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Original Research

Histopathological Significance of Tumor Budding as a Prognostic Marker in Colorectal Carcinoma: A Tertiary Care Centre Study

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Abstract

Background: Colorectal cancer (CRC) is a heterogeneous disease with varying clinical outcomes. Tumor budding, defined as the presence of individual or small clusters of tumor cells at the invasive front of the tumor, has emerged as a significant histopathological marker. This study aimed to assess the associations between tumor budding and various clinicopathological parameters in CRC, emphasizing its potential as a prognostic indicator. **Methods:** This study followed a retrospective and prospective design over a period of 5 years and 6 months. It was conducted at the Department of Pathology, GMC Jammu on CRC patients to evaluate tumor budding and its correlation with histopathological factors such as tumor size, histological grade, lymphovascular invasion, nodal involvement, and extent of invasion (pT stage). **Results:** The study revealed a significant association between tumor budding and histological grade ($p=0.005$), with higher tumor budding observed in poorly differentiated (Grade 3) tumors. Lymphovascular invasion (LVI) was present in 39.1% of cases and was strongly correlated with high tumor budding ($p=0.001$). Additionally, nodal involvement (N status) showed a significant association with tumor budding ($p<0.001$), with all patients exhibiting N2 status demonstrating high tumor budding. While no statistically significant association was found between tumor budding and tumor size ($p=0.156$) or pT stage ($p=0.321$), there was a trend toward increased budding in larger and more advanced tumors. **Conclusion:** Tumor budding is a valuable histopathological marker in CRC, significantly associated with higher histological grade, lymphovascular invasion, and nodal involvement. These findings suggest that tumor budding reflects tumor aggressiveness and may serve as a prognostic factor, aiding in clinical decision-making and guiding the use of adjuvant therapies.

Keywords: Colorectal cancer (CRC), tumor budding, histological grade, lymphovascular invasion, nodal involvement, prognostic marker, clinicopathological parameters.

Introduction

Colorectal carcinoma (CRC) is one of the most common malignancies worldwide, representing a significant cause of morbidity and mortality.[1]Despite advances in early detection and treatment, prognosis remains poor in many patients, particularly in advanced stages of the disease. As a result, identifying reliable prognostic markers that can guide therapeutic decisions is essential for improving clinical outcomes. One such marker that has gained increasing attention in recent years is tumor budding. Tumor budding refers to the presence of small clusters of cancer cells, often less than or equal to five, that detach from the main tumor mass and invade the surrounding stroma at the invasive front of the tumor.[2] This histopathological feature is thought to represent an early step in the metastatic cascade, reflecting the tumor's potential for invasion, dissemination, and ultimately, poor prognosis.From a mechanistic perspective, tumor budding is thought to represent an epithelial-mesenchymal transition (EMT) process, in which cancer cells lose their epithelial characteristics and gain mesenchymal properties, enabling them to migrate and invade surrounding tissues.[3,4] This process is driven by complex molecular signaling pathways, including the Wnt/β-catenin pathway, which plays a central role in colorectal

