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Original Research

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

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Abstract

Background: Tumor budding is increasingly recognized as a significant prognostic factor in various malignancies, including esophageal carcinoma. This study aims to determine the prognostic significance of tumor budding in esophageal carcinoma and its correlation with other clinicopatholigical parameters. **Methods:** This study utilized a mixed retrospective and prospective design spanning 5 years and 6 months and was conducted in the Department of Pathology at GMC Jammu. Tumor budding was assessed and correlated with demographic, pathological, and nodal status data. Statistical analysis was performed to identify significant associations among these variables. **Results:** The analysis categorized patients into low, intermediate, and high tumor budding groups, revealing several significant associations. Demographic factors, including age and gender, did not show a significant correlation with tumor budding. However, tumor size exhibited a notable relationship, with 83.3% of tumors measuring ≤3.5 cm classified as low budding (p=0.008). The World Health Organization (WHO) grade demonstrated a significant association as well; 22.2% of patients in the low budding group had Grade 1 tumors, whereas 57.1% of those in the high budding group were classified as Grade 3 (p=0.015). Furthermore, lymphovascular invasion was present in 92.9% of high tumor budding cases compared to 44.4% in the low group (p=0.014). A strong correlation was also observed with pT stage (p=0.007) and nodal involvement, underscoring the aggressive nature of tumors exhibiting high levels of budding. **Conclusion:** Tumor budding serves as an essential marker in the pathological evaluation of esophageal carcinoma. Its integration into clinical practice could enhance risk stratification and inform treatment decisions, ultimately improving personalized cancer care strategies.

Keywords: Tumor budding, esophageal cancer, Lymphovascular invasion, Nodal involvement, Histopathological factors, pT stage, Prognostic marker.

Introduction

Esophageal carcinoma (EC) is one of the most prevalent malignancies affecting the gastrointestinal tract and is recognized as the sixth leading cause of cancer-related deaths globally.[1] This disease poses a significant health burden, with a high mortality rate driven by its aggressive nature and the frequent diagnosis at advanced stages. Most patients present with locally advanced or metastatic disease, contributing to poor outcomes and a high rate of recurrence even after definitive treatment.[2] Despite advancements in therapeutic strategies, the overall prognosis for esophageal carcinoma remains grim, necessitating the identification of reliable prognostic markers to better predict disease progression and guide clinical management. Given these challenges, the role of prognostic factors in esophageal carcinoma is critical. Identifying clinical and histopathological markers with prognostic value is essential for refining risk stratification, improving patient outcomes, and personalizing therapeutic approaches. Although established staging systems, such as the Tumor Node Metastasis (TNM) classification developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), remain integral to assessing esophageal cancer, there is

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growing recognition that these traditional systems may not fully capture the biological heterogeneity and aggressiveness of the disease.[3-5]As a result, the focus of recent research has shifted towards exploring novel prognostic factors that may provide deeper insights into tumor biology and clinical outcomes. Tumor budding, a histological feature observed at the invasive front of tumors, has emerged as one such promising prognostic marker.

Tumor budding refers to the presence of single tumor cells or small clusters of up to four cells at the invasive front of a carcinoma.[6,7] These small cell clusters represent a critical event in the process of tumor invasion and metastasis. Tumor budding has been identified as a manifestation of epithelial-to-mesenchymal transition (EMT), wherein epithelial tumor cells acquire mesenchymal properties, enhancing their ability to migrate, invade surrounding tissues, and establish distant metastasis. While tumor budding has garnered significant attention in various solid tumors, including colorectal cancer, where its prognostic impact has been extensively validated, its relevance in esophageal carcinoma is still under investigation. The International Tumor Budding Consensus Conference (ITBCC) has established clear guidelines for assessing tumor budding in colorectal cancer, but routine use of this histopathological marker in esophageal carcinoma has not yet been widely adopted.[3] Nevertheless, accumulating evidence suggests that tumor budding may hold significant potential as a prognostic marker in esophageal carcinoma, offering insights into tumor aggressiveness, recurrence risk, and overall survival.[9,10]

