7 cases with 3+). FGF10 expression in the stromal compartment was comparable to its expression in tumor cells, suggesting the importance of paracrine signaling within the tumor microenvironment. FGFR2 expression in tumor cells was observed in 114 of 117 cases (97.4%), with 29 cases (24.8%) showing weak expression (1+) and 85 cases showing high expression (≥2+) (72.6%; 49 cases 2+, 36 cases 3+). This extremely high expression frequency suggested an important role of FGFR2 in gastric adenocarcinoma.

When patients were divided into two groups based on the presence or absence of FGF10 expression in tumor cells (negative: 0, positive: 1+ to 3+), significant differences were observed in histological subtype (P=0.041, Fisher's exact test) and MIB-1 index (P=0.012, Mann-Whitney U test). A detailed analysis of histological subtypes revealed that moderately differentiated tubular adenocarcinoma (tub2) had a higher tendency for FGF10-positivity (30/37 cases, 81.1%), whereas poorly differentiated adenocarcinoma (por2) had a more balanced distribution (22/43 cases, 51.2%). The MIB-1 index was significantly higher in the FGF10-positive group compared with the FGF10-negative group (median: 45.7 vs. 37.1, respectively), indicating that FGF10 expression was associated with increased tumor cell proliferation.

Table I. Clinicopathological characteristics of patients with gastric cancer included in the immunohistochemical analysis.

Characteristic	Total (n=117)	%	FGF10 in tumor cells		P-value	FGF10 in stroma		P-value	FGFR2 in tumor cells		P-value
			0 (n=45)	1+ to 3+ (n=72)		0 (n=42)	1+ to 3+ (n=75)		0 (n=3)	1+ to 3+ (n=114)	
Sex					>0.999			0.842			>0.999
Male	76	65.0	29	47		28	48		2	74	
Female	41	35.0	16	25		14	27		1	40	
Median age, years	68 (31-92)[a]		70 (32-92)[a]	67 (31-91)[a]	0.306	67.5 (32-92)[a]	69 (31-91)[a]	0.989	68 (68-70)[a]	68 (31-92)[a]	0.877
T grade					0.097			>0.999			0.089
T1	2	1.7	1	1		1	1		1	1	
T2	8	6.8	4	4		3	5		0	8	
T3	29	24.8	6	23		10	19		0	29	
T4	78	66.7	34	44		28	50		2	76	
N grade					0.719			0.609			0.866
N0	15	12.8	6	9		4	11		0	15	
N1	26	22.2	8	18		10	16		0	26	
N2	28	23.9	10	18		8	20		1	27	
N3	48	41.0	21	27		20	28		2	46	
M grade					0.408			0.263			0.359
M0	101	86.3	37	64		34	67		2	99	
M1	16	13.7	8	8		8	8		1	15	
CY					0.834			0.369			0.680
CY0	79	67.5	29	50		25	54		3	76	
CY1	11	9.4	5	6		5	6		0	11	
CYX	27	23.1	11	16		12	15		0	27	
TNM stage					0.620			0.303			0.471
I	0	0.0	0	0		0	0		0	0	
II	27	23.1	10	17		11	16		0	27	
III	74	63.2	27	47		23	51		2	72	
IV	16	13.7	8	8		8	8		1	15	
Ly					0.371			>0.999			0.124
Ly0	5	4.3	3	2		2	3		1	4	
Ly1	112	95.7	42	70		40	72		2	110	
V					0.335			>0.999			>0.999
V0	21	17.9	6	15		7	14		0	21	
V1	96	82.1	39	57		35	61		3	93	

Table I. Continued.

