Original Article

Cocktail of MACC-1, Kisspeptin-1 and ALDH-1 Immunohistochemistry Biomarkers with Potential of Prognostication and Risk Stratification in Colorectal Carcinomas

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Abstract

Background: Metastasis Associated in Colon Cancer gene has emerged as regulator of epithelial mesenchymal transition and is associated with poor prognosis. Kisspeptin 1, tumor suppressor enzyme affects cellular motility, tumor invasion and metastasis. Its reduced expression implies tumor progression and poor prognosis. ALDH1 gene is marker of stem cell activity. Its increased expression is a marker of tumor progression and resistance to chemotherapeutic drugs and radiation. These biomarkers can be detected by immunohistochemistry. The aim of our study is to find an association of MACC-1, KISS-1 and ALDH1 with aggressiveness and tumor progression in colorectal carcinomas. All retrospective and prospective cases of colorectal adenocarcinomas received over period of five years, from 2017 to 2021, were included in this study and case control study was planned.

Methods: The study population was divided into two comparison groups based on TNM staging: (a) those with non-aggressive tumors (controls) (TNM stage I, II) and (b) those with aggressive tumors (cases) (TNM stage III, IV). A total of 36 controls and 27 cases were studied. Immunohistochemistry for MACC-1, KISS-1 and ALDH1 was done. Cytoplasmic and membranous staining was considered positive for these three immunomarkers. Chi-square test was used to find out an association among these biomarkers and aggressiveness and tumor progression of colorectal carcinomas. $P < 0.05$ was considered to be significant.

Results: We found an association of MACC1 and KISS1 with aggressiveness and tumor progression whereas no association could be established with ALDH1.

Conclusion: These biomarkers are promising targets for prognostication and developing novel anticancer therapeutics.

Keywords: biomarkers; colorectal carcinoma; immunohistochemistry; metastasis.

Introduction

Colorectal carcinoma (CRC) worldwide is a leading cause of cancer related mortality and morbidity. [1] It is the fourth most common cancer in the world with 1.3 million new cases each year and a 5-year prevalence rate of 3.2 million and an estimated 693,333 deaths due to CRC in 2012. CRC is the fifth most common cancer in India, following breast, cervix/uteri, lip/oral cavity and lung cancer. [2]

SRC Homology 3 Domain (SH3 domain) of Metastasis Associated in Colon Cancer (MACC-1) gene located on human chromosome 7 at 7p21.1, was first identified by Stein et al in 2009. MACC1 comprises of seven exons and six introns and till now five different splicing variables of this gene have been identified. [3] Further structural studies showed that this protein comprises of four domains: ZU5, SH3 and two Cterminal death domains (DD). Out of these four domains, the ZU5 domain is made up of two β-sheets. This domain mediates proteinprotein interactions. The SH3 domainand its SH3

binding motif contribute to the biological activity of this protein. Lack of any of the two leads to the loss of Met gene, an important transcriptional target of MACC1 protein. [3, 4] The two C-terminal death domains provide it a unique architecture that may help triggering cell death by apoptosis. Due to its functional activity, MACC-1 has emerged as a regulator of epithelial-mesenchymal transition in HGF/c-Met pathway and is associated with poor prognosis. [5] Thus, higher levels of MACC1 are associated with tumor progression and metastasis in various cancers like lung cancer, hepatocellular cancer, gastric cancer as well as CRC. MACC1 expression in various cancer patients can be studied either by measuring the MACC1 expressing micro-ribonucleic acid (mRNA) levels or by using immunohistochemistry (IHC) with specific MACC1 antibody. [3, 4]

