ORIGINAL ARTICLE

The role of CDX2 immunohistochemical marker in colorectal adenocarcinoma « CDX2 in colorectal adenocarcinoma »

Rôle du marqueur immunohistochimique CDX2 dans l'adénocarcinome colorectal « CDX2 dans l'adénocarcinome colorectal »

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Abstract

Introduction: Caudal-type homeobox transcription factor 2 (CDX2), a marker of intestinal differentiation, has shown potential as a prognostic biomarker in colorectal cancer(CRC). Its loss is associated with aggressive disease features and poor survival, yet its routine clinical use remains limited. In this study, we aimed to explore the immunohistochemical expression of CDX2 in sporadic colorectal adenocarcinomas and to assess its prognostic significance.

Methods: This was a retrospective longitudinal study including patients with sporadic colorectal adenocarcinoma. CDX2 expression was assessed via automated immunohistochemistry on formalin-fixed, paraffin-embedded sections using monoclonal antibody CDX2-DAK (Dako, Glostrup, Denmark). Only nuclear staining was considered positive. Clinicopathological data, including tumor stage, differentiation, and survival, were collected over a 36-month median follow-up. Statistical analysis was performed using SPSS version 20 ($p < 0.05$).

Results: Thirty cases were included with a mean age of 57 ± 2 years and a male-to-female ratio of 1.7. CDX2 expression was observed in 80% (24/30) of tumors. Its loss was significantly associated with poor differentiation (p=0.04),lymph node involvement (p=0.0027), advanced stage (p=0.043), and reduced overall survival (p=0.0024). Loss of CDX2 expression combined with pT4 stage identified a high-risk subgroup with worse disease-free and overall survival. Tumors were predominantly colonic (80%), with 90% adenocarcinomas and 10% mucinous carcinomas.

Conclusions: CDX2 loss is a robust prognostic indicator in CRC, particularly when combined with pT4 stage, highlighting its potential for risk stratification and treatment planning. Larger, prospective studies are needed to standardize CDX2 assessment and validate its clinical utility in colorectal adenocarcinoma.

Keywords : CDX2, colorectal, adenocarcinoma, immunohistochemistry, prognostic marker

Résumé

Introduction: De nombreuses études ont suggéré que la perte d'expression du transcription homéobox de type caudal 2(CDX2) est associée à un mauvais pronostic, cependant son utilisation en pratique courante reste limitée. Le but était de décrire l'expression phénotypique globale du CDX2 dans les CCR sporadiques et d'évaluer sa valeur pronostique.

Méthodes: Il s'agissait d'une étude longitudinale rétrospective incluant des patients atteints d'adénocarcinome colorectal sporadique. L'expression de CDX2 a été évaluée par immunohistochimie automatisée(anticorps monoclonal CDX2-DAK). Le marquage était considéré positif s'il était nucléaire. Les données clinico-pathologiques et évolutives ont été recueillies sur une période de suivi médiane de 36 mois.

Résultats: Trente cas ont été inclus avec un âge moyen de 57 ± 2 ans et un ratio homme-femme de 1,7. L'expression de CDX2 a été observée dans 80% des tumeurs, avec une perte significativement associée à une mauvaise différenciation (p=0,04), à une atteinte ganglionnaire (p=0,0027), à un stade avancé (p=0,043) et à une survie globale réduite (p=0,0024). Une faible expression de CDX2 combinée à un stade pT4 a identifié un sous-groupe à haut risque avec une survie sans maladie et une survie globale pires. Les tumeurs étaient principalement coliques (80%), avec 90% d'adénocarcinomes et 10% de carcinomes mucineux.

Conclusions: La perte de CDX2 est un indicateur pronostique potentiel dans le CCR, en particulier lorsqu'elle est combinée au stade pT4, soulignant son potentiel pour la stratification du risque et la planification du traitement. Des études multicentriques et prospectives pour standardiser l'évaluation de CDX2 et confirmer son utilité clinique sont toutefois nécessaires.

