Histopathological and Immunohistochemical Evaluation of CDX2 and Ki67 in Colorectal Lesions with their Expression Pattern in Different Histologic Variants, Grade, and Stage of Colorectal Carcinomas

Jhasaketan Nayak, Pranita Mohanty, Anasuya Lenka, Nibedita Sahoo, Sunil Agrawala, Sandeep Kumar Panigrahi

Department of Hemato-Oncology, AIIMS, Departments of 1Pathology, 2Surgical Oncology and 3Community Medicine, IMS and SUM Hospital, Bhubaneswar, Odisha, India

Abstract

Background: A variety of colorectal lesions are surgically treated encompassing both benign and malignant polyps and colorectal cancer (CRC). CRC is the third most common cause of death in developed countries. Over the last decade, CDX2 has been linked to CRC progression, with reduced expression of the protein associated with more advanced tumor stage, vessel invasion, and metastasis. Aims and Objectives: To analyze the histopathology and immunohistochemistry (IHC) of CDX2 and Ki67 with their expression pattern; in different lesions of colon and rectum with special reference to various grade/stage/histological variants of CRC and to find out whether they can be used as possible predictive marker. Materials and Methods: The study conducted was hospital based, both retrospective and perspective type comprising colorectal samples of total 367 cases (N) within a period of 2½ years. Surgical samples were collected, thengrossed, processed, stained with routine hematoxylin and eosin stain in our department followed by IHC of CDX2 and Ki67 in only 60 randomly selected cases (n = 60). Results: Out of total 367 cases, 265 cases were prospective study and 102 cases were retrospective study (240 cases were colonic lesions, and 127 are rectal lesions). The samples included were both from colonoscopy biopsy (small) 319 cases and 48 colectomy specimen (large). Mean age of the study participants was 49.62 years with a standard deviation of 17.34 years and predominantly male, but the difference was not statistically significant (P > 0.05). Colon (238 cases, 64.9%) as a whole affected more than rectum and left sided tumors more than the right side. All 60 cases were found to be positive for CDX2 expression (i.e., 100%); majority (n = 38) being carcinoma cases possessing high score and was statistically significant (P = 0.008, using Chi-square test) indicating strong association, whereas Ki-67 showed an increased index from noneoplastic to neoplastic cases. Conclusion: These markers can be used as future predictive biomarkers which will precisely evaluate risk group, prognosis, and response to therapy hence can be used as target therapy reducing irrational treatment.

Keywords: Adenocarcinoma, adenomatous polyp, CDX2, colorectal carcinoma, transcription factor

Introduction

According to the World Health Organization, colorectal cancer (CRC) is the fourth common cancer, comprising 11% in the world and is steadily rising because of the western lifestyle. The molecular genesis of CRC involves four key mutations, including the oncogenes APC, KRAS, DDC, and the tumor-suppressor gene p53 that occurs only in 10% of tumors. CDX2 is a homeobox protein responsible for the maintenance of the intestinal.

Phenotype is over expressed in CRC. Ki67 antigen is a proliferative marker and is used as predictive biomarker for many cancers that is yet to be proved in CRC.

Address for correspondence: Dr. Pranita Mohanty, Department of Pathology, IMS and SUM Hospital, Bhubaneswar - 751 003, Odisha, India. E-mail: dr.pranitamohanty@gmail.com

Access this article online

Quick Response Code:

Website: http://www.jmau.org/

DOI: 10.4103/JMAU.JMAU_69_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Nayak J, Mohanty P, Lenka A, Sahoo N, Agrawala S, Panigrahi SK. Histopathological and immunohistochemical evaluation of CDX2 and Ki67 in colorectal lesions with their expression pattern in different histologic variants, grade, and stage of colorectal carcinomas. J Microsc Ultrastruct 2021;9:183-9.
**Materials and Methods**