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carcinogenesis.[5] The loss of cellular adhesion molecules such as E-cadherin and the upregulation of mesenchymal markers such as vimentin are hallmarks of EMT, which contribute to the formation of tumor buds and the enhanced invasive capacity of cancer cells. Tumor budding has been extensively investigated in colorectal cancers, and recent research has expanded its significance to other malignancies, including carcinomas of the head-and-neck, upper gastrointestinal tract, breast, and lung. Initially, tumor budding was not routinely included in diagnostic pathology reports due to the absence of standardized assessment guidelines, the existence of multiple reporting systems with limited consensus, and challenges related to poor reproducibility.[6-8] However, in 2016, the International Tumor Budding Consensus Conference (ITBCC) established a standardized classification system, categorizing tumor budding into three tiers: low budding (Bd 1) with 0–4 buds, intermediate budding (Bd 2) with 5–9 buds, and high budding (Bd 3) with 10 or more buds.[2] The ITBCC strongly recommends the assessment of tumor budding in specific scenarios, particularly in pT1 and Stage II colorectal cancers. Tumor budding has been shown to be an independent predictor of lymph node metastasis in pT1 tumors and a reliable prognostic marker for survival in Stage II tumors, further underscoring its clinical importance.[2] Studies have consistently demonstrated that the presence of high tumor budding correlates with more aggressive tumor behavior, including enhanced invasion, resistance to treatment, and recurrence.[2,8,9] As such, tumor budding is recognized as a key marker of aggressive behavior in colorectal carcinoma (CRC), yet its routine inclusion in pathology reports has been hindered by variability in assessment techniques. Although the ITBCC has standardized its classification, there is still a need for more studies to validate its prognostic value across diverse populations and clinical settings. Understanding the relationship between tumor budding and patient outcomes, especially in early-stage CRC, is crucial for identifying high-risk individuals who may benefit from more aggressive treatment. This study is necessary to further solidify tumor budding as a reliable prognostic marker and to guide treatment decisions more effectively.

Methodology

This study followed a retrospective and prospective design over a period of 5 years and 6 months. The retrospective phase covered cases from August 2017 to September 2022, while the prospective phase included cases from September 2022 to February 2023. It was conducted at the Department of Pathology, GMC Jammu. For the retrospective cases, histopathological requisition and reporting forms, along with tissue blocks and slides from all colorectal carcinoma (CRC) cases diagnosed during the specified period, were retrieved from the archives. Where necessary, slides were freshly cut and restained. For the prospective cases, all CRC cases received in the department during the study period were included. Data from both retrospective and prospective cases were compiled and analyzed to explore correlations between histopathological parameters, such as tumor budding, tumor grade, lymph node involvement, and lymphovascular invasion. The inclusion criteria encompassed all colorectal carcinoma cases diagnosed during the study period, while the exclusion criteria included poorly preserved specimens and inadequate tissue samples.

Histopathological analysis was conducted using hematoxylin and eosin (H&E) stained slides. Tumor type, grade, tumor budding, lymph node metastasis, lymphovascular invasion, and other relevant findings were recorded. Special stains and immunohistochemistry (IHC) markers such as Cytokeratin 20 were used when required, particularly to assess tumor budding and lymphovascular invasion.The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and line diagrams. Chi-square test or Fisher's exact test, whichever appropriate, was employed for assessing correlation of tumor budding with various parameters. A P-value of less than 0.05 was considered statistically significant.

Since the study involved no active intervention, no ethical issues or risks were encountered. No costs were incurred by the participants, and no compensation was required. The findings provided valuable insights into the prognostic role of tumor budding in colorectal carcinoma.

Results

Table 1: Demographic and clinicopathological characteristics of study patients [n=64]

Parameter		Number	Percentage
Age (Years)	≤ 40 Years	3	4.7
	41-50 Years	7	10.9
	51-60 Years	11	17.2
	61-70 Years	33	51.6

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	71-80 Years	10	15.6
Gender	Male	30	46.9
	Female	34	53.1
Tumor site	Right colon	29	45.3
	Left colon	28	43.8
	Transverse colon	7	10.9
Tumor size	< 5 cm	31	48.4
	5-10 cm	25	39.1
	> 10 cm	8	12.5
Histological Grade	Grade 1	33	51.6
	Grade 2	29	45.3
	Grade 3	2	3.1
Lymphovascular invasion	Present	25	39.1
	Absent	39	60.9
Extent of tumor invasion (pT)	pT1	4	6.3
	pT2	9	14.1
	pT3	31	48.4
	pT4	20	31.3
Nodal status	N0	37	57.8
	N1	15	23.4
	N2	12	18.8