Characteristic	Total (n=117)	%	FGF10 in tumor cells		P-value	FGF10 in stroma		P-value	FGFR2 in tumor cells		P-value
			0 (n=45)	1+ to 3+ (n=72)		0 (n=42)	1+ to 3+ (n=75)		0 (n=3)	1+ to 3+ (n=114)	
Differentiation					0.041[b]			0.133			0.505
pap	1	0.9	0	1		0	1		0	1	
tub1	6	5.1	3	3		0	6		0	6	
tub2	37	31.6	7	30		12	25		2	35	
por1	21	17.9	9	12		9	12		1	20	
por2	43	36.8	21	22		15	28		0	43	
sig	9	7.7	5	4		6	3		0	9	
HER2					0.573			0.394			0.340
Negative	102	87.2	38	64		35	67		2	100	
Positive	15	12.8	7	8		7	8		1	14	
EGFR					0.260			0.184			0.244
Negative	57	48.7	25	32		24	33		0	57	
Positive	60	51.3	20	40		18	42		3	57	
cMET					0.191			0.512			>0.999
Negative	30	25.6	15	15		9	21		1	29	
Positive	87	74.4	30	57		33	54		2	85	
CD44					0.202			0.828			0.564
Negative	31	26.5	15	16		12	19		0	31	
Positive	86	73.5	30	56		30	56		3	83	
MIB-1 index, median	42.7 (4.3-137.9)[a]		37.1 (4.3-114.0)[a]	45.7 (7.4-137.9)[a]	0.012[b]	41.4 (4.3-137.9)[a]	44.5 (4.5-98.3)[a]	0.656	34.2 (33.7-55.6)[a]	42.9 (4.3-137.9)[a]	0.924

[a]Median (range); [b]P<0.05 was considered statistically significant. FGF10, fibroblast growth factor 10; FGFR2, fibroblast growth factor receptor 2; Ly, lymphatic invasion; V, venous invasion; pap, papillary adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por1, solid-type poorly differentiated adenocarcinoma; por2, non-solid-type poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; CY, cytology.

