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High CDX2 Expression Predicts a Favorable Prognosis in Patients with Early-Stage Gastric Adenocarcinoma

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Abstract

Background: Caudal-type homeobox transcription factor 2 (CDX2) is an important molecule for Gastric Intestinal Metaplasia (GIM). Experiments have shown that ectopic expression of CDX2 in normal gastric tissue induces GIM, which gradually develops into Gastric Adenocarcinoma (GAC).

Objectives: This study aimed to investigate the correlation between CDX2 expression and the prognosis of GAC patients with different clinical features, especially, to indicate whether high CDX2 expression predicts a favorable prognosis in patients with early-stage diffuse type gastric adenocarcinoma.

Methods: A total of 619 gastric tissues from GAC patients were analyzed. Tissue microarrays and immunohistochemistry were used to investigate the expression and prognostic significance of CDX2 in GAC. The associations' between CDX2 expression, clinicopathological parameters and prognosis were evaluated.

Results: CDX2 expression was higher in early-stage GAC tissues than in other tissues. High CDX2 expression positively correlated with gender (P<0.001), Lauren classification (P=0.024), depth of invasion (P<0.001), TNM stage (P<0.001), tumor site (P=0.037) and perineural invasion (P=0.002). Patients with high CDX2 expression had better overall survival (OS; P=0.033) and disease-free survival (DFS; P=0.031) than patients with lower expression. In T1 GAC, high CDX2 expression was also associated with better OS (P=0.033) and DFS (P=0.020). Multivariate analysis confirmed that high CDX2 expression was an independent prognostic factor of OS and DFS in GAC patients (P<0.05).

Conclusion: High CDX2 expression correlates with better OS and DFS and can serve as an independent prognostic marker in GAC, especially in the early stage.

Keywords: Gastric adenocarcinoma; CDX2; Immunohistochemistry; Clinical pathology; Prognosis

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Introduction

Gastric Cancer (GC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide. In 2018 alone, more than 1,000,000 patients were diagnosed with GC, and about 783,000 died from the disease [1]. The occurrence and development of GC constitute a multistage process, with a variety of molecular biomarkers involved [2], including inactivation of cancer-suppressing genes, activation of primary cancer genes, and epigenetics regulation and so on [3-5]. Gastric Adenocarcinoma (GAC) is the most common type of GC. Because of its significant heterogeneity in histopathological features, tumor invasiveness and patient responses to treatment, its pathogenesis is not fully understood [6,7].

Caudal-type homeobox transcription factor 2 (CDX2) is a member of the homeobox gene family that was first reported in Drosophila [8]. The CDX2 gene is located on chromosome 13q12-13, which has a length of 22 kb to 23 kb and includes three exons and two introns [9]. CDX2 plays an important role in early embryonic development, during which it is required for the growth of posterior embryonic tissues until the axis is fully extended [10,11]. CDX2 is expressed in human intestinal epithelial cells and participates in the regulation of the proliferation and differentiation of intestinal epithelial cells and the promoter activity of various intestine-related genes [12,13], which

is essential for maintaining intestinal stability [14,15]. The expression of CDX2 in normal intestinal tissues varies, gradually increasing from the duodenum to the proximal colon, gradually decreasing from the ascending colon and reaching its highest level in the ileum. CDX2 is not expressed in normal gastric and esophagus epithelial cells. Abnormal expression of CDX2 can lead to various diseases. CDX2 overexpression in the intestine can lead to over-maturation of intestinal epithelial cells [16], where a slow expression can cause Meckel's diverticula [17]. Ectopic expression can cause Gastric Intestinal Metaplasia (GIM), Barrett's esophagus and acute myeloid and lymphoblastic leukemia [18-22].

This study presents the role of CDX2 and other clinicopathological characteristics among gastric adenocarcinoma patients. This study aimed to evaluate the expression of CDX2 in GAC patients and to determine the relationships between CDX2 expression, clinicopathological characteristics and GAC prognosis.

Materials and Methods

Patients

Tumor tissues from 619 GAC patients collected between January 2007 and February 2015 were obtained from the tissue bank of Sun Yat-sen University. Patients who had received neoadjuvant chemotherapy or chemoradiotherapy before surgical resection were excluded from the study. Comprehensive clinicopathological data are listed in Table 1.