The demographic and clinicopathological characteristics of the 64 study patients are summarized as follows: The majority of patients (51.6%) were between 61-70 years of age, while 17.2% were aged 51-60 years, 15.6% were 71-80 years, 10.9% were 41-50 years, and only 4.7% were 40 years or younger. In terms of gender distribution, 53.1% were female, and 46.9% were male. Regarding tumor site, 45.3% of tumors were located in the right colon, 43.8% in the left colon, and 10.9% in the transverse colon. Tumor size was less than 5 cm in 48.4% of cases, between 5-10 cm in 39.1%, and larger than 10 cm in 12.5%. Histological grading revealed that most patients (51.6%) had Grade 1 tumors, 45.3% had Grade 2, and 3.1% had Grade 3 tumors. Lymphovascular invasion was present in 39.1% of cases, while 60.9% had no invasion. In terms of tumor invasion, 48.4% of tumors were classified as pT3, 31.3% as pT4, 14.1% as pT2, and 6.3% as pT1. Regarding nodal status, 57.8% of patients had no lymph node involvement (N0), while 23.4% had N1 involvement, and 18.8% had N2 involvement.

Table 2: Status of tumor budding among study patients

Tumor Budding	Number	Percentage
Low tumor bud (0-4)	45	70.3
Intermediate tumor bud (5-9)	11	17.2
High tumor bud (≥ 10)	8	12.5
Total	64	100

The majority of patients (70.3%) had low tumor budding, defined as 0-4 buds. Intermediate tumor budding, with 5-9 buds, was observed in 17.2% of cases. High tumor budding, characterized by 10 or more buds, was present in 12.5% of patients. Overall, all 64 patients were classified into these categories.

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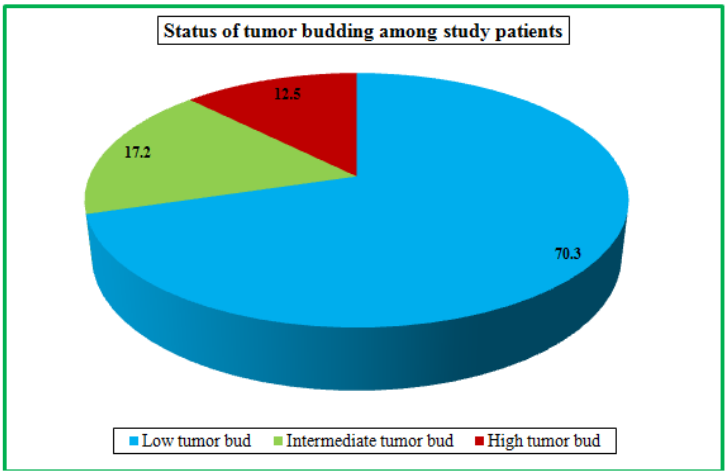

Table 3: Correlation of tumor budding with demographic and clinopathological parameters

Parameter		Low tumor bud		Intermediate tumor bud		High tumor bud		P-value
		No.	%age	No.	%age	No.	%age	
Age (Years)	≤ 60 Years	19	42.2	2	18.2	0	0.0	0.034*
	> 60 Years	26	57.8	9	81.8	8	100	
Gender	Male	21	46.7	5	45.5	4	50.0	0.979
	Female	24	53.3	6	54.5	4	50.0	
Tumor site	Right colon	22	48.9	4	36.4	3	37.5	0.869
	Left colon	19	42.2	5	45.5	4	50.0	
	Transverse colon	4	8.9	2	18.2	1	12.5	
Tumor size	< 5 cm	26	57.8	4	36.4	1	12.5	0.156
	5-10 cm	15	33.3	5	45.5	5	62.5	
	> 10 cm	4	8.9	2	18.2	2	25.0	
Histological Grade	Grade 1	25	55.6	5	45.5	3	37.5	0.005*
	Grade 2	20	44.4	6	54.5	3	37.5	
	Grade 3	0	0.0	0	0.0	2	25.0	
Lymphovascular invasion	Present	11	24.4	7	63.6	7	87.5	0.001*
	Absent	34	75.6	4	36.4	1	12.5	
Extent of tumor invasion (pT)	pT1	4	8.9	0	0.0	0	0.0	0.321
	pT2	8	17.8	1	9.1	0	0.0	
	pT3	22	48.9	6	54.5	3	37.5	
	pT4	11	24.4	4	36.4	5	62.5	
Nodal status	N0	34	75.6	3	27.3	0	0.0	<0.001*
	N1	11	24.4	4	36.4	0	0.0	
	N2	0	0.0	4	36.4	8	100	