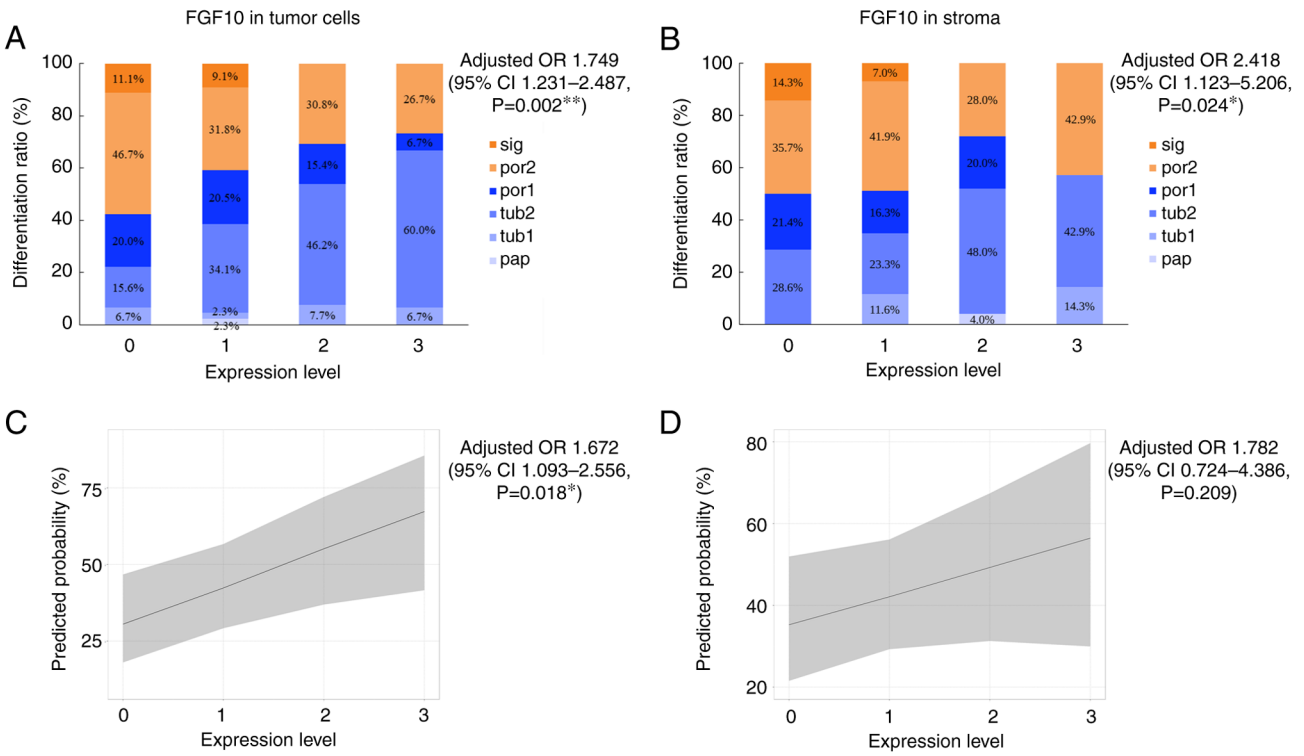

Figure 2. Association between FGF10 expression in tumor cells and stroma and histological subtype. (A) Association between FGF10 expression levels in tumor cells and histological subtypes (pap, tub1, tub2, por1, por2, sig). (B) Association between FGF10 expression levels in stroma and histological subtypes (pap, tub1, tub2, por1, por2, sig). (C) Predicted probability plot showing the association between FGF10 expression levels in tumor cells and histological tumor classifications. (D) Predicted probability plot showing the association between FGF10 expression levels in stroma and histological tumor classifications. In the predicted probability plots, pap, tub1, tub2, and por1 were classified as intestinal/indeterminate type, and por2 and sig were classified as diffuse type. Solid lines represent the point estimate of the predicted probability and gray shaded areas indicate the 95% CIs, both derived from a logistic regression model. Estimates calculated using maximum likelihood estimation. *P<0.05, **P<0.01. FGF10, fibroblast growth factor 10; pap, papillary adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por1, solid-type poorly differentiated adenocarcinoma; por2, non-solid-type poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; OR, odds ratio; CI, confidence interval.

FGF10 and FGFR2 expression in gastric adenocarcinoma and its association with gland-forming differentiation pattern and survival. We clarified the relationship between FGF10 and FGFR2 expression levels and the histopathological gland-forming differentiation pattern in gastric adenocarcinoma using a multivariable ordinal logistic regression model. Expression levels of FGF10 showed significant positive associations with histological classification in tumor cells and stromal tissue (Fig. 2). Multivariable ordinal logistic regression analysis, adjusted for age, HER2 status, and EGFR expression, revealed adjusted ORs of 1.749 (95% CI 1.231-2.487, P=0.002) for FGF10 expression in tumor cells (Fig. 2A) and 2.418 (95% CI 1.123-5.206, P=0.024) for stromal FGF10 expression (Fig. 2B). These findings indicate that increased FGF10 expression was associated with a higher probability of well-differentiated histological subtypes. This association was consistently observed in tumor cells and stromal tissue, with stromal FGF10 expression demonstrating a stronger association (higher adjusted OR). Subsequent analysis of FGFR2 found no significant association between FGFR2 expression levels and differentiation (P=0.788) (Fig. 3A).

A predicted probability plot is shown for the classification of pap, tub1, tub2, and por1 as intestinal/indeterminate type and por2 and sig as diffuse type. FGF10 expression in tumor cells had an adjusted OR in multivariable binary logistic regression analysis of 1.672 (95% CI 1.093-2.556, P=0.018), demonstrating a significant association with histological classification (Fig. 2C); however, FGF10 expression in the stroma (adjusted OR=1.782, 95% CI 0.724-4.386, P=0.209) (Fig. 2D) and FGFR2 expression in tumor cells (adjusted OR=0.831, 95% CI 0.31-2.227, P=0.713) showed no significant associations with histological classification (Fig. 3B). These results suggest that higher FGF10 expression levels were more strongly associated with the intestinal/indeterminate type. Furthermore, the association between FGF10 expression and histological classification was stronger in tumor cells than in the stroma.

Survival analysis revealed no significant associations between OS and the expression levels of FGF10 (in tumor cells and stroma) and FGFR2. In addition, Kaplan-Meier survival curve analysis (Fig. 4) showed no significant differences in survival rates in relation to the expression levels of each marker (log-rank test: FGF10 in tumor cells, P=0.596; FGF10 in stroma, P=0.806; FGFR2 in tumor cells, P=0.594). Multivariable Cox proportional hazards regression analysis, adjusted for age, sex, and disease stage, demonstrated no significant associations for FGF10 expression in tumor cells [hazard ratio (HR) 0.823, 95% CI 0.640-1.057, P=0.127], stromal FGF10 expression (HR 0.675, 95% CI 0.385-1.183, P=0.170), or FGFR2 expression in tumor cells (HR 1.080, 95% CI 0.559-2.085, P=0.819).