Ethical considerations

This study was approved by the Clinical Ethics Review Committee of Sun Yat-sen University. Written informed consent was obtained from all patients.

Immunohistochemistry staining and evaluation

Tissue Microarrays (TMAs) were performed as we described previously [23]. To detect CDX2 expression, rabbit polyclonal antibody against CDX2 was used (1:100 dilution). The TMAs were sectioned at 4-μm intervals. The slides were first incubated at 60°C for 3 h and then deparaffinated in xylene and rehydrated in graded alcohol. To increase immunoreactivity, microwave antigen retrieval was performed in citrate buffer (pH 6.0) and left to cool at room temperature for 30 min. The sections were subsequently incubated in hydrogen peroxide for 10 min and then in bovine serum albumin for 10 min. Subsequently, anti-CDX2 antibody was added to the sections and incubated at 4°C in a humidified chamber overnight. Afterwards, the sections were treated with a secondary antibody (immunoglobulin G) at room temperature for 30 min, followed by 3,3'-diaminobenzidinestaining until brown granules were visible. Counterstaining was performed using hematoxylin at room

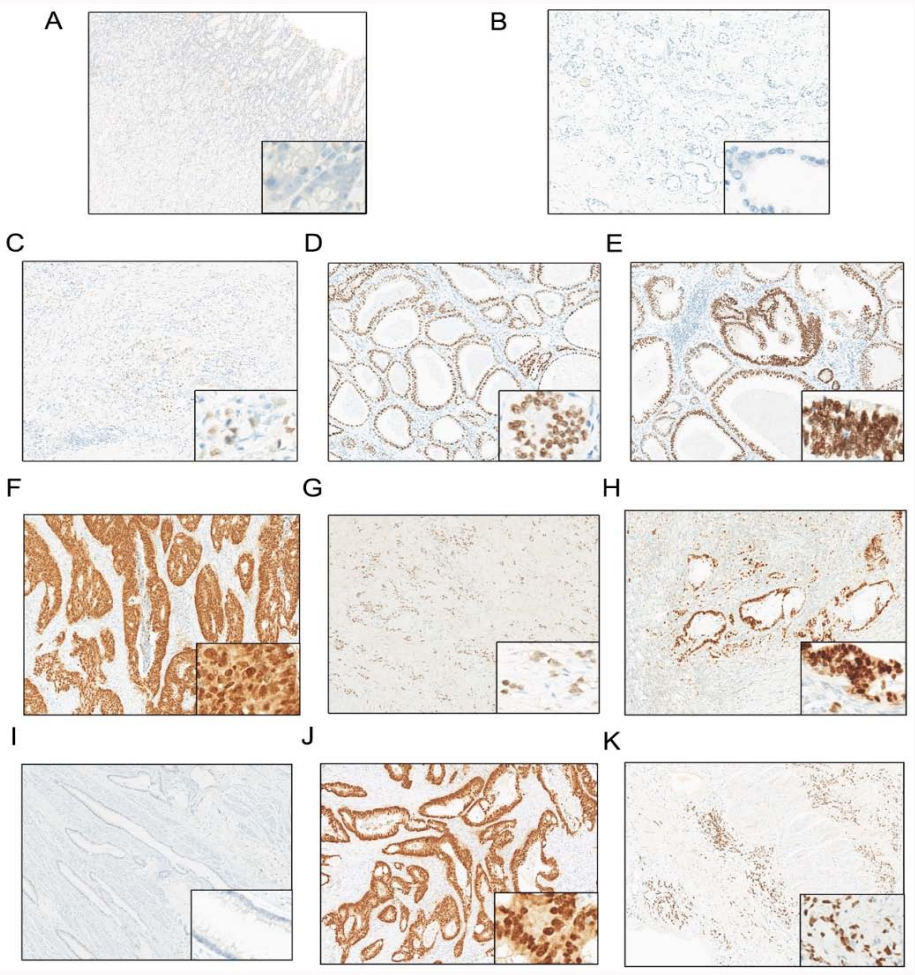

Figure 1: CDX2 expression in normal stomach tissue and GAC tissue (immunohistochemistry staining; x100 and x600). (A) Normal stomach tissue. CDX2 expression in GAC: (B) score 0, (C) score 1, (D) score 2 and (E) score 3. (F) Intestinal-type GAC. (G) Diffuse-type GAC. (H) Mixed-type GAC. (I) Well-differentiated GAC. (J) Moderately differentiated GAC. (K) Poorly differentiated GAC.