Kisspeptin 1 enzyme, first described in malignant melanoma, is located on chromosome 1q32 and is known as suppressor of metastasis. KiSS-1 binds to G-protein coupled receptor KiSS-1R and encodes a protein of KiSS peptin family. KiSS-1 affects cellular motility, tumor invasion, cellular proliferation of tumor cells and metastasis. [5, 6] Any deregulation in the normal function of this tumour suppressor enzyme will lead to tumor progression and metastasis. Such dysfunction or down-regulation may occur by various mechanisms like promoter methylation or homozygous deletion. [5] KISS1 expression and its ability to suppress breast cancer to metastasize has been well documented. Matrix metalloproteinase 9 (MMP9) is known for its role in epithelial-mesenchymal transition and promoting invasion and metastasis. KISS 1 interacts with MMP9 and leads to inhibition of expression of MMP9. [7] There are no known mechanisms till now which have been ableto explain this interaction between MMP9 and KISS1 protein. Since this newer molecule has gained an attention for research in the recent years, it is being studied that reduced expression of KiSS-1 can be associated with tumour progression and metastasis. [7] KISS1 expression can be evaluated by using IHC utilizing the corresponding antibody application on formalin fixed paraffin embedded tumor tissue blocks. Positive staining of KISS1 by IHC produces cytoplasmic and membranous pattern.

ALDH superfamily enzymes function in detoxifying endogenous and exogenous aldehydes. ALDH1 gene, located on chromosome 12, has a role in oxidation of intracellular aldehydes and retinoic acid biosynthesis. Retinoic acid is required as a signaling molecule for cell differentiation and proliferation. There is evidence for role of ALDH superfamily enzymes as a marker of stem cell activity. [8, 9] It regulates cell function in stem cells. Increased expression of ALDH1 in cancer stem cells is a marker of tumor progression, differentiation, resistance to chemotherapeutic drugs and radiation. [8, 10] Such function depends on the isoform expressed in the particular tissue. Among ALDH1 family of its isoforms, ALDH1A1 and ALDH1A3 members are required for retinoic acid biosynthesis and through this functional activity, both these members have an important role in regulating cell function in stem cells-normal as well as tumor-initiating stem cells. The expression of ABC transporters is noted on mesenchymal stem cells, somatic stem cells as well as on multipotent adult progenitor cells. [10] This functional activity helps utilization of increased expression of ALDH1 in tumor-initiating cells/ cancer stem cells as a marker of tumor progression, differentiation, and also, resistance to chemotherapeutic drugs and radiation. [8, 10] It is seen that increased expression of ABC transporters along with increased expression of ALDH1 results in a synergistic interplay of their chemo-resistant potentials in various cancers like breast cancer, hepatocellular carcinoma, lung cancer, pancreatic carcinomas, gastric cancer and CRC. Hence, ALDH1 gains prognostic importance. ALDH1 expression can be studied by IHC by utilizing antigen retrieval method on formalin fixed paraffin embedded blocks of the tumor tissues.

A cocktail of these novel IHC markers helps in prognostication and risk stratification in CRC patients. The goal of our current study is to find out an association of MACC1, KISS1 and ALDH1 with aggressiveness and tumor progression in CRC by using IHC. Also, these new markers hold good potential to be studied for targeted therapy and its utility in patients of CRC.

Materials and Methods

In this study, all retrospective and prospective cases of adenocarcinomas of CRC over a period of five years, from 2017 to 2021 were studied. Patients of all ages and both sexes were included. Patients with any other primary carcinoma of colon and rectum except adenocarcinoma, secondary malignant lesions, blocks with insufficient material and patients who underwent small biopsies were excluded from the study. Demographic details and available data on tumor metastasis (CT/PET scan reports of the patients pre-operatively) were noted. Patients with evidence of pre-operative metastasis were excluded from the study. Institutional Ethics Committee clearance was obtained prior to proceeding with the study vide certificate number IEC/OCT/2018 dated 23 Oct 2018. Informed consent was taken from all subjects for obtaining clinical data and consent from institutional head was obtained for review of tissue blocks and slides for study of MACC1, KISS1 and ALDH1 on such samples. A case control study was planned, and the selected study population was divided into two comparison groups based on TNM staging (AJCC, 8th edition): (a) those with non-aggressive tumors (TNM stage I, II; controls); (b) those with aggressive tumors (TNM stage III, IV; cases). A sample size of 63 was studied, out of which 36 were controls and 27 were cases. Archival formalin fixed and paraffin embedded blocks were retrieved and sections of 3-4 micron thickness were cut. IHC was done using antibodies directed against MACC1, KISS1 and ALDH1. Streptavidin-biotin method was utilized and DAB was used as chromogen with hematoxylin as counterstain. H&E stained slides were evaluated to ascertain the diagnosis and pathological staging (AJCC 8th edition) of CRC by an experienced gastrointestinal pathologist [Fig. 1].