Mots clés : CDX2, colorectal, adénocarcinome, immunohistochimie, marqueur pronostic

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Introduction

The caudal-type homeobox transcription factor 2 (CDX2), a marker of intestinal differentiation, has garnered significant interest during the last five years with a diagnostic and potential prognostic role in digestive cancers (1). Encoded by a homeotic gene, CDX2 is expressed in both normal and pathological intestinal cells playing a key role in regulating cell growth and differentiation (2). In routine practice, it is commonly used by pathologists as a marker for the identification of tumors of intestinal origin especially in cases of metastatic carcinomas of unknown origin (2). However, recently, it has been reported that CDX2 is commonly downregulated or totally lost in a subset of CRC, making CDX2 an interesting emerging prognostic biomarker in CRC (1,3–6).

Indeed, many studies have demonstrated that decreased CDX2 expression is associated with advanced disease stage, poor differentiation, lymphovascular invasion and reduced overall survival suggesting that the loss of CDX2 expression should be considered when deciding for adjuvant chemotherapy (1,3,5–12). Yet, it seems that this marker has not reached a sufficient level of evidence to be included in routine practice for prognostic risk stratification in patients with CRC nor to be considered in the decision of adjuvant chemotherapy (1). Further research is hence necessary to definitively confirm CDX2's prognostic and predictive role in CRC.

In this study, we aimed to explore the immunohistochemical expression of CDX2 in sporadic colorectal adenocarcinomas and to assess its prognostic significance.

Methods

Study Design and Patient Cohort

This retrospective longitudinal study analyzed patients with sporadic colorectal adenocarcinoma, diagnosed in our pathology department during a period of 8 years (2010-2018).

Inclusion Criteria:

- Surgical specimens
- Patients with sporadic colorectal adenocarcinoma
- Complete clinical records
- Sufficient tumor tissue for IHC analysis.

Non-inclusion criteria:

- Other histological types (mesenchymal tumors / neuroendocrine tumors)
- Biopsy samples
- Samples from metastatic sites

Exclusion Criteria:

- Patients with hereditary colorectal cancer syndromes (Lynch Syndrome, colorectal cancer in familial adenomatous polyposis)
- Inadequate samples.for IHC analysis (Extensive necrosis , poorly fixed specimens with altered morphology)

Data Collection

Clinical and pathological data were extracted from medical records, including age, sex, tumor location, histological type, differentiation grade, pTNM stage (per the 8th edition AJCC), and presence of vascular emboli or perineural invasion. Survival data, including recurrence and metastasis, were tracked over a median follow-up of 36 months. Two senior pathologists independently reviewed all cases using the 2019 WHO classification to confirm histopathological features.

Immunohistochemical Analysis

CDX2 expression was evaluated via automated immunohistochemistry (Automate Leica Bond Max) on 4-µm formalin-fixed, paraffin-embedded tissue sections. The process utilized the monoclonal antibody CDX2-DAK (Dako, Glostrup, Denmark).

Scoring CDX2 Expression

Consistent with established protocols, any nuclear immunoreactivity qualified as positive. Cytoplasmic staining, when present, was noted but not required for positivity. Negative controls (tonsil mucosa) and positive controls (normal colon mucosa) were included according to the manufacturer's recommendations. For descriptive purpose, the staining intensity was assessed as weak (+), moderate (++), or strong (+++).

We have also assessed the percentage of positive cells according to the thresholds used by Singh et al (13) and for statistical purposes , we have categorized them as follows :

- < 5%
- 5–75%
- >75%

Statistical Methods

Data were analyzed using SPSS version 20. Associations between CDX2 expression and clinicopathological variables were assessed with Fisher's exact tests for categorical data and t-tests for continuous variables. Survival curves were generated using the Kaplan-Meier method, with differences evaluated by the log-rank test. Statistical significance was set at $p < 0.05$

Results

Thirty patients were included in this study with a mean age of 57 ± 2 years and a male-to-female ratio of 1.7. Tumors were predominantly colonic (80%, 24/30), with 54% (13/24) located on the right side and 46% (11/24) on the left. The tumor was located in the rectum in 20% (6/30). Histologically, 90% of tumors(27/30) were common adenocarcinoma subtypes, and 10% (3/30)

were mucinous carcinomas.