Given the established role of tumor budding in colorectal cancer and its increasing recognition in other cancers such as pancreatic, lung, and head-and-neck cancers, it is reasonable to hypothesize that tumor budding could be similarly valuable in esophageal carcinoma. The application of tumor budding in routine histopathological evaluation could help to stratify patients into distinct risk categories, guiding decisions on adjuvant therapy and follow-up care. The present study has been conducted to evaluate the prognostic significance of tumor budding in esophageal carcinoma and to examine its correlation with various clinicopathological parameters. By investigating these associations, the study seeks to contribute to the growing body of evidence on the clinical utility of tumor budding as a valuable tool for risk stratification and therapeutic guidance in esophageal carcinoma.

Methodology

This study consisted of a five-year retrospective and a six-month prospective analysis, covering cases from September 2017 to August 2022 for the retrospective arm and from September 2022 to February 2023 for the prospective arm. The data was collected from histopathology requisition and reporting forms, as well as from archived blocks and slides stored in the Department of Pathology at Government Medical College (GMC) Jammu. The material was retrieved for analysis and the histopathological sections were examined. For the retrospective cases, slides were either freshly cut or re-stained where necessary. The data available on the requisition forms was compiled and analyzed, focusing on clinicopathological parameters such as tumor type, grade, tumor budding, lymph node metastasis, and lymphovascular invasion, among other findings. Hematoxylin and eosin (H&E) stained slides were examined microscopically to document the findings, particularly highlighting tumor budding and its associated histopathological features. In the prospective phase of the study, all newly diagnosed esophageal carcinoma cases received in the department during the specified timeframe were included. Immunohistochemistry (IHC) markers and special stains were applied where necessary to further evaluate specific histological features.

The inclusion criteria for the study encompassed all esophageal carcinoma cases diagnosed within the study period. However, cases were excluded if the specimens were poorly preserved, such as those received without formalin, or if the samples were inadequate for histopathological evaluation. The compiled data from both the retrospective and prospective cases was entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). The recorded data 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. This study did not involve vulnerable populations, and no active interventions were required. Specimens were collected from the histopathological section of the Department of Pathology, GMC Jammu. There were no ethical concerns, anticipated risks, associated costs, or conflicts of interest. Additionally, no compensation provisions were necessary, as no patients or volunteers were directly involved.

Results

In this section, the results of the study will be described:

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Table 1: Demographic and clinicopathological characteristics of study patients [n=45]			
Variable		**Number**	**Percentage**
Age (Years)	31-40 Years	5	11.1
	41-50 Years	8	17.8
	51-60 Years	12	26.7
	61-70 Years	17	37.8
	> 70 Years	3	6.7
Gender	Male	34	75.6
	Female	11	24.4
Tumor size	≤ 3.5 cm	26	57.8
	> 3.5 cm	19	42.2
WHO Grade	Grade 1	7	15.6
	Grade 2	27	60.0
	Grade 3	11	24.4
Lymphovascular invasion	Present	28	62.2
	Absent	17	37.8
Extent of tumor invasion (pT)	pT1	9	20.0
	pT2	11	24.4
	pT3	25	55.6
Nodal status	N0	22	48.9
	N1	12	26.7
	N2	11	24.4

The study included 45 patients, with the majority aged between 61 and 70 years (37.8%), followed by those in the 51-60 age group (26.7%). The patient population was predominantly male (75.6%), with females comprising 24.4%. Tumor size was ≤3.5 cm in 57.8% of the cases, while 42.2% had tumors larger than 3.5 cm. Regarding WHO grade, most tumors were classified as Grade 2 (60.0%), followed by Grade 3 (24.4%) and Grade 1 (15.6%). Lymphovascular invasion was present in 62.2% of the cases, indicating a significant proportion of patients had more aggressive tumor features. In terms of the extent of tumor invasion (pT), over half (55.6%) of the tumors were classified as pT3, with fewer cases being pT2 (24.4%) and pT1 (20.0%). Nodal status revealed that nearly half of the patients (48.9%) had no lymph node involvement (N0), while the rest showed nodal involvement, with 26.7% having N1 and 24.4% having N2 nodal status. This data highlights the variety of tumor characteristics within the study group.