Further the results of IHC for MACC1, KISS1 and ALDH1 were noted. Cytoplasmic and membranous staining pattern was considered positive result for all the three IHC markers [Fig. 2]. We examined a minimum of ten high power fields per section and averaged out the count. Cases with $\leq$25% tumor cells showing positivity for IHC were considered negative. Strong staining intensity with any staining frequency above 25% was considered to be a positive result. Any case showing only a background blush and weak/intermediate intensity of staining were considered negative. IHC status was correlated with tumor stage, grade, tumor budding, lymphovascular invasion (LVI), perineural invasion (PNI) and inflammatory response at the tumor normal junction. Statistical analysis of the data was done using a two-tailed test. The proportion of IHC positivity among cases and controls was used to calculate the Odds ratio. Chi-square test was used to find out an association between aggressiveness of CRC and IHC positivity for the three antibodies. $P < 0.05$ was considered to be significant. SPSS software (SPSS version 25.0, IBM corporation, USA) for MS Windows was used for statistical analysis.

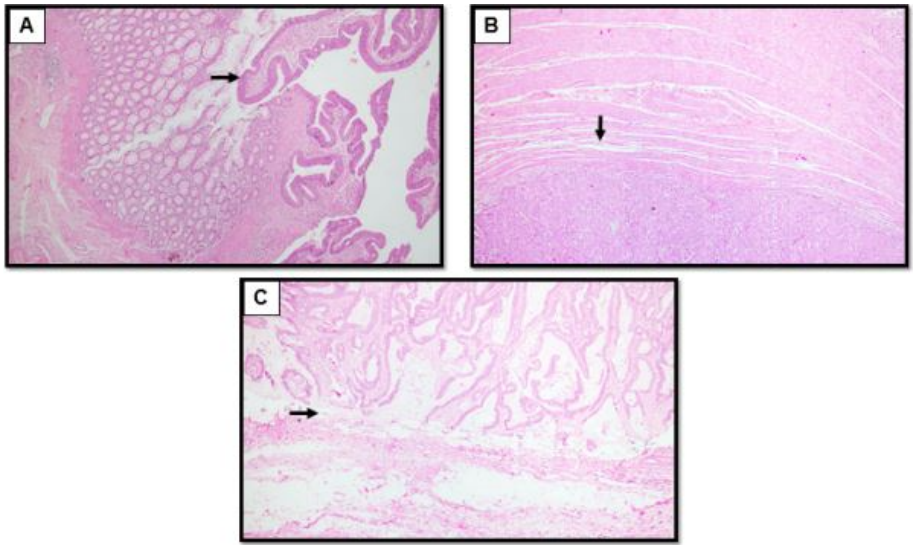

Figure 1: Stages of tumour invasion: (A) T1 stage with submucosal invasion; (B) T2 stage with muscularis propria invasion; (C) T3 stage with tumour invading through muscularis propria into subserosal fat (H&E; 40X)

