# CDX2 as a prognostic marker in gastric cancer

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## Abstract

***Background :*** **There is considerable evidence in the literature to suggest a role for CDX2 in intestinal metaplasia and development of gastric cancer, but its impact on the prognosis of gastric cancer continues to be a matter of debate.**

***Objective :*** **We conducted this study to assess the prognostic implications of CDX2 in gastric cancer.**

***Methods :*** **We retrospectively reviewed our database for gastric carcinoma cases diagnosed at our hospital from 2004 to 2008. Histopathology slides of these were subsequently stained with CDX2 immuno-histochemical stain. CDX2 positive and negative groups were then compared for overall survival.**

***Results :*** **A total of 101 patients (mean age 50y ; 60% male) were included in the study. 31/101 (30.7%) cases were CDX2 positive. Of these, 23/31 (74%) patients underwent curative surgical resection. In the CDX2 negative group, only 12/70 (17%) patients underwent curative surgery (p = .0001). Of those who underwent surgical resection, 9% had stage I, 37% had stage II, 43% had stage III, and 11% had stage IV tumours on TNM staging of post-surgical histological specimens. Mean overall survival of CDX2 positive group was 17 months, compared to 6 months in the CDX2 negative group (p = 0.0001).**

***Conclusion :*** **CDX2 positive gastric carcinomas are more likely to be resectable and patients whose tumours stain positive for CDX2 have significantly better survival.** (Acta gastroenterol. belg., **2016**, 79, **197-200**).

**Key words** : CDX2, gastric cancer, prognostic marker, immunohistochemical stain.

## Introduction

Gastric cancer is one of the leading causes of mortality around the world (1). 3-10% of cancer-related deaths worldwide are attributed to gastric cancer (2). Most patients with gastric cancer tend to present at an advanced stage, often because initial symptoms are non-specific, or are ignored (3). Approximately 65% of gastric cancers in the US present at an advanced stage (III/IV) and nearly 85% have lymph node metastases at the time of diagnosis (4). There is also a high recurrence rate of 40-65% despite resection with curative intent (5). Helicobacter pylori infection is implicated as one of the risk factors for gastric cancer as are diets rich in salt and smoked and poorly preserved foods (6,7). The exact pathogenesis of gastric cancer is still unknown but a suggested pathway is Correa's cascade - a multistep process starting from gastritis leading to atrophy, through intestinal metaplasia and dysplasia and eventually to gastric cancer (8).

CDX2 is a member of the caudal related homeo-box gene family which is essential for the development of the normal embryo and in the differentiation and proliferation of intestinal epithelium (9-13). Expression of CDX2 has been linked with gastric intestinal metaplasia in a number of studies (14-18), but its role in the development of gastric cancer is still controversial. There are studies demonstrating that the presence of CDX2 is associated with a more favorable prognosis in patients with colon cancer, through the inhibition of tumour proliferation (19,20). Whether CDX2 has the same favorable role in gastric cancer continues to be the subject of debate (21,22). We conducted this study to determine the relationship of CDX2 with the resectability and prognosis of gastric cancer in our patient population.

## Objective

The objective of this study was to compare the pathological features and overall survival in patients with CDX2 positive and negative gastric carcinoma.

## Methods

### *Settings*

This was a single center retrospective study conducted at a tertiary care cancer center in Pakistan. All patients registered with a diagnosis of gastric carcinoma between January 2004 and December 2008 were included.

### *Data collection and analysis*

After obtaining institutional ethical committee approval, histological slides containing tumour of all included patients were stained with CDX2 and interpreted as either positive or negative by a consultant pathologist. Gastric carcinomas were considered CDX2 positive when nuclear expression of CDX2 immuno-histochemical stain was seen in tumour cells. Data regarding age, gender, diagnosis, histopathology, staging, adjuvant therapy, surgery and CDX2 status were collected and analyzed using SPSS 20.0. CDX2 positive and negative cases were compared for resectability and overall survival.