Table 1: Patient characteristics.

Variable	Case (n, %)	CDX2-Negative (n, %)	CDX2-Positive (n, %)	*P*-value
Age (yrs)				
≤ 60	271 (43.8)	101 (37.3)	170 (62.7)	0.201
>60	348 (56.2)	112 (32.2)	236 (67.8)	
Gender				
Male	421 (68.0)	169 (40.1)	252 (59.9)	**<0.001**
Female	198 (32.0)	44 (22.2)	154 (77.8)	
Lauren classification				
Intestinal type	181 (29.2)	50 (27.6)	131 (72.4)	**0.024**
Diffuse type	307 (49.6)	121 (39.4)	186 (60.6)	
Mixed type	131 (21.2)	42 (32.1)	89 (67.9)	
TNM stage				
I	113 (18.3)	21 (18.6)	92 (81.4)	**0.001**
II	193 (31.2)	73 (37.8)	120 (62.2)	
III	259 (41.8)	100 (38.6)	159 (61.4)	
IV	54 (8.7)	19 (35.2)	35 (64.8)	
T stage				
T1	95 (15.3)	16 (16.8)	79 (83.2)	**0.001**
T2	62 (10.0)	20 (32.3)	42 (67.7)	
T3	343 (55.4)	129 (37.8)	214 (62.4)	
T4	119 (19.2)	48 (40.3)	71 (59.7)	
N stage				0.15
N0	213 (34.4)	67 (31.5)	146 (68.5)	0.15
N1	105 (17.0)	31 (29.5)	74 (70.5)	
N2	113 (18.2)	48 (42.5))	65 (57.5)	
N3	188 (30.4)	67 (35.6)	121 (64.4)	
M stage				
M0	566 (91.4)	194 (34.3)	372 (65.7)	0.88
M1	53 (8.6)	19 (35.8)	34 (64.2)	
Differentiation				
Well	27 (4.4)	7 (25.9)	20 (74.1)	0.069
Moderate	142 (22.9)	39 (27.5)	103 (72.5)	
Poor	450 (72.7)	167 (37.1)	283 (62.9)	
Lymphovascular Invasion				
No	430 (69.5)	153 (35.6)	277 (64.4)	0.408
Yes	189 (30.5)	60 (31.7)	129 (68.3)	
Perineural invasion				
No	352 (56.9)	103 (29.3)	249 (70.7)	**0.002**
Yes	267 (43.1)	110 (41.2)	157 (58.8)	
Location				
Upper	190 (30.7)	68 (35.8)	122 (64.2)	**0.037**
Middle	93 (15.0)	40 (43.0)	53 (57.0)	
Lower	326 (52.7)	99 (30.4)	227 (69.6)	
Whole	10 (1.6)	6 (60.0)	4 (40.0)	

temperature for 2 min. A placebo antibody was used as a negative control.

Semi-quantitative analysis was performed to evaluate the expression of CDX2. Immunohistochemistry (IHC) staining in the nuclei of GAC tumor cells was scored according to the intensity and extent by two pathologists independently. The staining intensity was scored as follows: 0, negative; 1, weak; 2, moderate; and 3, high. The extent was scored as follows: 0, 1% to 5%; 1, 6% to 25%; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100%. The overall intensity plus extent scores were calculated, with 0-1 considered negative and 2-12 considered positive.

Clinical outcome assessments

After surgical resection, the patients were followed up every three months during the first two years and every six months thereafter. Overall Survival (OS) was defined as the time from surgery to the date or when censored at the latest date if the patient was still alive. Disease-Free Survival (DFS) was defined as the time from surgery to the date of local failure/distant metastasis or to the date of death or when censored at the latest date.