Regarding tumor differentiation, 27% (8/30) were well-differentiated, 53% (16/30) moderately differentiated, and 20% (6/30) poorly differentiated.

All tumors were classified as pT3 (67%, 20/30) or pT4 (33%, 10/30). Lymph node involvement was absent (pN0) in 50% (15/30), limited (pN1) in 17% (5/30), and extensive (pN3) in 33% (10/30). Distant metastases were present in 30% (9/30) of cases.

Immunohistochemical findings

CDX2 expression was observed in 80% (24/30) of tumors and 100% of control tissues. The staining intensity was strong (+++) in 23 of 24 positive cases and moderate(++) in one case. The percentage of positive cells was : <5% (either negative or less than 5% of positive cells) in 6 cases, 5-75% in 4 cases and >75% in 20 cases. The association between the percentage of CDX2 positive cells and tumor stage is summarized in table 1.

Table 1. Association of the percentage of CDX2 expression and tumor stage

Percentage of CDX2 positive cells	pT		p value	pN			p value
	pT3 (n=20)	pT4 (n=10)		N0 (n=15)	N1 (n=5)	N3 (n=10)	
- <5%	2	4	0.0013	0	0	6	<0.0001
- 5-75%	0	4		3	0	1	
- >75%	18	2		12	5	3	

Among adenocarcinomas, CDX2 positivity was 81% (22/27), compared to 67% (2/3) in mucinous types. CDX2 expression was noted in (100%) of well-differentiated (Figure 1),75% of moderately differentiated (Figure 2), and 50% of poorly differentiated tumors (Figure3). The associations of CDX2 expression and the clinicopathological and survival data are summarized in the table 2.

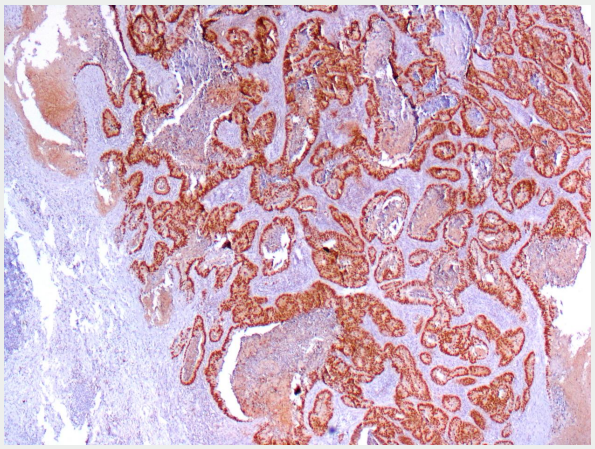


Figure 1. IHC x 100 : Diffuse and marked nuclear staining for CDX2 in a case of Well Differentiated colon adenocarcinoma

Table 2. Association of CDX2 and the studied clinicopathological and survival data

Variable	CDX2-positive (n=24)	CDX2-negative (n=6)	p-value
Age (years, mean ± SD)	57 ± 2*	57 ± 2*	0.45
Sex, n (%)			0.62
- Male	15 (62.5%)	4 (66.7%)	
- Female	9 (37.5%)	2 (33.3%)	
Tumor location, n (%)			0.38
- Colonic, right	10 (41.7%)	3 (50.0%)	
- Colonic, left	9 (37.5%)	2 (33.3%)	
- Rectal	5 (20.8%)	1 (16.7%)	
Histological type, n (%)			0.45
- Adenocarcinoma	22 (91.7%)	5 (83.3%)	
- Mucinous carcinoma	2 (8.3%)	1 (16.7%)	
Differentiation, n (%)			**0.04**
- Well	8 (33.3%)	0 (0)	
- Moderate	12 (50.0%)	4 (66.7%)	
- Poor	4 (16.7%)	2 (33.3%)	
Vascular inasion n (%) :			0.25
-Yes	5 (20%)	1(17%)	
-No	19 (80%)	5 (83%)	
Peri-neural invasion :			0.30
-Yes	8 (33%)	2	
-No	16 (67%)	4	
pT stage, n (%)			0.12
- pT3	15 (62.5%)	5 (83.3%)	
- pT4	9 (37.5%)	1 (16.7%)	
pN stage, n (%)			**0.0027**
- pN0	15 (62.5%)	0 (0%)	
- pN1	5 (20.8%)	0 (0%)	
- pN3	4 (16.7%)	6 (100%)	
Distant metastasis, n (%)			**0.0534**
- Absent	19 (79.2%)	2 (33.3%)	
- Present	5 (20.8%)	4 (66.7%)	
Disease stage, n (%)			**0.043**
- Stage II	13 (54.2%)	2 (33.3%)	
- Stage III	11 (45.8%)	1 (16.7%)	
- Stage IV	0 (0%)	3 (50.0%)	
Overall survival (months, median) (Figure4)	60	25	0.0024