Table 2: Status of tumor budding among study patients		
Tumor Budding	**Number**	**Percentage**
Low tumor bud (0-4)	18	40.0
Intermediate tumor bud (5-9)	13	28.9
High tumor bud (≥ 10)	14	31.1
Total	45	100

Table 2 presents the status of tumor budding among the study patients, categorized into three distinct groups based on the number of tumor buds observed. Out of a total of 45 patients, 18 exhibited low tumor budding, defined as having between 0 and 4 tumor buds, representing 40.0% of the cohort. A total of 13 patients, or 28.9%, fell into the intermediate category with 5 to 9 tumor buds. Lastly, 14 patients, accounting for 31.1%, were classified as having high tumor budding, characterized by 10 or more tumor buds. This distribution highlights a notable prevalence of low tumor budding among the patients, while also indicating a substantial proportion of individuals with high tumor budding, which may have important implications for prognostic evaluations and treatment considerations in esophageal carcinoma.

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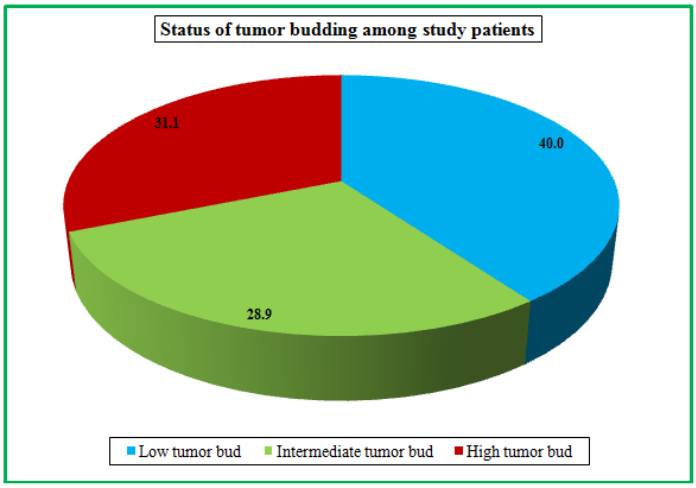

Table 3: Correlation of tumor budding with demographic and clinopathological parameters

Parameter		Low		Intermediate		High		P-value
		No.	%age	No.	%age	No.	%age	
Age (Years)	≤ 60 Years	12	66.7	7	53.8	6	42.9	0.401
	> 60 Years	6	33.3	6	46.2	8	57.1	
Gender	Male	14	77.8	10	76.9	10	71.4	0.909
	Female	4	22.2	3	23.1	4	28.6	
Tumor size	≤ 3.5 cm	15	83.3	7	53.8	4	28.6	0.008*
	> 3.5 cm	3	16.7	6	46.2	10	71.4	
WHO Grade	Grade 1	4	22.2	2	15.4	1	7.1	0.015*
	Grade 2	13	72.2	9	69.2	5	35.7	
	Grade 3	1	5.6	2	15.4	8	57.1	
Lymphovascular invasion	Present	8	44.4	7	53.8	13	92.9	0.014*
	Absent	10	55.6	6	46.2	1	7.1	
Extent of tumor invasion (pT)	pT1	7	38.9	2	15.4	0	0.0	0.007*
	pT2	7	38.9	4	30.8	2	14.3	
	pT3	4	22.2	7	53.8	12	85.7	
Nodal status	N0	14	77.8	6	46.2	2	14.3	0.004*
	N1	4	22.2	3	23.1	5	35.7	
	N2	0	16.7	4	30.8	7	50.0	