The correlation of tumor budding with demographic and clinicopathological parameters among the 64 study patients showed significant associations in several categories. Patients over 60 years had a significantly higher proportion of high tumor budding (100%) compared to those under 60 years (p=0.034). There was no significant gender difference in tumor budding (p=0.979). Tumor site and tumor size did not show statistically significant associations with budding (p=0.869 and p=0.156, respectively). However, tumor budding was significantly associated with histological grade, with higher tumor budding observed more frequently in Grade 3 tumors (p=0.005). Lymphovascular invasion also correlated strongly with

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tumor budding, with 87.5% of patients with high tumor budding showing lymphovascular invasion (p=0.001). Tumor invasion depth (pT) showed no significant correlation with tumor budding (p=0.321), but nodal status was significantly associated, with high tumor budding observed in 100% of patients with N2 nodal involvement (p<0.001).

Discussion

Colorectal cancer (CRC) is a heterogeneous disease with a complex etiology, necessitating the investigation of new prognostic factors. In this study, we focused on the histopathological significance and prognostic impact of tumor budding in CRC.The demographic and clinicopathological characteristics of the study population revealed several key findings in relation to tumor budding and its prognostic significance in colorectal carcinoma.The age distribution showed that the majority of patients (51.6%) were between 61-70 years, and this age group had a higher prevalence of high tumor budding. Tumor budding was significantly associated with age, with patients older than 60 years more likely to exhibit higher tumor budding (p=0.034). This aligns with previous studies indicating that advanced age is often linked with more aggressive tumor behavior and poorer prognosis, possibly due to age-related immune changes and delayed detection of advanced tumors.[10-12] Gender distribution in this study showed slight female predominance over males and females (53.1% vs. 46.9%), however, no significant correlation between gender and tumor budding (p=0.979) was observed. This suggests that tumor budding may not differ significantly between sexes, a finding consistent with other studies where no gender predilection was observed in colorectal carcinoma progression.[11-14]

In this study, 45.3% of tumors were located in the right colon, 43.8% in the left colon, and 10.9% in the transverse colon, with no significant association between tumor location and tumor budding (p=0.869). Although some literature suggests that right-sided tumors exhibit more aggressive behavior, this trend was not observed in relation to tumor budding. A similar lack of association was reported by Naik et al., who found equal prevalence of tumors in both the right and left colon, suggesting that tumor location alone may not strongly influence budding behavior.[11] One possible explanation for this finding is that tumor budding may be more influenced by the molecular characteristics of the tumor, such as microsatellite instability (MSI) or specific mutations like BRAF, rather than anatomical location. Right-sided colorectal cancers are more frequently associated with MSI and may follow different biological pathways compared to left-sided tumors. However, tumor budding, which reflects local invasion and metastatic potential, might operate independently of these location-based molecular distinctions. In contrast, studies by Baran B et al. and Munireddy et al. reported a higher prevalence of right-sided colorectal cancer and noted that these tumors tend to be larger, more advanced, and poorly differentiated.[10,15] This could be due to delayed presentation or differences in symptomatology for right-sided tumors, which often manifest later and are more difficult to detect. However, despite these aggressive features, tumor budding did not show a significant correlation with tumor site in this study, indicating that other histopathological or genetic factors might be playing a more critical role in budding behavior than tumor location alone.