Statistical analysis

Statistical analysis was performed using IBMSPSS Statistics version 22.0 (IBM, Armonk, NY, USA). The correlations between CDX2 and the clinicopathological features of GAC patients were analyzed using the chi-square test. Survival curves were obtained using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards regression model was used to identify independent prognostic factors. P-values of less than 0.05 were considered statistically significant.

Results

Demographic data

Of the 619 patients, 421 (68%) were male, and 198 (32%) were female. Their ages ranged from 24 to 87 years, with 56.2% being older than 60 years. The detailed clinicopathological data is listed in Table 1.

CDX2 expression and its relationships with the clinicopathological characteristics of GAC patients

CDX2 was not expressed in normal stomach tissue but was expressed in the nuclei and cytoplasm of GAC cells (Figure 1A). The CDX2 expression scores (0 to 3) are shown in Figure 1. CDX2 was expressed in 406 (65.6%) GAC patients. The chi-square test showed that CDX2 expression was significantly associated with gender (P<0.001), Lauren classification (P=0.024), TNM stage (P=0.001), T stage (P=0.001), perineural invasion (P=0.002) and tumor location (P=0.037). No significant associations were observed between CDX2 expression and other clinicopathological features, such as age, N stage, M stage, differentiation and lymphovascular invasion (Table 1).

Regarding the T stage, CDX2 expression was higher in T1 than in the other stages. No significant differences were detected between T2, T3 and T4. For further analysis, the T1 stage was compared to the T2-T4 stages collectively. According to the Lauren classification, CDX2 expression was higher in T1 than in T2-T4 in both diffuse-type (P=0.024) and intestinal-type GAC (P=0.009; Table 2).

Multivariate Cox regression analysis of OS and DFS prognostic factors in GAC patients

Multivariate OS and DFS analysis indicated that negative CDX2 expression (P=0.033), distant metastasis (P<0.001), perineural invasion (P=0.003) and lymph node metastasis (P<0.001) were poor OS predictors. Negative CDX2 expression (P=0.031), lymphovascular invasion (P=0.020), perineural invasion (P<0.001) and lymph node

Table 2: CDX2 expression of GAC patients in different Lauren types and different T stages.

Lauren classification	Case (n)	CDX2 Positive		*P*-value
		T1 stage (n, %)	T2 to T4 stage (n, %)	
Intestinal type	181	26 (89.7)	105 (69.1)	**0.024**
Diffuse type	307	36 (78.3)	150 (57.5)	**0.009**
Mixed type	131	17 (85.0)	72 (64.9)	0.117

Table 3: Multivariate cox regression analysis of the prognostic factors for OS and DFS of GAC patients.

		OS			DFS		
		Odd ratio	95% CI	*p*-value	Odd ratio	95% CI	*p*-value
CDX2	Negative *vs.* Positive	1.35	1.025-1.777	0.033 <0.001	1.322	1.026-1.703	0.031 <0.001
N stage	N1 *vs.* N0	1.456	0.856-2.476	0.166	1.22	0.766-1.941	0.402
	N2 *vs.* N0	2.479	1.590-3.865	<0.001	2.237	1.511-3.312	<0.001
	N3 *vs.* N0	3.892	2.589-5.851	<0.001	3.47	2.409-4.998	<0.001
M stage	M1 *vs.* M0	3.514	2.488-4.964	<0.001			
Perineural invasion	Absent *vs.* Present	1.537	1.154-2.046	0.003	1.689	1.304-2.189	<0.001
Lymphovascular invasion	Absent *vs.* Present			NS	1.369	1.050-1.784	0.02

OS: Overall Survival; DFS: Disease Free Survival

metastasis (P<0.001) were poor DFS predictors (Table 3).

Correlations between CDX2 expression and OS and DFS in GAC patients

The patients were divided into a positive CDX2 expression group (CDX2+) and a negative CDX2 expression group (CDX2-). The median OS was significantly longer in the CDX2+ group (28.5 months) than in the CDX2- group (27 months; P=0.006; Figure 2A). Likewise, the median DFS was significantly longer in the CDX2+ group (25 months) than in the CDX2- group (24 months; P=0.019; Figure 2B).

