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Histopathologic and Prognostic Significance of Tumor Budding in Colorectal Adenocarcinoma: A Retrospective Cohort Study Conducted in Shiraz, Iran

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ABSTRACT

Background & Objective: Colorectal cancer is the second reason for cancer-associated death. The prognosis of the malignancy is defined by TNM scoring. However, tumor grading, lymphovascular invasion, perineural invasion, and tumor buddings may affect its prognosis. This study aimed to assess the prognostic and histologic impact of tumor budding in colorectal adenocarcinoma.

Methods: This study is a retrospective cohort of 192 patients with colorectal adenocarcinoma. All four stages of colorectal adenocarcinoma patients were included, but the patients in stages I and II were also analyzed separately. We used pathology reports to extract the histopathologic data. The prognostic values were extracted by calling the patients.

Results: Less than half of the patients were in stages I and II of the disease. According to our analysis, tumor extension and lymphovascular invasion were correlated with tumor budding count in patients in stages I and II, and lymphovascular invasion, tumor grade, tumor stage, lymph node involvement, tumor extension, tumor site, metastasis, and five-year survival were correlated with tumor budding within all stages.

Conclusion: It is recommended that tumor budding count should be assessed and reported in pathology reports of adenocarcinomas due to its high correlation with poor prognosis.

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Introduction

Based on current studies, colorectal cancer is the second leading cause of cancer-related deaths globally in both genders (1). While the prognosis of malignancy is typically determined by TNM scoring, other factors can impact prognosis, such as tumor grading, lymphovascular invasion, perineural invasion, tumor border configuration, and tumor budding (2). Therapeutic management of different types of colorectal cancers also presents challenges. For example, stage II colorectal carcinomas exhibit a wide spectrum of prognoses, ranging from poor to good. Some stage II patients may require adjuvant therapy, while others may not (3, 4).

Tumor budding refers to small clusters of tumor cells, consisting of a maximum of five cells, found at the invasive surface of tumors, extending from the main malignant gland into the neighboring stroma (5, 6). Studies have shown that the presence of tumor budding is correlated with tumor metastasis (7). Additionally, detecting tumor budding in the early stages of colorectal cancers can be utilized to guide preventative surgical management (8, 9).

The aim of this study was to evaluate the prognostic and histopathologic significance of tumor budding in different stages of colorectal adenocarcinoma and its relationship with demographic, macroscopic, and microscopic findings. Furthermore, we specifically assessed these factors in stages I and II to elucidate the importance of tumor budding in the early stages. Additionally, we investigated the association between tumor budding and survival years as an indicator of disease prognosis.

Material and Methods

This study was a retrospective cohort conducted on 192 patients with colorectal adenocarcinoma who had undergone surgical resection from 2010 to 2017 in hospitals affiliated with Shiraz University of Medical Sciences. The inclusion criteria were all the patients with colorectal adenocarcinoma who had undergone surgical resection without previous adjuvant therapy. The patients' pathologic slides were prepared using the H&E technique; their reports were collected from the laboratory and evaluated to confirm their reports and check for tumor budding counts. The Olympus BX50

Lai *et al.*'s studies (15, 18). However, this finding contradicted results of the studies conducted by Horcic *et al.*, Nakamura *et al.*, and Jagadale *et al.*, who revealed no significant association between the mentioned factors (16, 19, 20).

Regarding metastasis, although some studies have shown that a higher tumor budding increases the chance of recurrence and distant metastasis, Mehta's study found no relationship between these factors. Additionally, Nakamura *et al.*'s study considered tumor budding as an independent factor in predicting lung metastasis. In our study, we attempted to assess both nodal metastasis and metastasis to different organs. In contrast to Mehta *et al.*'s study, which showed no significant relationship between tumor budding and metastasis, our study revealed a significant correlation between tumor budding and the likelihood of distant metastasis (3, 13, 21-24). Additionally, the correlation was significant when analyzing the tumor budding and nodal involvement, as stated in previous studies (13, 14, 25).

Regarding recurrence, our findings were in line with Mehta *et al.*'s study, showing no significant association (13). Similarly, in stages I and II, this study's correlation was not significant, contrary to the Nakamura's and Mitrovic's studies (16, 26). This difference may be attributed to the smaller sample size in our study. Additionally, Rogers *et al.* conducted a study on patients with rectal adenocarcinoma and found a correlation between tumor recurrence and tumor budding (27). This divergent result could be due to the difference in the site of adenocarcinoma.

Regarding survival rate differences, the survival rate of the low tumor budding group was better in Mehta *et al.*'s study. Still, the five-year survival was not correlated with tumor budding (13). There is also evidence from retrospective and prospective studies indicating that presence of high tumor budding in stage II colorectal carcinomas reflects poor survival (23, 26, 28, 29). Ryan *et al.* also conducted a prospective cohort study on all stages of colorectal cancer, which revealed a worse five-year survival rate of higher budding (30). Our study compared tumor budding within all stages of colorectal carcinoma and showed that the correlation was significant with both survival rate and five-year survival. In cases with higher counts of tumor buds, survival years were lower independently from the tumor stage and vice versa. Also, assessment of five-year survival and survival rate differences for patients in stages I and II revealed that the results were not meaningful, in contrast to Nakamura *et al.* and Lai *et al.*'s studies (15, 16).

Demographic factors, such as age, sex, and tumor site, were correlated with the tumor budding neither in this study nor in other previously reported studies (15, 16).

Conclusion

To sum up, tumor budding seems to be a significant prognostic factor in colorectal adenocarcinoma. This study found a correlation of tumor budding with nodal involvement, tumor stage, grade, extension, lymphovascular invasion, metastasis, and five-year survival. Moreover, in early stages of the colorectal cancer, this factors seems to be a prognostic factor as well for re-evaluation of the patients and categorize them in groups of high or low risk. Thus, assessment and reporting of a tumor budding count by pathologists in colorectal adenocarcinoma is highly advised. Further prospective studies with larger sample sizes are needed to assess the prognostic factors in stages I and II. It will also be challenging to assess the role of tumor budding in other types of carcinomas.

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Conflict of Interest

The authors declared no conflict of interest.