Tumor size demonstrated a potential, though not statistically significant, association with tumor budding (p=0.156). Larger tumors, particularly those exceeding 10 cm, exhibited a tendency toward higher tumor budding, though this trend did not reach statistical significance. These findings align with the study by Naik et al., who reported similar results, indicating a trend without statistical confirmation.[11]In contrast, other studies, such as those by Rathod G et al. and Salhia B et al., have reported a strong correlation between tumor budding and poor prognostic factors, including tumor size.[16,17] These studies suggest that larger tumors may inherently possess more aggressive biological features, including elevated tumor budding, which is often associated with increased invasiveness and metastatic potential. The absence of statistical significance in this study may be attributed to the variability in tumor characteristics. Nevertheless, the observed trend that larger tumors tend to exhibit higher budding levels warrants further investigation, as it underscores the possibility that tumor size may influence the degree of tumor budding, thereby contributing to tumor progression and poor clinical outcomes.

Histological grading revealed that the majority of patients (51.6%) had Grade 1 tumors, followed by 45.3% with Grade 2 tumors, and 3.1% with Grade 3 tumors. The correlation between tumor budding and histological grade demonstrated a statistically significant association (p=0.005). Notably, low tumor budding was predominantly observed in Grade 1 tumors (55.6%), indicating that well-differentiated tumors were less likely to exhibit high levels of tumor budding. As the histological grade increased, there was a notable shift toward more aggressive behavior, evidenced by the absence of low or intermediate budding in Grade 3 tumors, with 25% of these tumors exhibiting high budding. This suggests that poorly differentiated tumors (Grade 3) are more prone to present with elevated levels of tumor budding, reflecting their aggressive characteristics. These findings support the established understanding that higher histological grades are often associated with worse prognostic outcomes, including

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increased rates of metastasis and recurrence. Research by Naik et al., Munireddy et al., and Sevda et al. corroborated these results, noting that a significant proportion of tumors were classified as Grade 1 and highlighting a positive correlation between histological grade and tumor budding intensity.[10.11,18] Similarly, studies by Ueno et al. and Lugli et al. reported that poorly differentiated tumors (Grade 3) frequently exhibited higher rates of tumor budding, correlating with adverse clinical outcomes.[2,19]Conversely, Mondal et al. reported no significant correlation between tumor budding and histological grade, suggesting variability in findings across different studies.[20] This discrepancy may arise from differences in sample sizes, methodologies, or definitions of tumor budding, underscoring the need for further investigation to clarify these associations.

Lymphovascular invasion (LVI) was a key parameter in colorectal cancer (CRC) in this study, present in 39.1% of cases, while 60.9% showed no invasion. A statistically significant association between LVI and tumor budding was observed (p=0.001), with 87.5% of high tumor budding cases demonstrating lymphovascular invasion. This suggests that higher tumor budding in CRC is linked to an increased likelihood of lymphovascular invasion, highlighting its role as an early indicator of metastatic potential and aggressive tumor behavior. These findings align with studies by Mehta et al., Roy et al., and Naik et al., who similarly found a positive correlation between LVI and tumor budding in CRC.[2,21,22]Naik et al. reported that 38.7% of CRC patients exhibited LVI, with 61.3% having no invasion, and they also noted that higher tumor budding intensity correlated with increased lymphovascular invasion.[2] This underscores the importance of tumor budding as a predictor of poor prognosis in CRC, emphasizing its potential to signal early metastatic activity.In terms of the extent of tumor invasion, 48.4% of tumors were classified as pT3, 31.3% as pT4, 14.1% as pT2, and 6.3% as pT1. The correlation between tumor budding and the extent of invasion (pT stage) did not reach statistical significance (p=0.321), although patients with more advanced stages (pT3 and pT4) tended to exhibit higher levels of tumor budding. This trend suggests that while tumor budding can emerge early in tumor invasion, its clinical relevance may become more prominent in advanced stages of tumor growth. These findings are consistent with the literature, including studies by Koelzer et al., Ozer et al., and Naik et al., who similarly observed no statistically significant relationship between tumor budding and pT stage.[6,23] However, likewise to our study, they also reported a trend toward higher tumor budding in pT3 tumors, indicating that while budding may be more frequent in advanced stages, this relationship requires further exploration to establish its prognostic value. The lack of statistical significance in this context suggests the complex nature of tumor progression and the need for further investigation into how tumor budding evolves across different stages of invasion.