Note : The small sample size of the CDX2-negative group (n=6) warrants cautious interpretation of survival differences

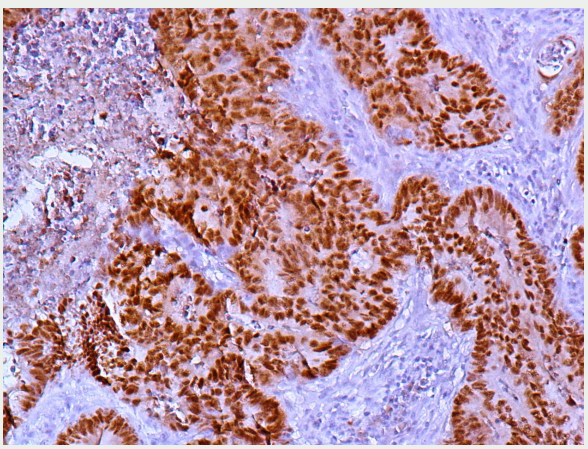


Figure 2. IHC x 200 : Diffuse and marked nuclear staining for CDX2 in a case of Moderately Differentiated colon adenocarcinoma

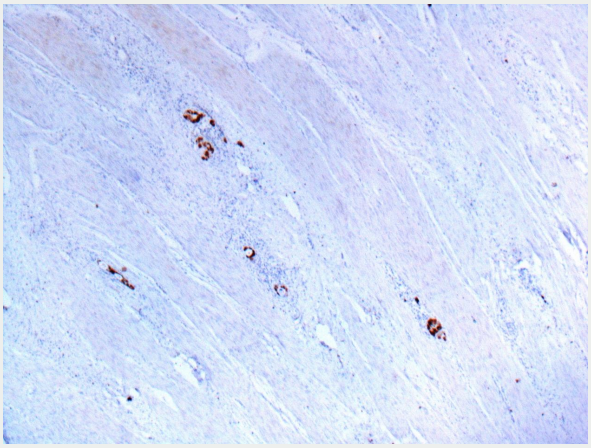


Figure 3. IHC x 200 : Marked nuclear staining for CDX2 in a case of Poorly Differentiated rectal adenocarcinoma

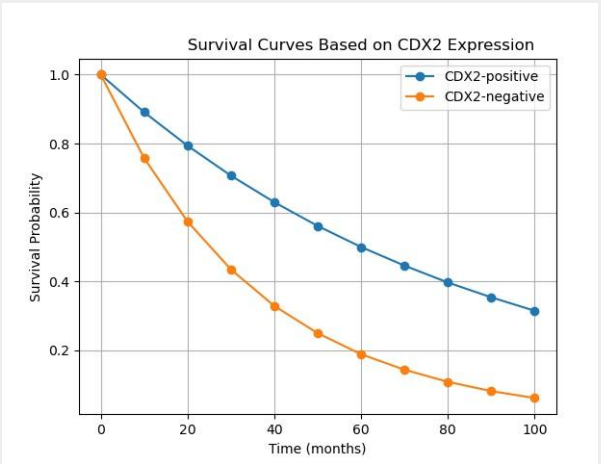


Figure 4. Kaplan-Meier Survival Curves by CDX2 Expression in Colorectal Adenocarcinoma. The estimated survival probabilities over time for patients with colorectal adenocarcinoma, stratified by CDX2 expression status. The blue curve represents patients with CDX2-positive tumors (n=24), while the red curve represents patients with CDX2-negative tumors (n=6). Median survival was 60 months for the CDX2-positive group and 25 months for the CDX2-negative group. The difference in survival between the two groups was statistically significant (p=0.0024, log-rank test). Note: The small sample size, particularly in the CDX2-negative group (n=6), limits the precision of these estimates and should be interpreted with caution