This was a hospital-based study undertaken over a period of 2½ years (June 2017–December 2019) in the department of pathology at a tertiary care teaching hospital. A total of 367 cases (N) of colorectal lesion samples were studied including both prospective (n = 265) and retrospective (n = 102) cases. Prospective cases included in the study were referred from the Department of General Surgery, Surgical oncology, Pediatric Surgery and gastrosurgery of our institute. Inclusion criteria set was, patient of either sex irrespective of age group presenting with gastrointestinal (GI) signs and symptoms with visible lower GI mucosal lesions by colonoscopy. Patients excluded were those refusing consent, uncooperative/with perforated viscus/recent myocardial infarction/inflammatory diseases of colon or rectum/Lymphoma/sarcoma/neoendocrine tumors/known hereditary cancer syndromes. Both large colectomy samples and small four quadrant colonoscopic biopsy samples were collected in 10% buffered formalin for proper fixation after taking patient consent. Moreover, then processed, stained with hematoxylin and eosin (H and E) stain routinely. Retrospective cases were selected from the record having data similar to prospective ones and their paraffin embedded blocks were retrieved, sections made and stained with H and E. Eighth Edition, AJCC Staging Manual, Version: Colon Rectum 4.0.0.1, June 2017, College of American Pathologist (CAP) guideline was followed for histological reporting of grading and staging systems of CRC.[7] This was followed by immunohistochemistry (IHC). IHC is a commonly used staining method where selective antibodies are utilized to quantify and assess distribution of molecular markers in tumor tissue. Hence, only 60 randomly selected cases were submitted for IHC (PathnSitu) of CDX2 and Ki67 because of the financial constraint. IHC done on the paraffin-embedded tissue block by standard immunohistochemical method using horseradish peroxidase-linked antibody. Primary anti-CDX2 (EP25) and Ki-67 antibody were rabbit and mouse monoclonal antibody respectively supplied from PathnSitu and the dilution factor was 1 in 100. CDX2, a nuclear transcription factor, is involved in the processes of differentiation, intestinal cell proliferation, adhesion and apoptosis, having organ-specific expression. Ki67 antigen (nuclear nonhistone protein), an important marker for cell proliferation, is expressed in all phases of cell cycle except for G0 phase. The cell growth fraction is directly correlated with tumor aggression. Positive tissue control taken for ki67: Reactive Lymph node, for CDX2: Normal colon. For Negative control, primary antibody was omitted in the procedure. While evaluating immunostaining, nuclear staining of tumor cells was taken into account for both CDX2, and Ki67. The Ki67 was calculated in the tumor hot spot area and percentage was given from 1000 cell count. Tumor cells that showed <5% for nuclear staining for Ki67, and CDX2, were considered score 0− (<5%), those that indicated 5%–25% staining were considered as Score 1+, those that showed 26%–75% staining were considered as Score 2++, and those that indicated more than 75% staining were considered as Score 3++. The intensity of staining was also scored on a categorical scale from 0 to 3: 0 indicated absent; 1+ very weak, dubious staining; 2+ definite, mild, or moderate staining; 3+ definite, strong staining.[9]

**Statistical analysis**

Qualitative data were expressed as proportion with percentages and quantitative data as mean with standard deviation. Statistical analysis of proportion was done on software version 20.0 licensed to the Institute. Ethical approval was sought and obtained from the institutional ethical committee.

**Results**

A total of 367 cases of colorectal lesions were studied in our department, out of which 265 cases were prospective and 102 cases were retrospective ones. Of these 319 cases were small biopsy and 48 cases were large (colectomy) biopsy specimen. Out of total 48 cases of colectomy specimens; 13 cases were T2 N0 M0 (i.e., tumor invades muscularis propria), 25 cases were T3N0M0 (i.e., tumor invades muscularis propria into pericolorectal tissues) and 10 cases were T4a N1 M0 (i.e., tumor penetrates to the surface of visceral peritoneum with metastasis in 1–3 regional lymph nodes). From the total of 367 cases which were included in the study (n = 367), 60 randomly selected cases (n = 60) were subjected to IHC analysis for CDX2 and Ki67 and scoring was done as described with their expression patterns noted in different histologic types, grade and stage of carcinoma cases. No IHC was done on metastatic lymph node/organ but proved by radiography.