In our study, 57.8% of patients had no lymph node involvement (N0), while 23.4% had N1 involvement, and 18.8% had N2 involvement, with N0 being the most frequent nodal status. This distribution aligns with findings from studies by Naik et al. and Jagadale et al., who similarly reported N0 as the predominant nodal status among colorectal cancer patients.[11,24] The significant association between tumor budding and nodal involvement (p<0.001) observed in this study is particularly notable, as all patients with N2 nodal status exhibited high tumor budding. This finding is consistent with other studies, including those by Koelzer et al., Naik et al., Sevda et al., Jagadale et al., Deb et al., and Rogers et al., which have similarly highlighted the association between increased tumor budding and higher rates of nodal involvement.[6, 11, 18, 24-26]The presence of high tumor budding in patients with advanced nodal involvement suggests that tumor budding reflects the invasive potential of the tumor and its likelihood to spread beyond the primary site. This observed relationship between tumor budding and nodal metastasis further supports its value as a key prognostic marker. Given its association with worse clinical outcomes, tumor budding can serve as a useful indicator for guiding clinical management, particularly in determining the need for adjuvant therapies. These findings emphasize the importance of assessing tumor budding in routine pathological evaluations, as it can aid in stratifying patients by risk and tailoring treatment strategies accordingly.

Conclusion

Tumor budding has demonstrated significant associations with several key clinicopathological parameters in colorectal cancer. Specifically, high tumor budding was strongly linked with age, higher histological grade, lymphovascular invasion, and nodal involvement, reinforcing its role as an indicator of more aggressive tumor behavior. While no significant correlation was found with tumor size or extent of invasion (pT stage), there was a noticeable trend toward higher tumor budding in more advanced stages. These associations highlight the prognostic value of tumor budding, suggesting its utility in predicting outcomes such as metastasis and guiding clinical decisions, particularly regarding the need for adjuvant therapies. Given its consistent correlation with critical factors of tumor aggressiveness, tumor budding should be integrated into routine pathological evaluations to improve risk stratification and treatment planning in colorectal cancer.