Discussion

CDX2 prognostic role in CRC

Our study highlighted the prognostic significance of CDX2 expression in colorectal adenocarcinoma, demonstrating that loss of CDX2 expression, particularly in combination with stage T4 tumors, is strongly associated with poor disease-free survival (DFS) and overall survival (OS). These findings are consistent with previous studies supporting CDX2 as a potentially valuable marker for identifying patients with more aggressive disease and guiding therapeutic decisions(1,6,8,12).

In this study, we demonstrated that loss of CDX2 expression correlated with adverse prognostic features such as poor differentiation (p=0.04), lymph node involvement (p=0.0027), metastases (p=0.0534), and reduced survival (p=0.0024). These findings are in line with most published studies such as. çalik et al, who demonstrated that decrease in CDX2 expression was closely associated with classical prognostic parameters such as histopathologic type, histologic grade, lymph node metastasis, distant metastasis, and TNM stage(5). Likewise, in their recent paper, Chan et al. reported that loss of CDX2 expression was linked to poor differentiation and reduced overall and disease free survival(1). In addition, in this study, a statistically significant association was found between the percentage of CDX2-positive cells and : tumor pT stage (p = 0.0013) and lymph node stage (p<0.0001), indicating that reduced CDX2 expression may be linked to advanced tumor stages, though this should be interpreted cautiously due to the limited sample size, the absence of cases of early stage (pT1/pT2) and potential unaccounted confounders.

Although Choi et al. reported no significant correlation between tumor differentiation and CDX2 expression, the observed reduction in CDX2 expression in a subset of poorly differentiated CRCs in our study should be known by pathologists and clinicians (6). Therefore, the decreased or loss of CDX2 expression in a metastatic poorly differentiated carcinomas does not necessary preclude an intestinal origin.

Although as demonstrated in the present study , the loss of CDX2 expression is commonly associated with advanced stage III and IV , some authors suggested that CDX2 could also predict a worse outcome even in early stage (II and III) CRCs (14,15), emphasizing its utility in identifying high-risk patients.

In their study, Korphaisarn et al concluded that loss of CDX-2 expression was associated with right-sided tumor and dMMR status (16). However, in our study, no statistically significant association was found between CDX2 expression and tumor location which may be in part attributed to the small sample size of our cohort.

As described in our study, loss of CDX2 expression in colorectal cancer (CRC) is associated with an increased risk of metastases (13,16,17). Previous studies have shown that CDX2 loss occurs in nearly 7.8 to 33.4% of metastatic CRC cases and CDX2-negative metastatic tumors are linked to shorter overall survival and progression-free survival compared to CDX2-positive tumors(13,17). Although some authors suggested that the prognostic relevance of CDX2 loss in CRCs is inferior to hematoxylin–eosin-based morphologic parameters(11), consistent findings across studies underscores CDX2's reliability as a prognostic biomarker. and highlight the need to include CDX2 in therapeutic decision-making (8).

Biological Role of CDX2 in CRC

CDX2 plays a key role in tumor differentiation and is normally expressed from the duodenum to the rectum in normal and pathological intestinal cells (5,6). It also has a tumor-suppressive role in CRC, by inhibiting cell proliferation and promoting differentiation(18). In the same context, Xu et al. suggested that CDX2 may suppress tumor progression and metastasis, potentially through regulating genes involved in epithelial integrity and cellular adhesion (14).