Mean age of the study participants was 49.62 years with a standard deviation of 17.34 years. It was seen that majority of the participants were from the age group of 40–60 years (165 cases, 45%) those reported with growth in the colon and rectum. Males were reported more among all the study participants (233 cases, 60.8%) in all age groups as compared to the females (144 cases, 39.2%). However, the difference was not statistically significant (P > 0.05, using Chi-square test) [Figure 1]. Three major complaints were found in these cases – pain abdomen, bleeding per rectum or constipation, or a combination of these. Bleeding per rectum was the most common presenting symptom both in male and female, with a total of 172 cases out of 367 (46.9%) presenting with this symptom. It was seen that left sided lesions were more compared to the right sided ones [Table 1] and rectum was the most common site of affection for both males and females (approximately 17% each) as compared to individual parts of colorectal region. But considering Rectum and the whole colon; colon was affected more, i.e., (238 cases, 64.9%). Again among colonic parts, descending colon was the most common site (23.2%) followed by ascending colon (19.3%), transverse colon (15.8%), and least common site was recto-sigmoid junction (1.4%). In the ascending and descending colon, males outnumbered females. Transverse
colon, sigmoid colon, and rectum were found to have more association with the female. This association was statistically significant ($P = 0.000$, Chi-square value was 47.296) [Figure 2].

In histopathology, the nonneoplastic lesions comprised of total 38 cases, out of which juvenile polyp followed by inflammatory polyps were in order of 15 and 13 cases, respectively. It was seen that left-sided distribution was more among cases of nonneoplastic polyp with more than 50% of the cases being limited to transverse and descending colon (20 cases, 52.6%).

Rectum was the single most important site that was affected among all cases of adenoma (nonneoplastic polyp) resulting in more predominant left-sided cases like nonneoplastic polyps. Within total neoplastic lesion; the adenoma (nonneoplastic polyp) evident was 218 cases with different grades of dysplasia. The tubulovillous adenoma with low-grade dysplasia was the highest in number with a total of 58 cases (26.6%). Moreover, majority of neoplastic polyps were found in the rectum followed by descending colon, whereas sigmoid colon was the least common site for neoplastic poly $n = 16, 7.34\%$) [Table 2].

Among all the carcinoma, adenocarcinoma number was the highest and adenosquamous carcinoma was only 6 cases (5.4%) and was lowest in number. The ascending and descending colon and rectum were the usual sites that are affected by carcinoma, and these cases were almost equal in numbers (25-28% each). Hence, carcinomas found to be more common in the left side.

IHC of both CDX2 and Ki67 was performed in total 60 cases from both colectomy and colonoscopic biopsy sections which included both neoplastic (carcinoma 38 cases, adenoma 20 cases) and nonneoplastic cases (inflammatory polyp 2 cases) and was interpreted as per the scoring system elaborated in material and method [Table 3 and Figure 3]. The expression pattern of both CDX2 and Ki67 was also correlated with the different histologic variant, grade and stage of the tumor as well as in polyps [Figure 4]. While seeing the pattern of expression of both CDX2 and Ki67 in the right side versus left side and in different age/sex group, no significant difference of pattern was discovered in our study. While considering nonneoplastic versus neoplastic polyp, CDX2 score 2++ was found in the majority of neoplastic polyp (adenoma) cases, whereas in all the nonneoplastic polyps (inflammatory polyp, $n = 2$) score 2++ were expressed. A strong intensity and high score (2++, 3+++ ) of CDX2 immunoeexpression was seen in colorectal carcinoma patient in stage pT2 and pT3 stages without lymphovascular invasion/lymph node/distant metastasis, and the positive index was decreased with score (0−, 1+) in patients with pT4 stage with or without lymphovascular invasion and/or distant metastasis. Among different subtype (histological variant)/grade of carcinoma, CDX2 expression showed different scores [Table 3]. Maximum score observed was 3+++ in 18 out of IHC proven 38 carcinomas; among which Signet ring-cell carcinoma was 4 of 6, adenocarcinoma was 12 of 20, and mucinous carcinoma was 2 out of 6 cases. All the cases in the current study were...
found to be positive for CDX2 expression (60 cases, 100%). CDX2 is identified with elevated mean expression levels in adenomatous polyp and carcinoma compared to normal tissue though the expression is reduced in PT4 tumor. Only carcinoma cases were found to be highest in number having high score and moderate to strong intensity of expression of this marker, which was statistically significant ($P = 0.008$, using Chi-square test) indicating a strong association.

