ORIGINAL ARTICLE

Tumor Budding in Colorectal Carcinoma: A Tertiary Care Center Study

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Abstract

Introduction: Tumor budding is when single or small groups of tumor cells break off from the main tumor, making it more aggressive and likely to spread. The aim of this study is to analyze tumor budding profile in colorectal carcinoma presenting in a tertiary level hospital.

Methods: A prospective observational study was conducted at Kathmandu Medical College from February 2023 to December 2023. Resected specimens were analyzed for tumor site, type, grade, lymphovascular and perineural invasion, lymph node status and tumor budding. TNM AJCC staging was done. The data was analyzed using SPSS version 16.0 with Chi-square test assessing the significance of association between the categorical variables.

Results: Among 33 cases, 18 (54.5%) were males and 15 (45.5%) were females, with a mean age of 52.4 ± 14 years. The caecum and ascending colon were the most common tumor sites each accounting for nine cases (27.3%). The average tumor size was 5.3 cm, with most adenocarcinomas classified as Grade 2, comprising 21 cases (63.6%). Lymphovascular invasion was present in 21 cases (63.6%), and perineural invasion in 18 cases (54.5%). T3 stage was the most frequent comprising of 19 cases (57.5%), and nodal metastasis occurred in 12 cases (36.4%). Tumor budding grades were low in eight cases (24.2%), intermediate in eight cases (24.2%), and high in three cases (9.1%). Tumor budding was significantly associated with lymphovascular invasion (P = 0.003) and nodal stage (P = 0.001).

Conclusions: Tumor budding grades were mostly low and intermediate, showing significant associations with lymphovascular invasion and nodal stage.

INTRODUCTION

Colorectal cancer (CRC), the third most commonly diagnosed type of cancer in men and women worldwide, is recognized as a complex multi-pathway disease. This complexity is evidenced by the fact that histologically identical tumors can have different outcomes, including varying responses to therapy.[1] Additional prognostic biomarkers are needed for predicting disease-free intervals and survival rates in CRC. Histopathological features such as lymphovascular invasion (LVI), tumor deposits in lymph nodes, and perineural invasions (PNI) have shown promising results in predicting patient survival. These markers can help identify patients at higher risk of recurrence and poor outcomes, allowing for more tailored and effective treatment plans.[2]

In recent years, tumor budding has been in focus as a valuable prognostic marker and its importance has been highlighted by many gastrointestinal pathologists. Tumor budding, characterized by single cells or clusters of fewer than five cells, is considered a histomorphologic indicator of aggressive tumor behavior.[3] This phenomenon mimics the embryologic epithelial-mesenchymal transition (EMT) and has been recognized over the past two decades as a poor prognostic factor in CRC. The presence of tumor budding suggests a higher likelihood of metastasis and a worse overall prognosis for patients, making it a critical factor in the pathological assessment and management of CRC.[4]

Several studies have shown the relationship between tumor budding and disease prognosis of CRC and especially tumor budding might be related to poor survival and high risk of recurrence.[3] The aim of this study is to analyze the tumor budding profile in CRC cases presenting at a tertiary-level hospital.

METHODS

This is a prospective observational study done at Pathology Department of Kathmandu Medical College Public Limited, Sinamangal, Nepal between 01 Feb 2023 to 31 Dec 2023. The ethical approval was taken from the Institutional Review Committee of Kathmandu Medical College Teaching Hospital (Reference number: 13012023 / 02). All resected CRC specimens received in the Department of Pathology were included this study. The specimens with prior history of neoadjuvant therapy and carcinoma other than adenocarcinoma on histopathological evaluation were excluded from the study. Informed written consent was taken. Relevant demographic data was obtained from requisition form provided with the specimens. Resected CRC specimens were fixed in 10% formalin. Grossing was done and site of tumor was assessed. The tissue was processed in automated histokinette, sectioned and stained with hematoxylin & eosin (H&E). The slides prepared were examined. Tumor typing, tumor grading, LVI and PNI, margin, lymph node status and tumor budding were assessed. Tumor, node and metastasis (TNM) staging of the tumor was done based on American Joint Committee on Cancer (AJCC) TNM classification.[6] The tumor budding was counted under X20 objective of Nikon eclipse 80i microscope with a field diameter of 22 mm. Obtained bud count was divided by normalization factor provided by International Tumor Budding Consensus Conference (ITBCC) to determine the tumor budding count per 0.785 mm^2.[5] The budding grade was be graded as low (0 - 4 buds), intermediate (5 - 9 buds) and high (10 or mode buds). The data was entered and analyzed using the statistical Package for Social Science (SPSS version 16.0). The quantitative data were presented in mean ± SD and categorial data in number and percentage. Chi square was used to test the significance of association between the categorical variables.