The patient groups were subdivided according to the Lauren classification. In diffuse-type GAC, the median OS was significantly longer in the CDX2+ group (28 months) than in the CDX2- group (24 months; P=0.015). The intestinal and mixed types showed no significant differences in OS between the two groups. The three types showed no significant differences in DFS between the two groups (Figures 2C-2H).

In terms of T stages, in T1, the median OS was significantly longer in the CDX2+ group (46 months) than in the CDX2- group (36 months; P=0.033). Likewise, the median DFS was significantly longer in the CDX2+ group (46 months) than in the CDX2- group (35 months; P=0.020). Conversely, T2, T3 and T4 showed no significant differences in OS or DFS between the two groups (Figure 3A, 3B).

In terms of TNM stages, in stage I, the median OS was significantly longer in the CDX2+ group (36 months) than in the CDX2- group (32 months; P=0.003). Likewise, the median DFS was significantly longer in the CDX2+ group (36 months) than in the CDX2- group (32 months; P=0.002). In contrast, stages II, III and IV showed no significant differences in OS or DFS between the two groups (Figure 3C, 3D).

In terms of gender, among female patients, the median OS was significantly longer in the CDX2+ group (25 months) than in the CDX2- group (24 months; P=0.014). Conversely, there was no significant difference in DFS between the two groups. Among male patients, there were no significant differences in OS or DFS between the two groups (Figure 4A).

In terms of perineural invasion, among patients without perineural invasion, the median OS was significantly longer in the CDX2+ group (31 months) than in the CDX2- group (24 months;

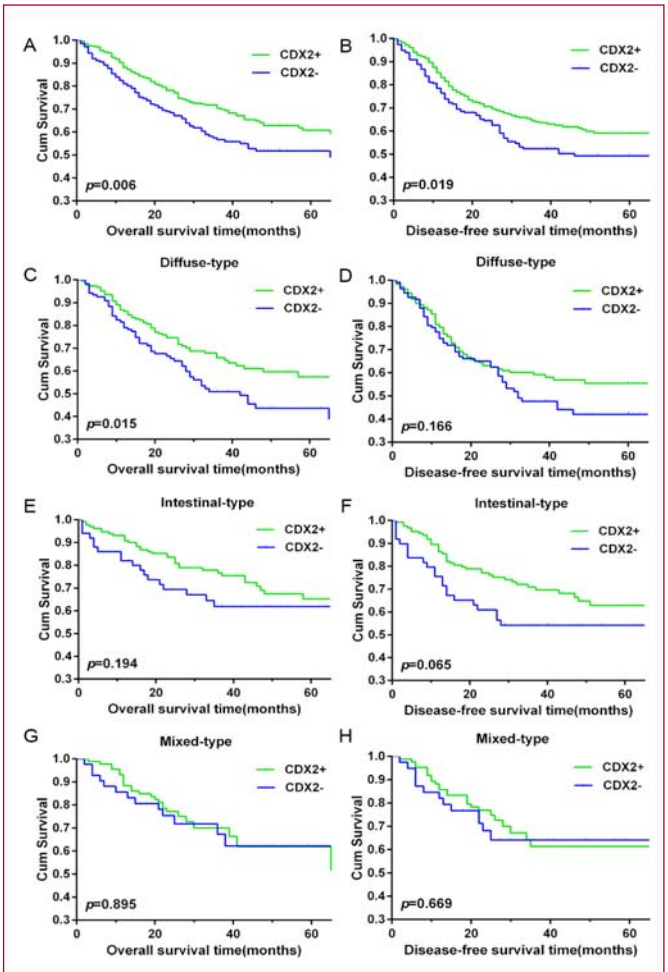

Figure 2: (A) Associations between CDX2 expression and (A) OS and (B) DFS in GAC patients. Associations between CDX2 expression and OS and DFS in (C, D) diffuse-type, (E, F) intestinal-type and (G, H) mixed-type GAC. The P-values are from Kaplan-Meier analysis with the log-rank test.