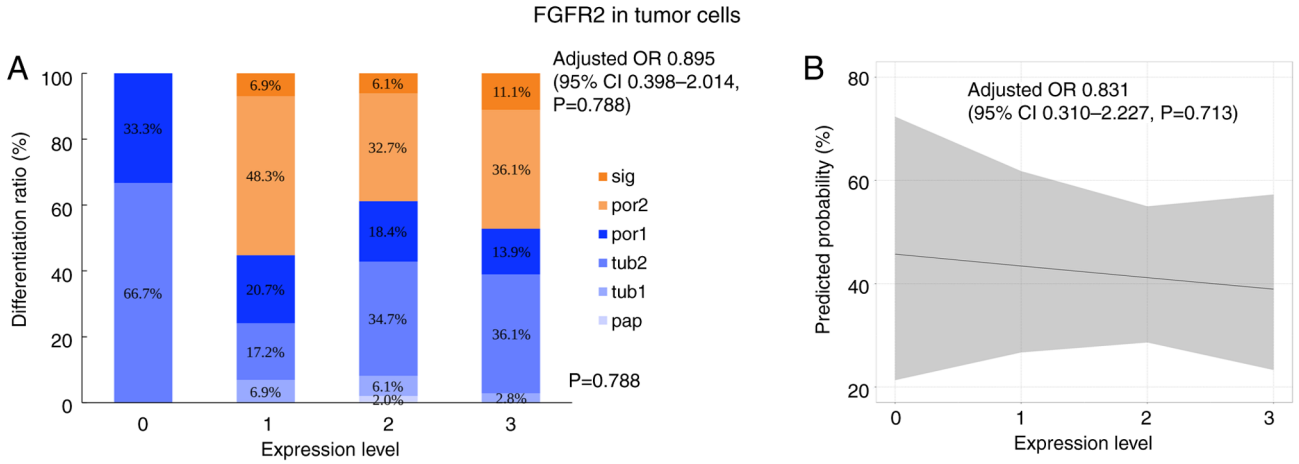

Figure 3. Association between FGFR2 expression in tumor cells and histological subtype. (A) Association between FGFR2 expression levels in tumor cells and histological subtypes (pap, tub1, tub2, por1, por2, sig). (B) Predicted probability plot showing the association between FGFR2 expression levels in tumor cells and histological tumor classifications. In the predicted probability plots, pap, tub1, tub2, and por1 were classified as intestinal/indeterminate type, and por2 and sig were classified as diffuse type. Solid lines represent the point estimate of the predicted probability and gray shaded areas indicate the 95% CIs, both derived from a logistic regression model. Estimates calculated using maximum likelihood estimation. FGFR2, fibroblast growth factor receptor 2; pap, papillary adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; por1, solid-type poorly differentiated adenocarcinoma; por2, non-solid-type poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; CI, confidence interval; OR, odds ratio.