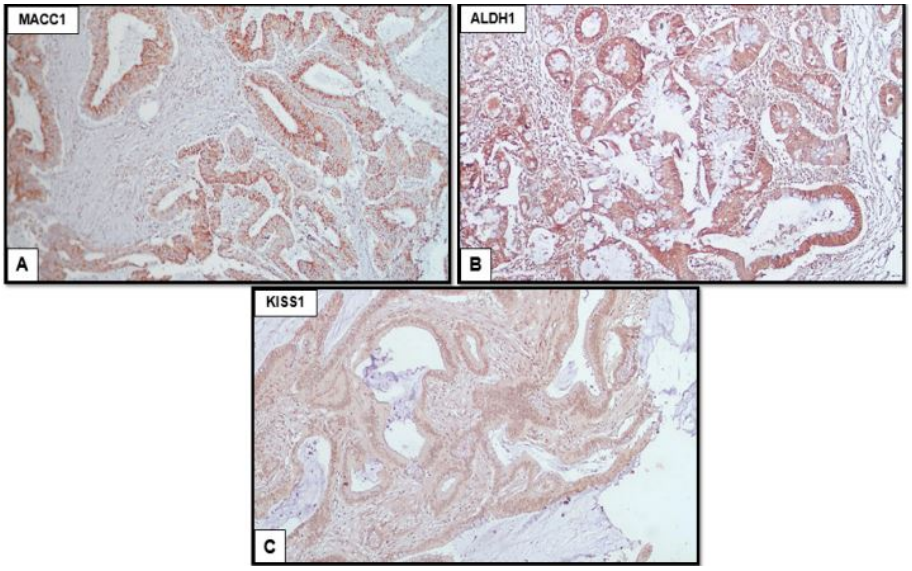

Figure 2: (A) MACC1; (B) ALDH1; (C) KISS1 immunohistochemistry showing cytoplasmic and membranous positivity for the three markers (40X)

Results

Study population of total 63, with 27 patients having aggressive tumors (TNM stage III and IV; cases) and 36 patients having non-aggressive tumors (TNM stage I and II; controls). IHC studies with MACC1 revealed a significant association between MACC1 and aggressiveness of CRC (P=0.0028) [1]. Out of 36 controls, 13 (36.11%) were MACC1 positive, whereas of the 27 cases, 20 (74.07%) were MACC1 positive. Out of the total study population of 63 cases, a total of 11 cases showed well differentiated histologic grade, 44 cases were moderately differentiated and only eight cases showed

poorly differentiated histologic grade. There was no statistically significant association between tumor grade and MACC1 (P=0.4106) [1], which can be attributed to small population size of 63 cases with a relatively very less number of cases showing poorly differentiated histology. 22 (66.7%) of 33 MACC1 positive cases showed tumor budding at the advancing edge of tumor. Of the 30 MACC1 negative cases, 15 cases (50.0%) showed tumor budding. P value for an association between MACC1 and tumor budding was not significant (P=0.180), however, higher percentage of MACC1 positive cases showed tumor budding. Of the total 36 non-aggressivecases, 21(58.3%) showed inflammatory response, whereas 11(40.7%) of 27 aggressive cases showed inflammatory response (P=0.259).24 (72.73%) of all 33 MACC1 positive cases had LVI, whereas nine (27.27%) of MACC1 positive cases showed no LVI. The P value was statistically significant (P=0.001) [1]. Ten (30.30%) out of all the 33 MACC1 positive cases had PNI, whereas four (13.33%) out of 30 MACC1 negative cases had PNI (P=0.1056) [1].

Of the 36 controls, 29 (80.56%) were KISS1 positive, whereas of the 27 cases, six (22.22%) were KISS1 positive. A statistically significant association was seen between KISS1 and aggressiveness of CRC (P=0.001) [2]. All the eight poorly differentiated tumors were negative for KISS1 (P= 0.158) [2]. Out of 37 cases showing tumor budding, 16 (43.24%) were KISS 1 positive by IHC (P=0.019) [2]. 12 (34.29%) of all 35 KISS1 positive cases had an inflammatory response and P value was found to be statistically significant (P=0.003) [2]. Only five (14.29%) of the total 35 KISS1 positive cases had LVI, which is a marker of tumor aggressiveness and progression (P=0.001) [2]. Only two (14.29%) out of 14 PNI positive tumors showed KISS1 positivity, and only two (5.71%) out of 35 KISS1 positive tumors had PNI (P=0.0004) [2].