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## Results

293 patients with gastric cancer were registered from January 2004 to December 2008 at our institution. After exclusion of patients with gastro-oesophageal junction tumours (n = 108) and those with insufficient material in the paraffin for additional slide formation (n = 84), we were left with 101 for further analysis.

The mean age of included patients was 50y, with a preponderance of males at 60.4% (n = 61). On staging investigations, 66.3% (n = 67) had radiological T3 tumours, while 23.8% (n = 24) had radiological T4 tumours. In 5.2%, (n = 5) the primary tumour was not visible on CT scan while in five patients initial imaging results could not be retrieved. In 20.8% (n = 21) no peri-gastric lymph nodes were visible (radiological N0), in 57.4% (n = 58) up to two peri-gastric lymph nodes were visible (radiological N1) while in 16.8% (n = 17) three to six peri-gastric lymph nodes were seen (radiological N2). 24.8% (n = 25) patients had distant metastases on initial imaging. In 57.4% (n = 58) the tumour involved the fundus and/or body of the stomach, while in 42.6% (n = 43) the antrum and/or pylorus were involved. On histopathology, 5.9% (n = 6) had well differentiated adenocarcinoma, 13.9% (n = 14) had moderately differentiated adenocarcinoma, 79.2% (n = 80) had poorly differentiated adenocarcinoma while one patient had high grade dysplasia. 60.4% (n = 61) had signet ring cell features on histopathology. CDX2 staining was performed in all 101 patients. 30.7% (n = 31/101) of these were CDX2 positive while the remaining 69.3% (n = 70/101) were CDX2 negative. Radiological staging and histology of tumour were compared between CDX2 positive and negative groups as shown in table 1. All of the patients were discussed in a weekly multidisciplinary gastrointestinal cancer meeting prior to initiation of treatment. 65.3% (n = 66) had unresectable tumour while the remaining 34.7% (n = 35) underwent curative resection of the tumour. Out of these 35 patients, 68.6% (n = 24) underwent partial gastrectomy while the remaining 31.4% (n = 11) underwent total gastrectomy. We found a significant difference in the resectability of the tumours with respect to their CDX2 status. 74% (n = 23/31) of CDX2 positive tumours were resectable while only 17% (n = 12/70) of CDX2 negative tumours were found to be resectable ($p = 0.0001$). The pathological staging of surgical specimens and comparison with respect to CDX2 status are shown in table 2 and 3 respectively. Neo-adjuvant chemotherapy was given to 11.4% (n = 4/35) of these patients. Adjuvant chemotherapy was given in 57% (n = 20/35) of patients. On comparing the overall survival of CDX2 positive and negative groups, we found it to be 17 vs. 6 months, respectively, which was also statistically significant ($p = 0.0001$).

## Discussion

In the quest for finding a useful prognostic marker for gastric cancer, CDX2 has shown promising results in previous studies (23-26). The exact role of CDX2 in Correa's cascade for the development of gastric carcinoma is still not understood, however. On the one hand, it has been implicated in the development of gastric intestinal metaplasia, which is considered to be a precursor of dysplasia and cancer (14-18). But, on the other hand, it appears to have an inhibitory role in tumour call invasion and migration (27,28). CDX2 is normally present in the intestinal mucosa from the duodenum to the anal canal (29). It is vital for intestinal differentiation and proliferation. Risk factors such as Helicobacter pylori cause