Though Ki67 staining had no correlation with age, gender or tumor location; high Ki67 index (2++ and 3+++) was found in higher grade and stage of tumor. Ki67 was found usually in the lower third of normal colonic crypts. Patients with colorectal polyps (non-neoplastic) revealed increased positivity index (2++) and distribution was with medium intensity while neoplastic polyps showed uniformly high intensity and high score (2++, 3+++), like that of carcinomas. Considering different histological subtypes of carcinoma; Ki67 showed variable expression with highest percentage in carcinoma cases showing high intensity and score without any case of negative expression [Figure 3]. In our study majority carcinoma cases were showed score 2++ and 3+++ i.e., $n = 15$ (39.47%) each. Signet ring-cell carcinoma: highest cases had score of 3+++ (3 cases out of 6 cases), Adenocarcinoma: maximum cases had score of 3+++ (10 out of 20 cases) whereas Mucinous carcinoma: showed highest score of 2++ immunoreexpression of Ki67 antigen (3 out of 6 cases). Like that of CDX2 staining, all 60 cases were found to have positive Ki-67 expression. None of our case had negative expression.

**Discussion**

In India, the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1/1 lakh respectively accounting for eighth and ninth rank. In women, the AAR for colon cancer is 3.9/1 lakh with the rank ninth whereas, rectal cancer does not figure in the top 10 cancers. Risk factors for CRC are broadly divided into genetic and environmental/lifestyle factors including sedentary habit, consumption of red meat, low fat diet, alcohol, tobacco. Carcinogenesis of CRC is heterogeneous resulting from different pathways. Majority of the CRCs are sporadic, and tumorigenesis occurs in a
was reported in up to 50% of villous adenoma and up to 18% of tubular adenoma.\cite{11} Adenoma development and recurrence are complex genetic processes driven by multiple gene copy number changes and CDX2 identified as a potential marker of recurrence.\cite{12} In human, CDX2 (caudal type homeobox 2), a the transcription factor that is expressed in the nucleus of intestinal epithelial cells and the gene encoding it functions as a tumor suppressor. Normally CdX2 expressed throughout the small and large intestines, beginning from the duodenum, peaks in the proximal colon and decreases caudally with even expression along the crypt-cuff axis of the colonic crypt. It regulates the development, differentiation, and maintenance of colonic epithelium. Hence, CDX2 was used as a diagnostic marker of colonic origin for many years and is found to be positive in majority of colon and appendix carcinomas. In recent era, several studies have demonstrated that the lack of CDX2 expression in CRC and associated with an aggressive behavior, poor prognosis, high tumor grade, high tumor stage, BRAF mutation, MSI high phenotype, owing to the tumor-suppressor action.\cite{13,14}

Hence, we carried out this study to observe the heterogeneity in the expression pattern of CDX2 and Ki67 in different types of colorectal lesions, also among the different histological subtypes, grades and stages of CRC which were then correlated with similar studies. The current study included both neoplastic as well as nonneoplastic polyps and CRC of total 367 Cases whose demographic data like age, sex, locations, and presenting symptoms were also compared.

The present study showed highest affection of colorectal lesions between 40 and 60 years of age with mean age = 49.62 years and male preponderance (male:female = 1.5:1) that was well correlated with the findings of Sen et al., Nayak et al., and Peedikayil et al.\cite{9,15,16} In Nabi study, 88% of colorectal carcinoma were between 41 and 69 years.\cite{17} Mesina et al. studied 82 cases of colorectal adenocarcinoma between 31 and 93 years with predominance of male. Location of both malignant polyps and carcinoma in their study was more in left side like our study.\cite{18} Whereas Peedikayil et al. found 74% of the tumor located distal to the splenic flexure.\cite{19} Nayak et al. reported sigmoid colon to be the most common site followed by the cecum and rectum.\cite{15}