Of the 36 controls, 18 (50.0%) were ALDH1 positive, whereas out of the 27 cases, 15 (55.56%) were ALDH1 positive with no significant association between ALDH1 and tumor stage (P=0.662) [3]. Like-wise, no association was noted among tumor grade and tumor budding and ALDH1 (P=0.683 and 0.751, respectively) [3]. Only 12 (36.4%) of all 33 ALDH1 positive cases had inflammatory response, as compared to a significantly larger number (20/30; 66.7%) ALDH1 negative cases that showed inflammatory response. P value was found to be statistically significant (P=0.016) [3].Out of 33 ALDH1 positive cases, 24 (72.73%) had LVI, whereas only seven (23.3%) out of 30 ALDH1 negative cases showed LVI. The P value was statistically significant (P=0.0009) [3]. 11 cases (33.33%) of all the 33 ALDH1 positive cases had PNI, whereas only three (10.0%) of 30 ALDH1 negative cases had PNI with a significant association of ALDH1 with PNI (P=0.026) [3].

Discussion

Various prognostic markers that have been utilized routinely to determine the aggressiveness of colorectal carcinomas include: stage, tumor grade, LVI, PNI, tumor budding, tumor infiltrating lymphocytes. Till now, microsatellite instability markers (MLH 1, PMS 2, MSH 2, MSH6) and Her2 neu are being used in India for prognostication and treatment stratification. Still, it has been found that two patients of CRC in same tumor stage may still behave differently to the chemotherapy administered. Some patients show chemo-resistance which cannot be explained by the known pathological markers of aggressive tumor behaviour. These different responses to treatment are being widely studied and it is found that new biomarkers, like vasculogenic mimicry, MACC1, KISS1 and ALDH1 play important role in such inbuilt individual responses. These markers can be utilized as potential targets for administration of individualized drug therapy, achieving better cure rates and longer disease free overall survival.

In a study conducted by Bo Zhu et al (2017), 204 cases were taken as a study population for analyzing the prognostic markers VMM and ALDH1 against variables like tumor stage and histologic grade. [11] It was found that VMM was positive in a significantly higher number of CRC (36.8%; 75/204) as compared to normal controls (0%; 0/204) and that it was positively correlated with tumor stage ($P < 0.001$) but not with tumor grade ($P < 0.364$). In this study, 150 out 204 (73.5%) cases showed ALDH positive status by IHC, and there was a significant association between ALDH1 and CRC ($P < 0.001$). ALDH1 was positively correlated with tumor stage (P=0.024) but not with tumor grade (P=0.555).This study did not compare LVI, PNI, tumor budding and inflammatory response. [11]

A study was conducted on patients of ovarian carcinoma by Lan Yu et al (2017), in which 207 cases of epithelial ovarian carcinoma were analyzed for VMM, ALDH1, KISS1 and MACC1 expression and their role in tumor metastasis and prognosis. [5] These 207 cases were compared with 60 normal controls. It was noted that VMM, ALDH1 and MACC1 expression were significantly higher in cases with epithelial ovarian carcinomas (36.2%, 62.3%, and 60.9%, respectively) as compared to controls (0%, $P < 0.001$; 18.3%, $P < 0.001$, and 8.3%, $P < 0.001$, respectively). All the three markers were also found to be associated with tumor stage, lymph node metastasis, implantation and FIGO stage. It was further noted that KISS1 expression was reduced in epithelial ovarian carcinomas (33.8%, $P < 0.001$). Also, KISS1 expression was inversely related to tumour grade and FIGO stage. [5]

In a study conducted by Bo Zhu et al (2018), IHC for MACC1 and KISS1 was carried out on blocks of 212 patients with colorectal carcinomas and it was found that 61.3% (130/212 cases) showed cytoplasmic positivity for MACC1 immunostain. There was a significant association between MACC1 positivity and metastasis ($P < 0.001$) with positive correlation between MACC1 and TNM stage and grade. [12] On the contrary, it was found in this study that there was a strong negative correlation between loss of KISS1 (negative status by IHC) and tumor progression and metastasis ($P < 0.001$). [12]