***Statistically Significant (P-value<0.05)**

Table 3 outlines the correlation between tumor budding and various demographic and clinopathological parameters among the study patients. The analysis categorized patients into low, intermediate, and high tumor budding groups, revealing significant associations in several areas. Regarding age, of the 18 patients in the low tumor budding group, 12 (66.7%) were aged 60 years or younger. In contrast, in the high tumor budding group, only 6 (42.9%) were in this age bracket, with a P-value of 0.401, indicating no significant correlation. For gender, 14 out of 18 patients (77.8%) in the low tumor budding group were male, while the proportions remained relatively consistent across the other groups, with a P-value of 0.909, suggesting no significant association. Tumor size exhibited a notable correlation with tumor budding status. Among patients with tumors measuring 3.5 cm or less, 15 (83.3%) were categorized as having low tumor budding. Conversely, only 4 patients (28.6%) with tumors larger than 3.5 cm fell into the low category, with a P-value of 0.008, indicating statistical significance. The World Health Organization (WHO) grade also demonstrated a significant correlation. In the low tumor budding group, only 4 patients (22.2%) had Grade 1 tumors, while 8 patients (57.1%) in the high tumor budding group had Grade 3 tumors. This yielded a P-value of 0.015, highlighting the association between higher tumor grades and increased tumor budding. Lymphovascular invasion was present in 13 patients (92.9%) with high tumor budding, compared to 8 (44.4%) in the low category, resulting in a significant P-value of 0.014. Finally, the extent of tumor invasion (pT

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stage) showed significant association. In the low tumor budding group, 7 patients (38.9%) had pT1 status, while the high tumor budding group included 12 patients (85.7%) with pT3 status, yielding a P-value of 0.007, indicating a strong correlation. Nodal status also demonstrated a significant association with tumor budding.

Discussion

This study analyzed the correlation between tumor budding and various clinopathological parameters in patients with esophageal carcinoma. Tumor budding is increasingly recognized as an important prognostic factor, and its association with aggressive disease features has been noted in several cancers. By examining the relationships between tumor budding, age, gender, tumor size, WHO grade, lymphovascular invasion, tumor invasion (pT stage), and nodal status, this study offers valuable insights into how tumor budding may influence disease progression and patient outcomes. Out of 45 patients, 40.0% had low tumor budding (0-4 buds), 28.9% had intermediate budding (5-9 buds), and 31.1% had high tumor budding (10 or more buds).In the present study, the majority of patients aged between 61 and 70 years (37.8%), followed by those in the 51-60 age group (26.7%). The analysis showed no statistically significant association between age and tumor budding (P = 0.401), a finding consistent with reports from several authors, who also observed no significant correlation between age and tumor budding in esophageal and other cancers.[9-11] However, a trend was noted in which patients aged 60 years or younger exhibited a higher proportion of low tumor budding, while older patients (>60 years) demonstrated a greater prevalence of high tumor budding. These results align with previous studies in esophageal carcinoma, where younger patients tend to have more favorable prognostic factors, potentially reflecting a less aggressive tumor biology compared to older individuals.[9]

In this study, a male predominance over females was observed (75.6% vs. 24.4%), and the correlation between tumor budding and gender was not statistically significant (P = 0.909). Males were prevalent across all tumor budding categories, with 77.8% of low tumor budding patients being male. The consistent male predominance (approximately 70-80%) across all budding groups mirrors the higher incidence of esophageal carcinoma in men, a well-documented finding in the literature, largely attributed to higher rates of risk factors such as smoking and alcohol consumption. [12,13] Gender is not considered a strong independent prognostic factor in esophageal carcinoma, though some studies suggest women may have better overall survival rates.[14] The lack of a significant association between gender and tumor budding in this study indicates that tumor budding is more likely driven by biological tumor factors rather than demographic characteristics. These findings are consistent with previous studies, which similarly reported no significant association between gender and tumor budding.[15-17]