A study by Mesina et al. showed CDX2 expression in majority (84.70%) cases with variable intensity among which (45.12%) of tumors expressed high positivity index.\cite{8} CDX2 positivity was also reported in >70% colorectal mucinous carcinomas by Kaimakitchiev et al. tissue microarrays study. Strong nuclear staining for CDX2 was observed in 86% of colonic adenocarcinomas of their study without significant difference in the staining of well (Grade I) and moderately differentiated (Grade II) tumor.\cite{18} In another study by Bayrak et al., 97% CDX2 positive colorectal carcinomas was reported, of which 60% had high positivity index. Their study suggested no significant association between CDX2 expression and tumor grade/clinical stage of tumor in CRC because they found 98%

---

### Table 2: Type of lesion as per histopathological diagnosis of the cases (n=367)

| Type of cancer          | Frequency (%) |
|-------------------------|---------------|
| Nonneoplastic           |               |
| Hamartomatous polyp     | 4 (1.1)       |
| Hyperplastic polyp      | 6 (1.6)       |
| Inflammatory polyp      | 13 (3.5)      |
| Juvenile polyp          | 15 (4.1)      |
| Sub-total               | 38 (10.35)    |
| Adenoma (neoplastic polyp) |           |
| Tubular adenoma with high-grade dysplasia | 13 (3.5) |
| Tubular adenoma with low-grade dysplasia | 21 (5.7) |
| Tubulovillous adenoma with high-grade dysplasia | 7 (1.9) |
| Tubulovillous adenoma with low-grade dysplasia | 29 (7.9) |
| Tubulovillous high with grade dysplasia | 28 (7.6) |
| Tubulovillous with low grade dysplasia | 58 (15.8) |
| Villous adenoma with high-grade dysplasia | 35 (9.5) |
| Villous adenoma with low-grade dysplasia | 27 (7.4) |
| Sub-total               | 218 (59.40)   |
| Carcinoma               |               |
| Adenocarcinoma          | 63 (17.2)     |
| Adenosquamous carcinoma | 6 (1.6)       |
| Mucinous carcinoma      | 33 (9.0)      |
| Signet-ring cell carcinoma | 9 (2.5)     |
| Sub-total               | 111 (30.24)   |
| Total                   | 367 (100.0)   |

---

### Table 3: CDX2 and Ki67 expression among cases subjected for immunohistochemistry (n=60)

| Histopathology                  | n  | Marker | Positivity index |
|---------------------------------|----|--------|-----------------|
|                                 |    | CDX2   | 0- 1+ 2+ 3+     |
| Mucinous adenocarcinoma         | 6  | Ki67   | 1 3 2           |
| Adenocarcinoma                  | 20 | CDX2   | 0 2 6 12        |
| Adenosquamous carcinoma         | 6  | CDX2   | 1 4 1 0         |
|                                 |    | Ki67   | 3 2 1 0         |
| Signet ring cell carcinoma      | 6  | CDX2   | 0 0 2 4         |
|                                 |    | Ki67   | 0 0 3 3         |
| Tubulovillous adenoma with dysplasia |     | CDX2   | 0 1 5 4         |
|                                 |    | Ki67   | 0 0 4 6         |
| Low grade                       | 10 | CDX2   | 2 4 4 0         |
|                                 |    | Ki67   | 0 4 4 2         |
| Inflammatory polyp              | 2  | CDX2   | 0 0 2 0         |
|                                 |    | Ki67   | 0 0 2 0         |

---

conventional pathway in the stepwise manner called adenoma carcinoma sequence where adenoma is the early lesion. This process is associated with mutations in genes such as APC, p53, KRAS, SMAD2, SMAD4 or MMR; particularly KRAS
of low-grade tumors and 91% of high-grade tumors were positive for CDX2. Other studies showed down regulation in CDX2 immunoexpression in higher stage, similar to our study. Witek et al. found CDX2 over expression in most colorectal tumors compared to normal mucosa, similar feature was also observed by the current study and Sen et al. Saad et al. suggested that CDX2 should not be used as the sole diagnostic marker for the primary GI tract adenocarcinoma and be used with other immunohistochemical markers. Whereas Werling et al. reported that the high levels of CDX2 expression were found almost exclusively in adenocarcinomas of the colorectum, but the intermediate levels were found in adenocarcinomas arising elsewhere in the GI tract.