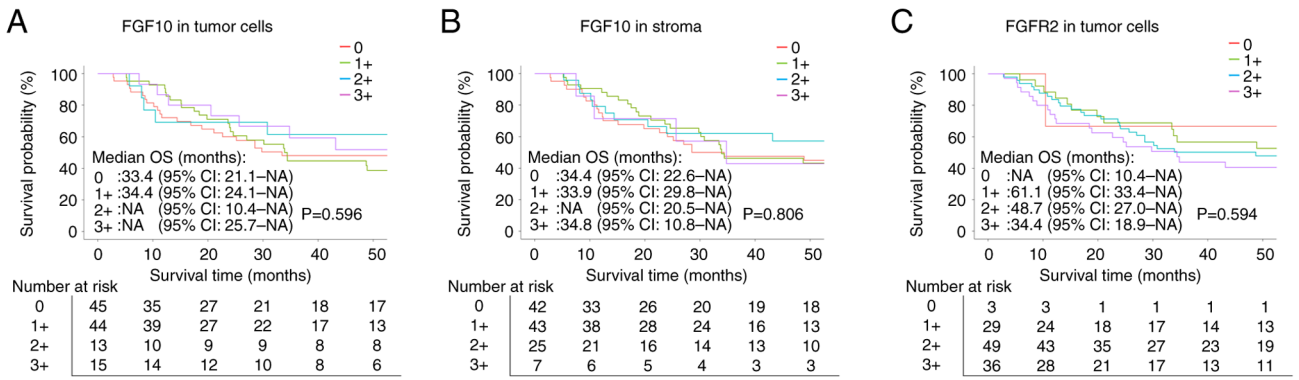

Figure 4. Association between FGF10 and FGFR2 expression and postoperative OS. OS was analyzed according to the four-tier expression scores (0, 1+, 2+, 3+) for (A) FGF10 in tumor cells, (B) FGF10 in stroma, and (C) FGFR2 in tumor cells. Kaplan-Meier curves are presented without shaded CIs for visual clarity, but corresponding 95% CI values are shown numerically. FGF10, fibroblast growth factor 10; FGFR2, fibroblast growth factor receptor 2; OS, overall survival; CI, confidence interval; NA, not available.

Assessment of multicollinearity indicated that all VIF values were close to 1.0 across all multivariable regression models, indicating no evidence of multicollinearity among the included covariates.

Discussion

FGF10 expression levels in tumor cells and the stroma were significantly associated with gland-forming differentiation patterns, with higher FGF10 expression levels associated with a higher degree of differentiation. In contrast, FGFR2 expression levels were not associated with differentiation, suggesting that FGF10 may play a specific role in gastric adenocarcinoma differentiation.

The mechanism by which the FGF10-FGFR2 signaling pathway contributes to the gland-forming differentiation pattern remains unclear. FGF10 has a critical role in organogenesis during embryonic development, and the findings of this study suggest that its function during development may be partially recapitulated in adult gastric cancer tissues. Notably, FGF10 may promote glandular formation and contribute to the maintenance of differentiation via epithelial-mesenchymal interactions (31). FGF10 has been reported to promote the maintenance of gastric epithelial progenitor cells and gland-forming differentiation pattern by binding to FGFR2b through epithelial-mesenchymal interactions and activating signaling pathways such as MAPK/ERK and PI3K/AKT (32,40). Moreover, FGF10 cooperates with the Notch and Wnt pathways to determine region-specific differentiation patterns through transcriptional regulation of factors such as Sox2 and GATA4 (32,41). FGF10 stimulation also induces downregulation of E-cadherin expression and induction of epithelial-mesenchymal transition-related molecules, thereby participating in cell adhesion and morphogenesis (42). FGF10 is considered to influence glandular formation and tumor differentiation grade via these molecular

mechanisms (32,43). Conversely, excessive activation of the FGF10-FGFR2b pathway has been suggested to enhance tumor cell proliferation and invasive capacity, highlighting its importance as a therapeutic target (43,44). FGF10 is also used to induce the differentiation of gastric epithelial cells in organoid culture systems, with potential for applications in regenerative medicine (43). Further elucidation of the molecular networks centered on FGF10 is expected to contribute to the development of diagnosis and personalized treatment for gastric adenocarcinoma (40,43).

It is noteworthy that, although FGF10 expression was associated with tumor differentiation, FGFR2 expression showed no such association. This finding suggests that FGF10 may act through receptors other than FGFR2, or that the activation state of FGFR2 is more critical than its expression level. Speer *et al* (33) reported that FGF10-FGFR2b signaling was dispensable for maintaining epithelial proliferation and differentiation in gastric tissues from adult mice under homeostatic conditions (33). The FGF10-FGFR2 signaling pathway, however, has been shown to play a major role in tumor formation in several other cancer types (44). A more detailed analysis of this pathway in gastric cancer is therefore warranted.