In the present study, tumor size was ≤3.5 cm in 57.8% of the cases, while 42.2% had tumors larger than 3.5 cm. A significant association was found between tumor budding and tumor size (P = 0.008). Patients with larger tumors (>3.5 cm) had a higher frequency of intermediate to high tumor budding. This relationship has been consistently reported in studies of esophageal and other cancers, where larger tumor size correlates with increased tumor budding, reflecting more aggressive tumor behavior.[10,18,19]Larger tumors are often associated with greater tumor heterogeneity and a more supportive microenvironment for tumor cells to undergo epithelial-mesenchymal transition (EMT), which facilitates tumor budding. Tumor buds, representing detached and invasive cancer cells, are indicative of enhanced invasion and metastatic potential. The significant correlation between tumor size and tumor budding underscores the importance of considering both parameters when evaluating tumor aggressiveness and potential for poor outcomes.

In this study, the majority of tumors were classified as Grade 2 (60.0%), followed by Grade 3 (24.4%) and Grade 1 (15.6%). A significant correlation was found between tumor budding and WHO grade (P = 0.015), with high-grade tumors (Grade 3) showing a higher likelihood of exhibiting high tumor budding. This finding is consistent with other studies, which demonstrate that high-grade tumors, due to their poorly differentiated state, are more prone to undergo epithelial-mesenchymal transition (EMT), leading to increased tumor budding. For instance, a study by Jesinghaus et al. involving 135 patients with esophageal squamous cell carcinomas revealed that higher tumor budding was strongly associated with both decreased disease-specific and disease-free survival.[20] Similarly, Zainab et al. reported that tumors with higher budding were significantly correlated with higher tumor grades (p = 0.02), with these higher grades being linked to poorer prognoses.[9] These studies support the current findings, indicating that high tumor budding is more frequent in poorly differentiated, high-grade tumors, which tend to have more aggressive behavior and worse clinical outcomes. The strong association between higher tumor budding and advanced tumor grade reflects the underlying biology of aggressive tumors, which are more likely to exhibit EMT and other processes that facilitate tumor progression and invasion.

We observed lymphovascular invasion (LVI) was present in 62.2% of cases, reflecting a substantial proportion of patients with more aggressive tumor features. A significant association was observed

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between LVI and tumor budding (P = 0.014), with 92.9% of patients with high tumor budding also exhibiting LVI, compared to only 44.4% in the low tumor budding group. This strong correlation suggests that tumors with high budding are more likely to invade lymphatic and vascular structures, indicative of a more invasive phenotype. These findings align with previous studies that have also demonstrated a positive relationship between tumor budding and LVI in esophageal cancer. For instance, Zainab et al. and Seki M et al. both reported a significant correlation between higher tumor budding and the presence of LVI in esophageal and oral squamous cell carcinomas (p = 0.0004).[9,21] Similarly, Du et al., in their study on early-stage gastric cancers, found that the association between LVI and tumor budding was significantly elevated, highlighting that tumor budding is a key marker of tumor aggressiveness and metastatic potential across various cancers.[22] The observed association between high tumor budding and LVI likely reflects the biological processes driving tumor dissemination, including epithelial-mesenchymal transition (EMT) and increased invasiveness, which facilitate the spread of tumor cells through lymphatic and vascular channels. These findings underscore the role of tumor budding as a critical prognostic factor, closely linked to more aggressive disease features such as LVI, which contributes to poorer outcomes and increased metastatic risk.