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References

1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *PrzGastroenterol*. 2019;14(2):89-103. doi:10.5114/pg.2018.81072
2. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, et al. Recommendations for reporting tumour budding in colorectal cancer based on the International tumour Budding Consensus Conference (ITBCC). Mod Pathol. 2017;30(9):1299-1311.
3. Palamaris K, Felekouras E, Sakellariou S. Epithelial to Mesenchymal Transition: Key Regulator of Pancreatic Ductal Adenocarcinoma Progression and Chemoresistance. *Cancers (Basel).* 2021;13(21):5532. Published 2021 Nov 4. doi:10.3390/cancers13215532
4. Wang M., Estrella J.S., Katz M.H., Kim M., Rashid A., Lee J.E., Maitra A., Wistuba I.I., Wolff R.A., Varadhachary G.R., et al. Expression of Epithelial-Mesenchymal Transition Markers in Treated Pancreatic Ductal Adenocarcinoma. *Pancreas.* 2019;48:1367–1372.
5. Zhao, H., Ming, T., Tang, S. *et al.* Wnt signaling in colorectal cancer: pathogenic role and therapeutic target. *Mol Cancer* **21**, 144 (2022). https://doi.org/10.1186/s12943-022-01616-7
6. Koelzer VH, Zlobec I and Lugli A. Tumor budding in colorectal cancer- -ready for diagnostic practice? Hum Pathol. 2016;47(1):4-19.
7. Lugli A, Karamitopoulou E and Zlobec I. Tumour budding: A promising parameter in colorectal cancer. Br J Cancer. 2012;106(11):1713-1717.
8. Roy P, Datta J, Roy M, Mallick I and Mohandas M. Reporting of tumor budding in colorectal adenocarcinomas using × 40 objective: A practical approach for resource constrained set-ups. Indian J Cancer. 2017;54(4):640-645.
9. Mitrovic B, Schaeffer DF, Riddell RH, Kirsch R. Tumor budding in colorectal carcinoma: time to take notice. Mod Pathol. 2012;25(10):1315-1325.
10. Munireddy S, Mahadevappa A and Susheel MS. Significance of tumour budding with cytokeratin 20 immunostaining as a histopathological prognostic marker in colorectal adenocarcinoma. J ClinDiagn Res. 2019;13(1):EC03-EC07.
11. Naik P, Hemalatha J, Sowmya TS, Nagesha KR. Significance of tumor budding in colorectal carcinoma–A tertiary care center study. Asian Journal of Medical Sciences. 2022 May 3;13(5):172-6.
12. Ladomersky E, Zhai L, Lauing KL, et al. Advanced Age Increases Immunosuppression in the Brain and Decreases Immunotherapeutic Efficacy in Subjects with Glioblastoma. *Clin Cancer Res*. 2020;26(19):5232-5245. doi:10.1158/1078-0432.CCR-19-3874
13. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC. Tumour 'budding' as an index to estimate the potential of aggressiveness in rectal cancer. Histopathology. 2002;40(2):127-32.
14. Graham RP, Vierkant RA, Tillmans LS, Wang AH, Laird PW, Weisenberger DJ, et al. Tumor budding in colorectal carcinoma: confirmation of prognostic significance and histologic cutoff in a population-based cohort. Am J SurgPathol. 2015;39(10):1340-6.
15. Baran B, MertOzupek N, YerliTetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. *Gastroenterology Res*. 2018;11(4):264-273. doi:10.14740/gr1062w
16. Rathod GB, Desai KN, Shrivastava A, Maru AM. Correlation of Tumor Budding With Known Clinicopathological, Histomorphological and Hormonal Receptor Status in Patients With Invasive Breast Carcinoma. *Cureus.* 2022;14(9):e29637. Published 2022 Sep 26. doi:10.7759/cureus.29637
17. Salhia B, Trippel M, Pfaltz K, Cihoric N, Grogg A, Lädrach C, Zlobec I, Tapia C. High tumor budding stratifies breast cancer with metastatic properties. Breast cancer research and treatment. 2015 Apr;150:363-71.
18. Sevda SB, Mamak GI, Ciris IM, Bozkurt KK and Kapusuoglu M. Tumor budding in colorectal carcinomas. Turk PatolojiDerg. 2012;28(1):61-66.
19. Ueno H, Kajiwara Y, Shimazaki H, *et al*. New criteria for histologic grading of colorectal cancer. *Am J SurgPathol* 2012; 36: 193–201. [PubMed] [Google Scholar]
20. Mondal P, Jain BB, Ghosh SK and Nandi A. Histopathological study of tumor budding in colorectal carcinoma and its correlation with clinicopathological parameters. Natl J Physiol Pharm Pharmacol. 2022;12(6)
21. Roy P, Datta J, Roy M, Mallick I and Mohandas M. Reporting of tumor budding in colorectal adenocarcinomas using × 40 objective: A practical approach for resource constrained set-ups. Indian J Cancer. 2017;54(4):640-645
22. Mehta A, Goswami M and Sinha R. Histopathological significance and prognostic impact of tumor budding in colorectal cancer. Ann Clin Lab Sci. 2017;47(2):129-135.
23. Ozer SP, Barut SG, Ozer B, Catal O, Sit M. The relationship between tumor budding and survival in colorectal carcinomas. Revista da AssociaçãoMédicaBrasileira. 2020 Jan 24;65:1442-7.
24. Jagadale K and Agarwal N. Tumour budding is a predictor of lymph node metastasis in colorectal carcinoma. Int J ClinDiagnPathol. 2020;3(1):299-301.
25. Deb B and Jacob SE. Predictive power of tumour budding for lymph node metastasis in colorectal carcinomas: A retrospective study. Indian J Med Res. 150(6):635-639.
26. Rogers AC, Winter DC, Heeney A, Gibbons D, Lugli A, Puppa G, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. Br J Cancer. 2016;115(7):831-840.