Table 1: Statistical analysis of MACC1 with variables using Chi-square test

Variable P value	MACC1 (Positive)	(%)	MACC1 (Negative)	(%)	Chi-square
TNM stage **0.0028**					**8.914**
Non-aggressive	13	(36.11%)	23	(63.89%)	
Aggressive	20	(74.07%)	7	(25.93%)	
Histologic Grade **0.4106**					**0.676**
Well differentiated	7	(63.64%)	4	(36.36%)	
Moderately differentiated	23	(52.27%)	21	(47.73%)	
Poorly differentiated	3	(37.50%)	5	(62.50%)	
LVI **0.0001**					**15.339**
Present	24	(77.42%)	7	(22.58%)	
Absent	9	(28.13%)	23	(71.87%)	
PNI **0.1056**					**2.618**
Present	10	(71.43%)	4	(28.57%)	
Absent	23	(46.94%)	26	(53.06%)	
Tumour budding **0.180**					**1.801**
Present	22	(59.46%)	15	(40.54%)	
Absent	11	(42.31%)	15	(57.69%)	
Inflammation **0.259**					**1.275**
Present	19	(59.37%)	13	(40.63%)	
Absent	14	(45.16%)	17	(54.84%)	

Yet another study conducted by VH Koelzer et al (2015), 187 cases of CRC were taken to establish a correlation between MACC1 and tumor metastasis and aggressiveness. [13] The study resulted in a significant over-expression of MACC1 in CRC as compared to normal mucosa ($P < 0.001$). Further, it was seen that MACC1 expression was positively associated with tumor stage ($P < 0.0023$), LVI ($P < 0.0004$) and tumor budding ($P < 0.0352$), but was not associated with tumor grade ($P < 0.126$). [13]

In the study conducted by NS Holah et al (2017), ALDH1 expression in CRC was correlated with tumor stage, tumor grade, LVI and PNI. [14] The study included 71 cases which comprised of49 CRC, 13 adenomas and nine normal cases. This study concluded that there was a statistically significant association between ALDH1 expression and LVI (P=0.04) whereas the study did not establish any correlation between ALDH1 expression and TNM stage, grade and PNI (P=0.8, P=0.78 and P=0.92, respectively). Also, the study highlighted a highly statistical significant difference between adenoma and CRC cases regarding ALDH1 expression (higher ALDH1 expression noted in CRC as compared to adenomas; $P < 0.001$). [14] On the contrary, study by Hessman CJ et al showed that ALDH1 expression was lost in advanced stage of CRC, hence its efficacy as a therapeutic target is questionable in late stage of CRC. [**?**] Our study did not show any such correlation of ALDH1 with aggressiveness of CRC.

ALDH1 was highly expressed in non-metastatic CRC, but expression was lost with advancing stage. ALDH1 could be an

Table 2: Statistical analysis of KISS1 with variables using Chi-square test

Variable P value	KISS1 (Positive)	(%)	KISS1 (Negative)	(%)	Chi-square
TNM stage **0.001**					**21.262**
Non-aggressive	29	(80.56%)	7	(19.44%)	
Aggressive	6	(22.22%)	21	(77.78%)	
Histologic Grade **0.158**					**1.988**
Well differentiated	4	(36.36%)	7	(63.64%)	
Moderately differentiated	31	(70.45%)	13	(29.55%)	
Poorly differentiated	0		8	(100%)	
LVI **0.001**					**38.422**
Present	5	(16.13%)	26	(83.87%)	
Absent	30	(93.75%)	2	(6.25%)	
PNI **0.0004**					**12.416**
Present	2	(14.29%)	12	(85.71%)	
Absent	33	(67.35%)	16	(32.65%)	
Tumour budding **0.019**					**5.504**
Present	16	(43.24%)	21	(56.76%)	
Absent	19	(73.08%)	7	(26.92%)	
Inflammation **0.003**					**8.586**
Present	12	(37.50%)	20	(62.50%)	
Absent	23	(74.20%)	8	(25.80%)	

effective therapeutic target in early CRC but not late stage disease. No correlation was found between ALDH1 and disease prognosis.