The loss of CDX2 expression, observed in our study and others, likely leads to dedifferentiation and increased tumor aggressiveness, explaining its association with poor prognosis (1,6,11,16,17). Wang et al suggested that the loss of CDX2 promotes epithelial to mesenchymal transition and facilitate tumor dissemination and metastasis (18). Indeed the authors demonstrated that overexpression of CDX2 reduced expression of EMT-associated markers and diminished cell proliferation, invasion, and migration, while knockdown of CDX2 enhanced EMT-associated markers expression and increased cell proliferation, invasion, and migration (18).
Moreover, CDX2 is also involved in the molecular pathogenesis of CRC. It has been associated with microsatellite instability (MSI), BRAF mutations, and the CpG island methylator phenotype (CIMP), which influence prognosis (4,16,19). Xu et al. speculate that CpG island hypermethylation could silence CDX2 expression, contributing to a CIMP-high phenotype and worse outcomes (14). Although our study did not evaluate these molecular characteristics, the reported association with CDX2 expression justifies further research to elucidate the mechanisms underlying its prognostic significance and to determine its potential as a therapeutic target.

Clinical Implications

The stratification of CRC patients based on CDX2 expression offers substantial clinical potential. Our findings suggest that patients with loss CDX2 expression, particularly in stage II disease, may benefit from intensified treatment, such as adjuvant chemotherapy, which is not systematically recommended for this group(8). Dalerba et al. reported improved survival with adjuvant chemotherapy in CDX2-negative stage II patients, a finding supported by our data (7,20). Additionally, the synergistic prognostic power of combining CDX2 with T stage, as demonstrated by Xu et al. and corroborated in our study, identifies a high-risk subgroup—patients with loss CDX2 and T4 tumors—who exhibit the worst DFS and OS (14)(12). These patients may require more aggressive interventions and closer follow-up, as suggested by Xu et al., who highlighted the importance of preoperative CDX2 assessment via immunohistochemistry to guide treatment planning in combination with pathological prognostic factors and imaging findings. [11].
Hence, CDX2 assessment by immunohistochemistry can help identify high-risk CRC patients, but standardization of evaluation methods is needed(21)

Limitations and Future Directions

Although our study supports the prognostic role of CDX2 in colorectal cancer, our results are limited by the sample size of 30 patients which limits the statistical power of our findings, particularly for subgroup analyses (CDX2-negative group, n=6), increasing the risk of type II errors. This issue has been raised by authors of meta-analysis such as Xu et al. and Çalık et al. who considered that the small cohort sizes and the retrospective designs of studies limits the generalization of the results (5,14). The retrospective nature introduces potential selection biases, and the absence of molecular data—such as MSI status, KRAS, or BRAF mutations—limits our ability to contextualize CDX2 within CRC's molecular heterogeneity. Xu et al. highlighted the association between loss of CDX2 and BRAF mutations, suggesting a link to the serrated neoplasia pathway, which we could not explore (14). Similarly, Çalık et al. noted the controversial relationship between CDX2 and distant metastasis, with some studies showing no significant difference in expression between primary tumors and metastases (5) Future prospective studies with larger, multicenter cohorts are required to validate our results and address these gaps.
Standardization of CDX2 assessment also remains a critical challenge. In our study like most similar studies, we defined positivity based on any nuclear staining regarding the percentage of positive cells of staining intensisty, whereas Xu et al. used a staining score threshold of ≤4 for low expression (14). Çalık et al. adopted a similar semiquantitative approach but reported variability in cutoffs across the literature (5). This inconsistency complicates clinical adoption, necessitating consensus guidelines for CDX2 scoring. The finding of a statisically significant association between the percentage of CDX2 positive cells and tumor stage in our study underscores the importance of establishing a uniform scoring approach to ensure consistent prognostic evaluation suggesting that not only the loss of CDX2 expression but also its decrease could be usefull.
Additionally, exploring CDX2's downstream targets and its interaction with signaling pathways, as suggested by Xu et al., could uncover novel therapeutic targets(14) .

Conclusions

This study confirms CDX2 as a valuable prognostic biomarker in colorectal adenocarcinoma, with loss of expression significantly associated with poor differentiation, lymph node involvement, advanced stage, and worse survival outcomes. Notably, combining CDX2 loss with pT4 stage identifies a high-risk subgroup requiring intensified treatment, such as adjuvant chemotherapy, particularly in stage II disease. Despite these findings, the small cohort size (n=30), retrospective design, and lack of molecular profiling limit generalizability. Prospective, multicenter studies with larger cohorts are essential to validate these results, standardize CDX2 scoring, and integrate molecular data for enhanced clinical utility

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