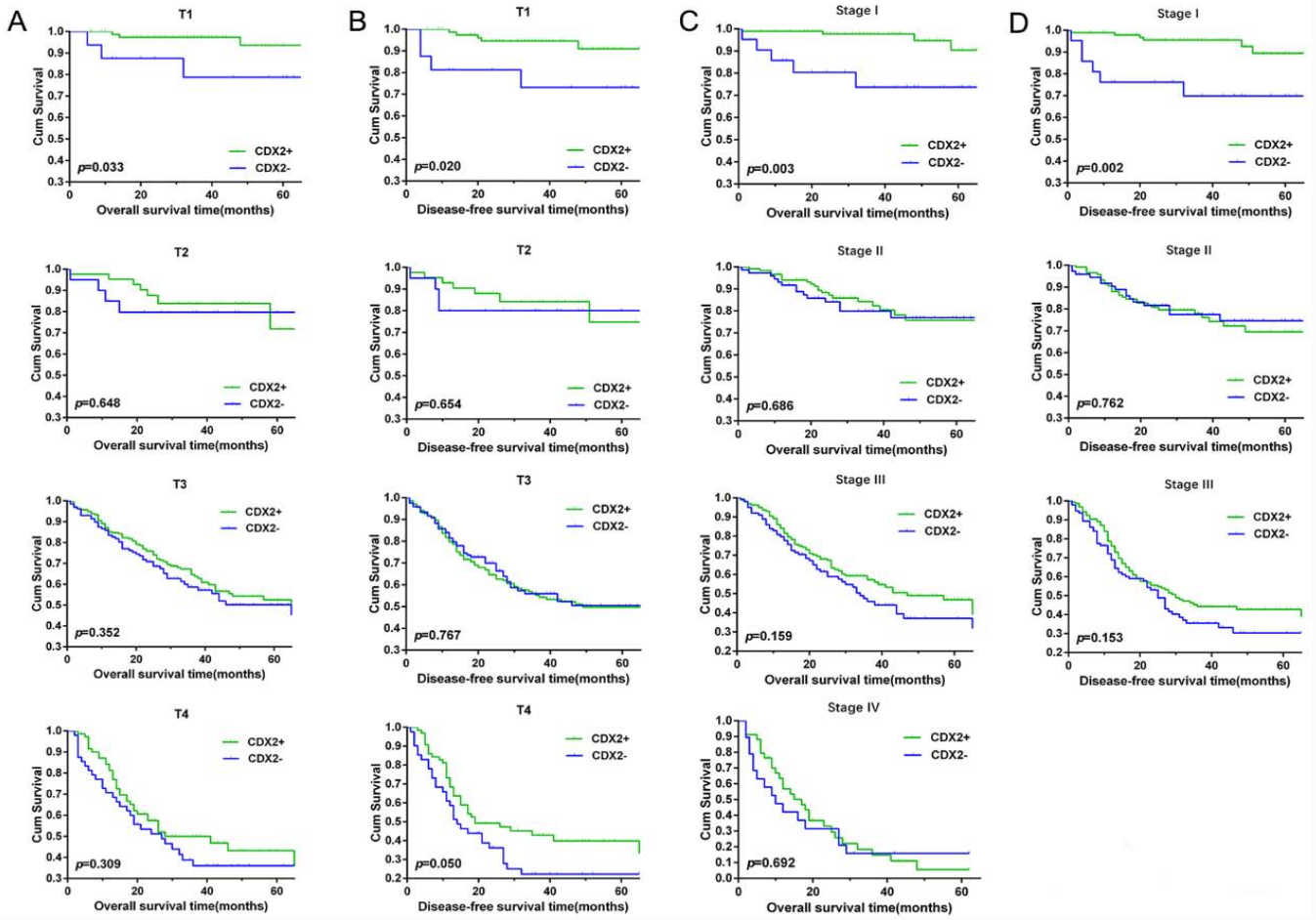

Figure 3: Survival curves of GAC patients with positive and negative CDX2 expression. (A) Overall survival curves in different T stages. (B) Disease-free survival curves in different T stages. (C) Overall survival curves in different TNM stages. (D) Disease-free survival curves in different TNM stages. The P-values are from Kaplan-Meier analysis with the log-rank test.