Table 1. — **Comparison of CDX2 positive and negative**

| | CDX2 Positive | CDX2 Negative | p-value |
|---|---|---|---|
| **Radiological T stage (n = 96)** | | | 0.201 |
| T0 | 02 | 03 | |
| T3 | 24 | 43 | |
| T4 | 04 | 20 | |
| **Radiological N stage (n = 96)** | | | 0.056 |
| N0 | 11 | 10 | |
| N1 | 14 | 44 | |
| N2 | 05 | 12 | |
| **Radiological M stage (n = 96)** | | | 0.023 |
| M0 | 27 | 44 | |
| M1 | 03 | 22 | |
| **Histology (n = 101)** | | | 0.392 |
| High grade dysplasia | 01 | 00 | |
| Well differentiated CA | 01 | 05 | |
| Mod. differentiated CA | 05 | 09 | |
| Poorly differentiated CA | 24 | 56 | |
| **Signet ring cells (n = 101)** | | | 0.662 |
| Absent | 11 | 29 | |
| Present | 20 | 41 | |

Table 2. — **TNM stages of patients who underwent curative resection (n = 35)**

| TNM Stage | Number of patients | Percentage | Percentage |
|---|---|---|---|
| IB | 03 | 8.6 | 8.6 |
| IIA | 03 | 8.6 | 37.2 |
| IIB | 10 | 28.6 | |
| IIIA | 11 | 31.4 | 42.9 |
| IIIB | 01 | 2.9 | |
| IIIC | 03 | 8.6 | |
| IV | 04 | 11.4 | 11.4 |

Table 3. — **Comparison of TNM stage in patients who underwent curative resection (*p*-0.469)**

| TNM Stage | CDX2 Positive (n = 23) | CDX2 Negative (n = 12) |
|---|---|---|
| I | 3 (13%) | 0 |
| II | 7 (30%) | 6 (50%) |
| III | 10 (43%) | 5 (41%) |
| IV | 3 (13%) | 1 (8%) |

gastric injury and lead to intestinal metaplasia through the expression of CDX2. Gastric intestinal metaplasia can be either complete or incomplete. Gastric dysplasia and cancer develops from incomplete intestinal metaplasia. Previous studies have shown less expression of CDX2 in incomplete metaplasia as compared to that seen in complete intestinal metaplasia and gradual loss of CDX2 expression along Correa's cascade (27).

Camilo *et al*. assessed CDX2 expression in 201 gastric cancer patients and found CDX2 expression in 43%. The CDX2 positive group had significantly lower TNM stage as compared to the CDX2 negative group. Interestingly, despite lower TNM stage, there was no significant difference in survival between the CDX2 positive and negative groups (23).

A meta-analysis by Wang *et al*. included 13 studies with 1513 patients. In this meta-analysis, CDX2 expression was associated with a lower TNM stage, better differentiation and survival (24).

Ge *et al*. assessed 161 patients for the impact of CDX2 expression on gastric cancer. 61% of their patients were CDX2 positive. CDX2 expression was associated with earlier stage of gastric cancer and better prognosis in this cohort (25).

Qin *et al*. analyzed 85 patients with gastric cancer for CDX2 expression. 48% of these were found to be CDX2 positive and a negative association was seen between CDX2 expression and nodal metastasis. Significantly higher survival was reported in the CDX2 positive group as compared to those negative for this marker (26).

All these studies have shown better survival and a lower TNM stage of gastric cancer when tumours were CDX2 positive (23-26). Our cohort of patients with CDX2 positive tumours had a greater proportion of resectable tumours, which translates into a lower tumour stage, and better overall survival as compared to CDX2 negative patients, findings consistent with the results of previous studies. The lack of a significant difference in the TNM stage of resected tumours in the CDX2 positive and negative groups in our study is due to the very low number of CDX2 negative tumours.

The main limitations of our study were it's retrospective design and the somewhat limited number of patients. We plan on performing a prospective study including all patients with gastric cancer, with their CDX2 status checked prior to initiation of treatment, so as to be able to study the outcome of treatment and the effect on survival of the presence or absence of this marker.

## Conclusion

Patients with CDX2 positive gastric cancer appear to be more likely to have resectable tumours and to have better overall survival as compared to those with CDX2 negative tumours, but further prospective studies are needed to prove this.

## Conflict of interest

The authors have no conflicts of interest to declare.

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