This study found no significant association between FGF10 or FGFR2 expression and OS, suggesting that these molecules may not serve as direct prognostic factors. Sun *et al* reported that FGF10 expression was associated with prognosis in patients with gastric adenocarcinoma; they found no association between FGF10 expression and tumor differentiation, but did identify significant associations with lymph node metastasis and distant metastasis (35). Several methodological differences may account for this apparent discordance. First, our cohort comprised predominantly patients with advanced-stage disease (Stage III-IV: 76.9%) compared with Sun *et al*'s study, which had a higher proportion of early-stage cases (Stage I-II: 45.3%), potentially masking subtle molecular prognostic influences in advanced disease states. Second, we employed a polyclonal antibody (Abcam ab80064) targeting amino acids 50-150 of human FGF10, whereas Sun *et al* are presumed to have utilized a monoclonal antibody against the C-terminus, which could result in differential detection of FGF10 isoforms or post-translational modifications. Finally, our multivariable Cox regression analysis incorporated comprehensive adjustment for established prognostic factors (age, sex, tumor stage), which may attenuate apparent associations observed in less rigorously adjusted analyses and provide a more precise estimate of independent prognostic impact.

Emerging evidence demonstrates that FGF10-FGFR2 signaling exhibits distinct, tissue-specific oncogenic functions across different cancer types. The FGF10-FGFR2 axis drives context-dependent oncogenic programs: it induces epithelial-mesenchymal transition and invasion in pancreatic ductal adenocarcinoma (45), while promoting invasion and a poor prognosis in gastric adenocarcinoma (35). Paracrine FGF10 enhances androgen receptor signaling and multifocal tumor formation in prostate adenocarcinoma, primarily via FGFR1, contrasting with gastric signaling, which operates independently of hormonal cues (46). Colorectal cancer cells co-express FGF10 and epithelial FGFR2-IIIb, enabling autocrine proliferation distinct from gastric mesenchymal-epithelial paracrine interactions (47). These organ-specific functions reflect unique embryological origins and FGFR2 isoform expression patterns, highlighting the need for tissue-adapted FGF10-FGFR2 targeting strategies (31).

This study had several limitations. The relatively small sample size of 117 patients and potentially limited observation period, evidenced by wide CIs in the survival analyses, may have affected the generalizability of the results. In addition, the study was a retrospective study conducted at a single institution, and the study population was thus limited to patients from Gifu University Hospital, and careful consideration is therefore needed when generalizing the results. Although the sample size of 117 patients was sufficient for certain analyses, a large-scale, multicenter collaborative study is needed to provide more reliable and generalizable findings. IHC scoring was based on visual assessment of staining intensity by two pathologists using a four-tier scale. While discrepancies were resolved by consensus and inter-observer agreement was substantial, the inherent subjectivity of this method may have introduced variability. Furthermore, although this study demonstrated an association between FGF10 and FGFR2 expression and gland-forming differentiation patterns, we did not conduct molecular biological analyses to elucidate the underlying mechanisms. Additionally, this study did not evaluate the relationship between FGF10-FGFR2 signaling and other key molecular markers or genetic mutations involved in gastric cancer progression, such as p53 and E-cadherin. As a result, the relative significance of the FGF10-FGFR2 signaling pathway in gastric cancer remains incompletely understood. Considering these limitations, the findings of this study can be expanded further and refined.

In conclusion, FGF10 expression is significantly associated with gland-forming differentiation patterns in gastric adenocarcinoma, contributing to molecular subtype characterization, despite a lack of prognostic significance. Future investigations into FGF10-FGFR2 signaling mechanisms may reveal novel therapeutic targets.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HT conceptualized the study. SF, DW and HT developed the methodology. DW performed the formal analysis. SF, ME, RY, KM, HH, MK, KK and HT conducted the investigation and data acquisition. KK and HT provided technical assistance. SF, HT, MF, IY, YS, RA, JYT, AH and NM contributed to data collection, organization and interpretation. SF, KK and HT confirm the authenticity of all the raw data. SF and HT wrote the manuscript and performed the subsequent review and editing. KK, DW, ME, RY, KM, HH, MK, MF, IY, YS, RA, JYT, AH and NM contributed to the critical review and revision of the manuscript. AH and NM supervised the study. AH provided research resources and HT acquired the funding. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Gifu University (approval no. 2024-253, approved on December 4, 2024) and conducted in accordance with The Declaration of Helsinki. The need for informed consent was waived due to the retrospective design, and the study was disclosed on the institutional website with an opt-out option.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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