Our study revealed a significant association between MACC1 and aggressive behaviour leading to progression of CRC (P=0.0028). MACC1 was also found to be associated with LVI (P=0.0001) as has been seen in the available literature. However, our study could not establish any correlation between MACC1 and histologic grade of tumor, PNI, tumor budding and tumor infiltrating lymphocytes (P=0.4106, P=0.1056, P=0.180, P=0.259, respectively), though previous studies have seen a correlation between MACC1 and tumor grade, [12] and tumor budding. [13] Our study could also establish a strong negative correlation between loss of KISS1 (negative by IHC) and aggressive behaviour with tumor progression in CRC (P=0.001). KISS1 was also found to be associated negatively with LVI (P=0.001), PNI (P=0.0004) and tumor budding (P=0.019). It was also noted that a there was a significant association between KISS1 and inflammatory response (P=0.003). Hence, it was noted that both variables contribute to a better prognosis. Our study, however, did not establish a positive association between ALDH1 and tumor progression (P=0.662). But a higher percentage of ALDH1 positivity was noted in the aggressive case group as compared to non-aggressive group (15/27, 55.6% and 18/36, 50% respectively). There was a positive correlation of ALDH1 with LVI (P=0.0009), PNI (P=0.026) and inflammatory response (P=0.016). However, there was no association of ALDH1 with tumor grade (P=0.683) and tumor budding (P=0.751).

Table 3: Statistical analysis of ALDH1 with variables using Chi-square test

Variable P value	ALDH1 (Positive)	(%)	ALDH1 (Negative)	(%)	Chi-square
TNM stage **0.662**					**0.191**
Non-aggressive	18	(50.0%)	18	(50.0%)	
Aggressive	15	(55.56%)	12	(44.44%)	
Histologic Grade **0.683**					**3.107**
Well differentiated	6	(54.55%)	5	(45.45%)	
Moderately differentiated	22	(50.0%)	22	(50.0%)	
Poorly differentiated	5	(62.50%)	3	(37.50%)	
LVI **0.0009**					**15.339**
Present	24	(77.42%)	7	(22.58%)	
Absent	9	(28.13%)	23	(71.87%)	
PNI **0.026**					**4.950**
Present	11	(78.57%)	3	(21.43%)	
Absent	22	(44.90%)	27	(55.10%)	
Tumour budding **0.751**					**0.101**
Present	20	(54.05%)	17	(45.95%)	
Absent	13	(50.0%)	13	(50.0%)	
Inflammation **0.016**					**5.773**
Present	12	(37.50%)	20	(62.50%)	
Absent	21	(67.74%)	10	(32.26%)	

A relatively small study population of 63 and out of this only 27 cases having aggressive tumors was a major limitation of our study. Since with wider use of better radio-diagnostic techniques for visualization of CRC, larger number of patients are being recognized at an early stage of tumour, hence this can be a cause for less number of patients with aggressive tumors. Also, there is wide spread use of chemotherapy and targeted drug therapies in present world for carcinomas, thus restricting the tumor stage to lower ones.

Conclusion

There are very few studies in CRC in Indian population comparing so many prognostic parameters with these three biomarkers. This study highlights the probable utility of MACC1 and KISS-1 in clinical practice for delineating the patients at higher risk of tumor progression. At the same time, ALDH 1 adds on to know if these patients will show response/resistance to chemotherapy chosen as the therapy of choice. However, further studies on larger study population using these potential biomarkers for their routine utilization and establishing therapeutic benefit would be helpful.

Abbreviations:
CRC: Colorectal carcinoma; IHC: Immunohistochemistry; LVI: Lymphovascular invasion; PNI: Perineural invasion.

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Nil

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