P=0.026; Figure 4B). In terms of cancer location, among patients with lower tumor location gastric cancer, the median OS was significantly longer in the CDX2+ group (30 months) than in the CDX2- (29 months; P=0.026). Likewise, the median DFS was significantly longer in the CDX2+ group (27 months) than in the CDX2- group (24 months; P=0.019). Caner in other locations showed no significant differences in OS or DFS between the two groups (Figure 4C).

Discussion

In this study, we used IHC to determine the expression of CDX2 in GAC patients. We found that CDX2 was expressed in 65.6% (406/619) of the patients. Moreover, CDX2 expression was significantly associated with gender, Lauren type, TNM stage, T stage, perineural invasion and tumor location. The findings suggest that positive CDX2 expression is a favorable prognostic factor in early stage diffuse-type GAC.

CDX2 is usually used in the clinical identification of intestinal adenocarcinomas [24]. A previous study found that CDX2 is highly expressed in all types of GIM, with the expression levels showing a decreasing trend in type I, II and III GIM [25]. Type III is more likely to progress to GC than types I and II [26,27]. CDX2 is an important molecule in the occurrence of GIM. Previous studies have found that CDX2 expression in the parietal cells of transgenic mice can induce GIM and further evolve into GAC [20,28].

We found that the CDX2 positivity rate was significantly higher in T1 than in T2, T3 and T4 GAC. Moreover, positive CDX2 expression in T1 GAC was associated with more favorable clinical outcomes than negative CDX2 expression. However, we found no significant correlations between CDX2 expression and clinical outcomes in advanced GAC. A previous study reported that CDX2 overexpression reduces the migration and invasion ability of GC cells [29]. Therefore, we can reduce that CDX2 may be an important factor in the occurrence of early GAC.

We also found that the CDX2 positivity rate was significantly higher in patients without perineural invasion than in those with perineural invasion. Our multivariate analysis indicated that perineural invasion was an independent predictor of OS and DFS in GAC patients. Moreover, our survival analysis indicated that among patients without perineural invasion, five-year OS was significantly better in patients with positive CDX2 expression than in those with negative expression. The reason may be that the nerve tracts in stomach tissue are mainly distributed in the submucosa. When perineural invasion occurs, the depth of tumor invasion is likely to reach T1b or more, whereas without perineural invasion, it may not reach the muscular is mucosa level (T1a or Tis).

Although previous studies have found no significant association between CDX2 expression and Lauren's classification [30-32], they have indicated that CDX2 expression tends to be higher in intestinal-