While depicting Ki-67 LI, Georgescu et al. found that the Ki-67 LI increased with the histological grade of adenocarcinomas that had an agreement with our study where highest index of Ki67 was seen in Signet ring-cell carcinoma (high grade) and pT4 stage of tumor. Nabi et al. had concluded that the proliferative activity measured by Ki-67 is related to histological type, grade and stage; Gurzu et al. found a significant increase of Ki67 median expression with poorer grade, age of patients and lymph node involvement. Mesina et al. had disagreed to the fact that Ki67 immunoexpression in patients with CRC had no correlation with tumor proliferative capacity and tumor invasion. Petrisor et al. found a wide range of Ki-67 LI in colonic carcinomas ranging from 5% to 95% and observed no relationship between Ki-67 LI of colonic adenocarcinomas and histopathology grade. However, existence of significant differences was advocated in their study, by comparing mean Ki-67 values with respect to different pathologic subtypes of rectal adenocarcinoma.

From the above studies, it had been observed that CDX2 usually overexpressed in any colorectal lesion than normal colonic epithelium, both in form of score and intensity. However, comparing CRCs versus nonneoplastic polyps and adenomatous polyps; CRCs show high level expression (high score). While considering different histological variants like mucinous/nonmucinous/signet ring-cell type carcinomas or different grades like G1 (well differentiated)/G2 (moderately differentiated)/G3 (undifferentiated) or even different stages (PT1-PT4), there were varied opinion. Considering Ki67 which is already in use as an established prognostic marker in many common cancers such as breast/ovarian/bladder cancers was also seen to have similar expression pattern in colorectal lesions found in the current study and several other studies. Steady rise of Ki67 was observed as the tumor progresses from low-to-high grade and stage. The limitation of our study was very less number of cases (n = 60) upon which we performed IHC, metastatic site IHC not done, also the survival analysis could not be analyzed which could have given a better impact on the study. As there is a significant rising trend of sporadic CRC in younger generation, emphasis is given for an early diagnosis by screening and to halt the process of spread at a lower stage for achievement of better survival.

Hence, CDX2 can act as a diagnostic marker though not a specific one and Ki67 can be utilized as a prognostic marker for CRC.

**Conclusion**

We concluded that CDX2 is a good indicator for any colorectal lesion, especially in all variants of adenocarcinoma but grade and stage are not directly correlated as that of Ki67. Hopefully these potential protein markers can be utilized in future to aid in assessing risk group and development of new consensus guidelines for individual prognosis and precession treatment in the clinical setup of India.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today. [last accessed on 2020 Dec 23]
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.
4. Smith G, Carey FA, Beattie J, Wilkie MJ, Lightfoot TJ, Coxhead J, et al. Mutations in APC, Kirsten-ras, and p53–alternative genetic pathways to colorectal cancer. Proc Natl Acad Sci U S A 2002;99:9433-8.
5. Brody H. Colorectal cancer. Nature 2015;521:s1.
6. McGuire S, Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press; 2015. Adv Nutr 2016;7:418-9.
7. Kakar S, Shi C, Berho ME, Driman DK, Fitzgibbons P, Frankel WL, et al., Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. College of American Pathologists (CAP). Version: Colon Rectum 4.0.0.1; 2017. Available from: http://www.cap.org/cancerprotocols. [Last accessed on 2018 Apr 04]
8. Mesina C, Stoean LC, Stoean R, Sandita VA, Gruia CL, Foarfa MC, et al. Immunohistochemical expression of CD8, CDX2, P53, D2-40 and Ki 67 in colorectal adenocarcinoma, conventional and malignant colorectal Polyps. Rev Chim (Bucharest) 2018;69:419-28. DOI: 10.3735/RCH.18.2.6120. Available from: https://www.researchgate.net/publication/32372461. [last accessed on 2020 Dec 23]
9. Sen A, Mitra S, Das RN, Dasgupta S, Saha K, Chatterjee U, et al. Expression of CDX-2 and Ki-67 in different grades of colorectal adenocarcinomas. Indian J Pathol Microbiol 2015;58:158-62.
10. NCRP. Three-year Report of the Population based Cancer Registries-2009-2011. National 2, Cancer Registry Programme, Indian Council of Medical Research (ICMR), Bangalore, India; 2013.
11. Erichsen R, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016;150:895-902.
12. Fiedler D, Haddad KH, Hirsch D, Hernandez LS, Torres I, Wanga D, et al. Single-cell genetic analysis of clonal dynamics in colorectal adenomas indicates CDX2 gain as a predictor of recurrence. Int J Cancer 2019;144:1561-73.
13. Baba Y, Nosho K, Shima K, Freed E, Irahara N, Philips J, et al. Relationship of CDX2 loss with molecular features and prognosis...
Nayak, et al.: CDX2 and ki67 in colorectal lesions with their expression pattern in colorectal carcinomas