RESULTS

A total of 33 cases were included in this study, with 18 (54.5%) males and 15 (45.5%) females (Table 1). The patient ages ranged from 24 to 80 years, with the mean age of 52.4 ± 14 years. The commonest tumor sites were the caecum and ascending colon, each accounting for nine cases (27.3%), followed by the sigmoid colon with six cases (18.1%) (Table 1). Tumor size ranged from 1.5 to 13 cm, with a mean size of 5.3 cm. Most adenocarcinomas were Grade 2 comprising of 21 cases (63.6%), followed by Grade 1 with nine cases (27.3%) (Table 1). LVI was present in 21 cases (63.6%) and PNI was observed in 18 cases (54.5%). Most tumors were classified as T3 stage accounting of 19 cases (57.5%), and nodal metastasis (N1) was identified in 12 cases (36.4%) (Table 1).

Table 1: Clinicopathological parameters of colorectal carcinoma patient (N = 33)

Parameters	Frequency	Percentage
Gender		
Male	18	54.5
Female	15	45.5
Tumor site		
Caecum	9	27.3
Ascending colon	9	27.3
Transverse colon	3	9.1
Descending colon	3	9.1
Sigmoid	6	18.1
Rectum	3	9.1
Tumor grade		
Well differentiated	9	27.3
Moderately differentiated	21	63.6
Poorly differentiated	3	9.1
Lymphovascular invasion		
Present	21	63.6
Absent	12	36.4
Perineural invasion		
Present	18	54.5
Absent	15	45.5
Tumor stage		
T1	2	6.1
T2	6	18.2
T3	19	57.5
T4a	5	15.2
T4b	1	3
Nodal stage		
N0	15	45.6
N1	12	36.4
N2	6	16.2

Tumor budding grades (Figures 1 - 3) were low in eight cases (24.2%), intermediate in eight cases (24.2%), and high

in three cases (9.1%) (Table 2).

The chi-square test was done to see the significance of association between various parameters and the grade of tumor budding, shown in Table 3 and the statistically significant association was seen for LVI and nodal stage.

Table 2: Frequency of tumor budding grade in colorectal carcinoma

Tumor budding	Frequency	Percentage
Not seen	14	42.5
BD1 (Low)	8	24.2
BD2 (Intermediate)	8	24.2
BD3 (High)	3	9.1
Total	33	100

Table 3: Chi-square test table summarizing the associations between tumor budding grades and various parameters.

Parameters	P value	Significance
Tumor site	0.4	No
Tumor grade	0.6	No
Lymphovascular invasion	0.003	Yes
Perineural invasion	0.08	No
Tumor stage	0.4	No
Nodal stage	0.001	Yes

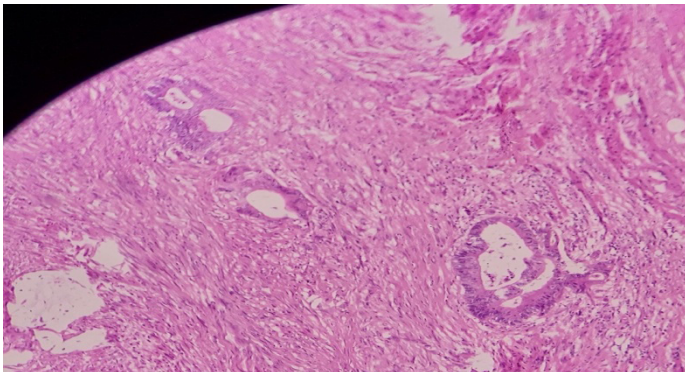

Fig 1: Tumor budding at invasive edge seen on 200X in an H&E stained section from a case of CRC - Low budding.

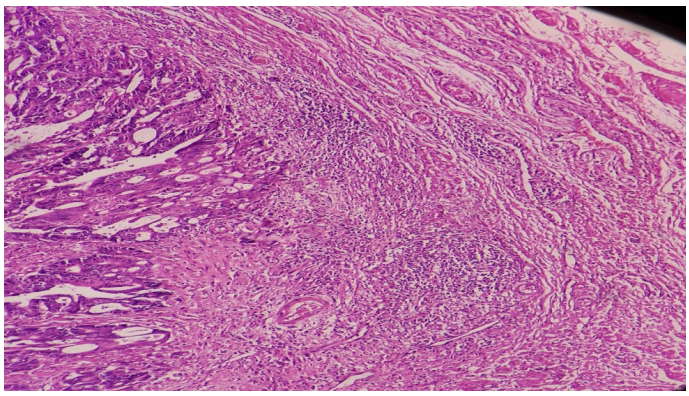

Fig 2: Tumor budding at invasive edge seen on 200X in an H&E stained section from a case of CRC - Intermediate budding.