In this study, the extent of tumor invasion (pT stage) revealed that more than half of the tumors (55.6%) were classified as pT3, with fewer cases categorized as pT2 (24.4%) and pT1 (20.0%). A significant association was observed between tumor budding and pT stage, where higher pT stages (pT3) were more prevalent among patients with high tumor budding (P = 0.007). This finding aligns with previous research, which consistently shows that high tumor budding is associated with deeper tumor invasion in esophageal carcinoma and other malignancies. Koelzer H et al. reported a strong correlation between higher tumor budding and advanced pT stage in esophageal squamous cell carcinomas, reinforcing the concept that tumor budding is a marker of more aggressive disease and increased invasiveness.[23] Similarly, Neppl C et al., in their study on pulmonary squamous cell carcinoma (pSQCC), found a comparable relationship between high tumor budding and more advanced pT stages.[24]These observations support the view that tumors with high budding are biologically more aggressive and capable of deeper tissue invasion, a hallmark of advanced cancer stages. However, not all studies have shown such associations. In contrast, Zainab et al. found no significant relationship between pT stage and tumor budding in their research on esophageal cancers.[9] This discrepancy may be attributed to differences in tumor biology, sample size, or methodologies across studies. Despite this, the current findings underscore the critical role of tumor budding as a strong prognostic indicator, particularly in relation to tumor invasiveness, reinforcing its relevance in predicting advanced disease stages and poor outcomes.

Nodal status in this study revealed that nearly half of the patients (48.9%) had no lymph node involvement (N0), while the remaining cases exhibited nodal involvement, with 26.7% classified as N1 and 24.4% as N2. A statistically significant correlation was observed between tumor budding and nodal status, indicating that patients with high tumor budding were more likely to have positive nodal involvement (N1 or N2). The association between tumor budding and nodal involvement is likely due to tumor budding promoting epithelial-mesenchymal transition (EMT), which increases tumor cell invasiveness. This enhanced invasiveness allows cancer cells to spread more easily to lymph nodes, explaining the higher rates of nodal metastasis in patients with high tumor budding. This finding is consistent with prior research showing that tumor budding is associated with nodal metastasis in esophageal carcinoma. Landau et al. reported that tumor budding serves as an independent predictor of nodal metastasis in superficial esophageal adenocarcinoma, reinforcing the role of tumor budding in identifying patients at higher risk for nodal spread.[25] Similarly, Zlobec et al. highlighted that tumor budding is an unfavorable prognostic factor across various tumor types, including esophageal cancer, where it is closely linked to lymph node metastasis.[26] They specifically noted that tumor budding is associated with an increased risk of lymph node metastasis and poor prognosis, particularly in superficial esophageal adenocarcinoma. Furthermore, studies by Seki et al. and Zainab et al. also found a statistically significant association between tumor budding and nodal status, which is in alignment with the results of this study.[9,21] These findings underscore the importance of tumor budding as a critical factor in assessing the metastatic potential of esophageal carcinoma, reinforcing its role as a prognostic marker for lymphatic spread and disease progression. The strong correlation between tumor budding and nodal involvement further supports its utility in guiding clinical decision-making, particularly in determining the likelihood of metastasis and the need for more aggressive treatment strategies.

Conclusion

Tumor budding has emerged as a critical prognostic factor in esophageal carcinoma, closely linked to more aggressive tumor behavior. The results demonstrated that tumor budding is strongly correlated with advanced pathological features, including elevated tumor grade, lymphovascular invasion, deeper tumor invasion (pT

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stage), and nodal metastasis. These associations underscore the role of tumor budding in facilitating epithelial-mesenchymal transition (EMT), thereby enhancing the tumor's invasive potential and metastatic spread, particularly to lymph nodes. While demographic factors such as age and gender did not exhibit a significant correlation with tumor budding, its relationship with biological tumor characteristics emphasizes its importance in understanding tumor progression. The presence of high tumor budding indicates a more aggressive disease trajectory, often associated with a poorer prognosis and increased likelihood of treatment resistance. Given these insights, tumor budding should be regarded as a vital marker in the pathological assessment of esophageal carcinoma. Its incorporation into clinical practice can aid in risk stratification, guiding treatment decisions and enhancing personalized cancer care strategies.

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