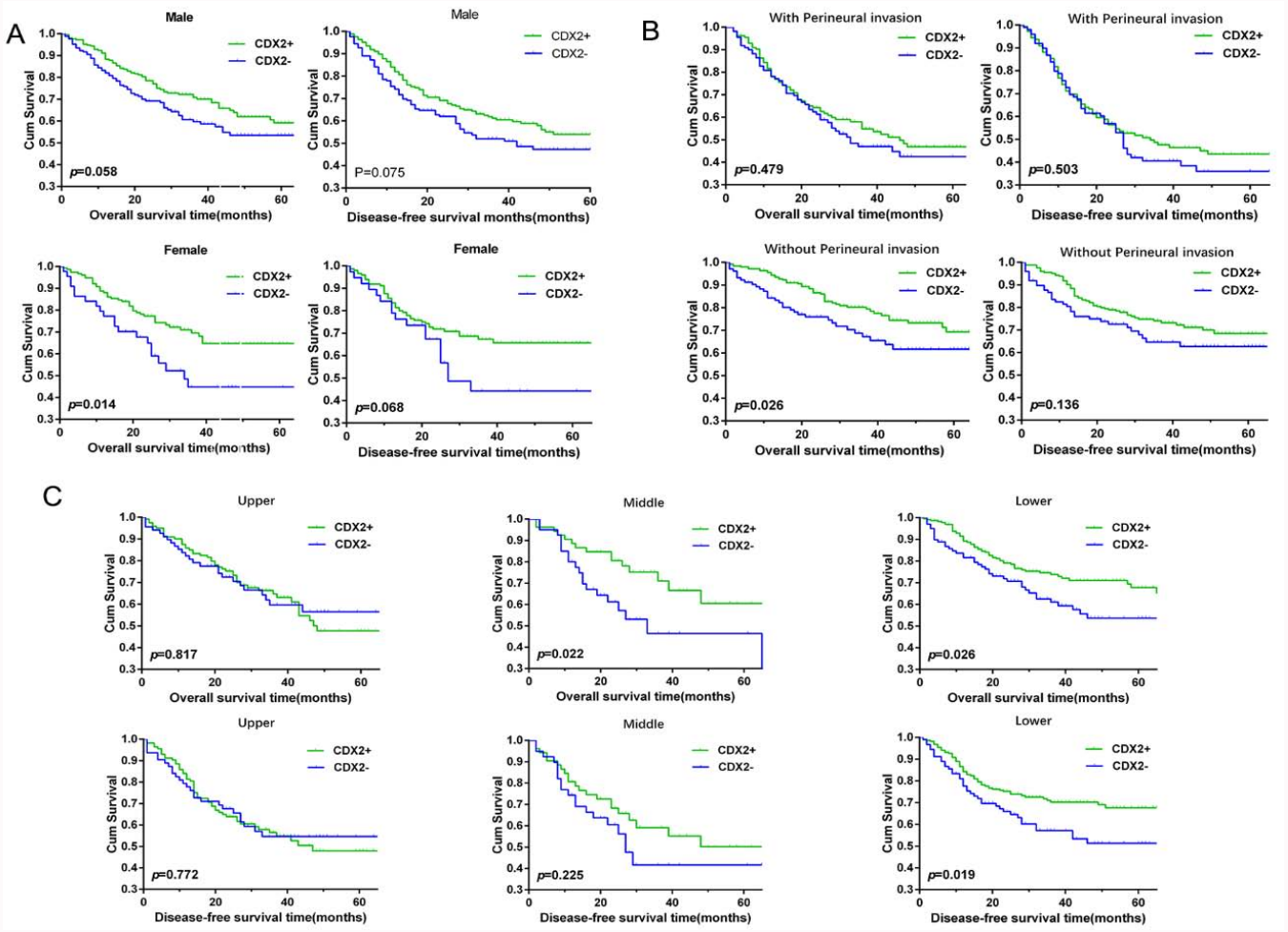

Figure 4: Overall and disease-free survival curves of GAC patients with positive and negative CDX2 expression. (A) Male and female patients. (B) Patients with and without perineural invasion. (C) Different tumour locations. The P-values are from Kaplan-Meier analysis with the log-rank test.

type than in diffuse-type GAC. Jass and Filipe [33] found that both intestinal-type and diffuse-type GC can be accompanied by GIM, but the frequency of GIM is higher in intestinal-type than in diffuse-type GAC. We found that in diffuse-type GAC, the clinical outcomes of patients with positive CDX2 expression were significantly better than those of patients with negative expression. Conversely, in intestinal-type GAC, CDX2 expression showed no significant correlation with clinical outcomes. Further, we found that in both intestinal-type and diffuse-type GAC, but especially in the latter, CDX2 expression was significantly higher in T1 than in T2-T4 stage GAC patients. These findings suggest that positive CDX2 expression may function as a tumor suppressor in T1 diffuse-type GAC.

This study is to evaluate the relationship between CDX2 and survival in all stages of GAC. Based on the pT stage and CDX2 expression level, our study raises potential clinical implications in GAC. pT1 GAC patients with a high CDX2 expression might have a better survival than low CDX2 expression patients. Similarly, pT1 diffuse-type GAC patients with a high CDX2 expression would benefit more than other type pT1 GAC patients. Our study however is not without its own limitations. Due to the restrictions on our research funding, we were hence unable to analyze the molecular mechanism of CDX2 expression affects the prognosis of pT1 diffuse-type GAC patients. We hope that we can unlock this mystery in a not too-distant future.

Conclusion

CDX2 expression is higher in early-stage diffuse-type GAC patients and may play a role as a tumor suppressor. Thus, it can be used as a prognostic indicator of the clinical outcomes of these patients.

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