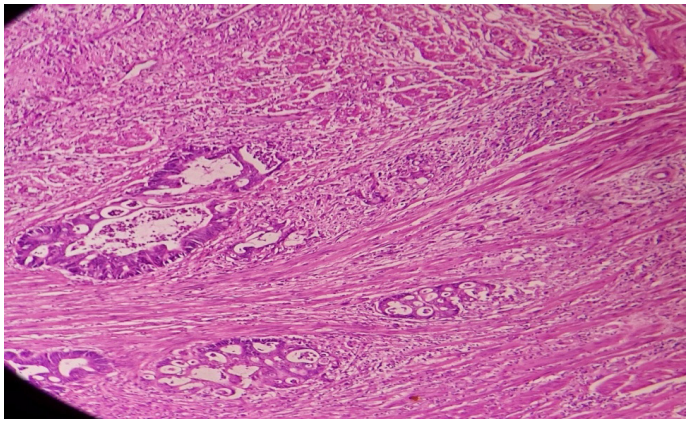

Fig 3: Tumor budding at invasive edge seen on 200X in an H&E stained section from a case of CRC - High budding

DISCUSSION

We observed higher number of CRC in males (54.5%) compared to females (45.5%) with a ratio of 1.2:1. The mean age was 52.4 ± 14 years in our study with age range of 24 - 80 years. These findings correspond with a similar studies done by Mehta et al and Thapa et al where the mean age was 45 years and 54 years respectively.[7,8] Gender disparities likely reflect differences in exposure to risk factors, such as cigarette smoking and alcohol intake, as well as hormonal influences and the complex interactions between these factors. These variations may contribute to differing rates of disease development and progression between males and females.[9]

We found the most frequent site of involvement was the caecum (27.3%) and ascending colon (27.3%), followed by the sigmoid (18.1%). Similar to our findings, Munireddy et al found right side of colon as a frequent site (60%).[10] However contrary to our findings Mehta et al found left side of colon as a frequent site of CRC comprising of

23 cases (38.3%).[7] The mean tumor size we found in our study was 5.3 cm (range 1.5-13 cm) which was similar to the study done by Naik et al.[3] In this study, moderately differentiated adenocarcinomas were the most common comprising of 63.6% of cases which was comparable with other studies.[8,11,12] Contrary to our study, Naik et al found well differentiated adenocarcinoma as a common grade.[3] These variations among various researches may be explained by the different lifestyles among different population groups.

LVI and PNI are relatively common pathological features of colorectal tumors. Both have been shown to carry significant prognostic value in several cancers, including CRC, as their presence often indicates a higher likelihood of tumor spread and a poorer overall prognosis.[13] We found LVI in 21 cases (63.6%) and PNI in 18 cases (54.5%). The rates of LVI and PNI observed in this study are higher with those reported in the literature across all tumor stages, with LVI occurring in 21-25% of cases and PNI in 9.9-14% of cases.[13,14] The reason for this discrepancy might be less number of cases in our study as compared to others and studies being conducted in different places.

Tumor budding has emerged as a promising prognostic marker, complementing conventional factors such as TNM staging, lymphovascular embolization, indeterminate margins, and microsatellite instability.[7] In this study, when the hotspot in the entire tumor section was assessed, low and intermediate - grade budding comprises eight cases (24.2%) each however high - grade budding was seen in three cases (9.1%). Naik et al and Lee et al found low grade budding as a commonest bud grade comprises of 77.5% and 71% respectively.[3,15] However the findings of the study done by Mehta et al and El-Gendi et al was not concordant to our result.[7,16] The difference in findings may be attributed to the smaller number of cases in our study and the use of immunohistochemical staining to define tumor buds in their study, which could have led to more precise identification of tumor budding.

Our study revealed that most tumors were in the T3 stage, accounting for 19 cases (57.5%). This finding is in accordance to other studies, which also identified the T3 stage as the most common stage in CRC.[3,17] In our study, N0 was the most frequent nodal status, comprising 15 cases (45.5%). This finding is consistent with the study conducted by Naik et al and Jagadale et al, which also reported N0 as the most common nodal status.[3,18]

Tumor budding was correlated with various clinical and histological parameters, including tumor site, tumor grade, LVI, PNI, tumor stage and nodal stage. No correlation could be established between tumor site, tumor grade, PNI and tumor stage with tumor budding in our study, and similar findings have been reported in other studies.[3,7,16] LVI (P=0.003) and nodal stage (P = 0.001) showed positive correlation with tumor budding intensity in our study. Similar observations were made by Naik et al and Jagadale et al in their studies.[3,18] Multiple previous studies have emphasized the association between tumor budding and aggressive tumor behavior.[3,7,15,16] Rogers et al described tumor budding as a predictor of lymph node metastasis in node-negative patients, suggesting it could be a deciding factor for chemotherapy in such cases. Tumor budding is also useful in predicting recurrence and long-term survival in CRC patients, as it indicates a more aggressive malignancy.[19]

CONCLUSIONS

In this study, the majority CRC were Grade 2 adenocarcinomas and T3 stage. LVI and PNI were frequently observed, and tumor budding grades were mostly low or intermediate. Significant associations were found between LVI, nodal staging, and tumor budding grade.

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CONFLICT OF INTEREST: None

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