14. Olsen J, Eiholm S, Kirkeby LT, Espersen ML, Jess P, Gögenür I, et al. CDX2 downregulation is associated with poor differentiation and MMR deficiency in colon cancer. Exp Mol Pathol. 2016;100:59-66. doi: 10.1016/j.yexmp.2015.11.009. Epub 2015 Nov 6. PMID: 26551082.

15. Nayak SP, Sasi MP, Sreejayan MP, Mandal S. A case-control study of roles of diet in colorectal carcinoma in a South Indian Population. Asian Pac J Cancer Prev 2009;10:565-8.

16. Peedikayil MC, Nair P, Seena SM, Radhakrishnan L, Sadasivan S, Naryanan VA, et al. Colorectal cancer distribution in 220 Indian patients undergoing colonoscopy. Indian J Gastroenterol 2009;28:212-5.

17. Nabi U, Nagi AH, Sami W. Ki-67 proliferating index and histological grade, type and stage of colorectal carcinoma. J Ayub Med Coll Abbottabad 2008;20:44-8.

18. Kaimaktchiev V, Terracciano L, Tornillo L, Spichtin H, Stoios D, Bundi M, et al. The homeobox intestinal differentiation factor CDX2 is selectively expressed in gastrointestinal adenocarcinomas. Mod Pathol 2004;17:1392-9.

19. Bayrak R, Halats H, Yenidunya S. The value of CDX and cytokeratins 7 and 20 expression in differentiating colorectal adenocarcinomas from extraintestinal gastrointestinal. Gastrointestinal oncological; adenocarcinomas: Cytokeratin 7-20+phenotype is more specific than CDX2 antibody. Diagn Pathol 2012;23:7-9.

20. Bakaris S, Creinkaya A, Ezberci F, Ekerbicer H. Expression of homeodomain protein CDX2 in colorectal adenoma and adenocarcinoma. Histol Histopathol 2008;23:1043-7.

21. Witek ME, Nielsen K, Walters R, Hyslop T, Palazzo J, Schulz S, et al. The putative tumor suppressor Cd×2 is overexpressed by human colorectal adenocarcinoma. Clin Cancer Res 2005;11:8549-56.

22. Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: Its utility and limitations. World J Gastrointest Surg 2011;3:159-66.

23. Werling RW, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: An immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 2003;27:303-10.

24. Georgescu CV, Saftoiu A, Georgescu CC, Ciurea R, Ciurea T. Correlations of proliferation markers p53 expression and histological findings in colorectal carcinoma. J Gastrointestin Liver Dis 2007;16:133-9.

25. Gurzu S, Jung J, Mezei T, Pávai Z. The correlation between the immunostains for p53 and Ki67 with bcl-2 expression and classical prognostic factors in colorectal carcinomas. Rom J Morphol Embryol 2007;48:95-9.

26. Petrisor O, Giusca SE, Sajin M, Dobrescu G, Caruntu ID. Ki-67, p53 and bcl-2 analysis in colonic versus rectal adenocarcinom. Rom J Morphol Embryol 2008;49:163-71.