IJPRP

Indian Journal of Pathology: Research and Practice
Volume 9 Number 1 (Part II), January - April 2020
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.9120.31

Original Research Article

Tumour Budding As Prognostic Tool in Gastrointestinal Tract Malignancies: A Diagnostic Analytical Study at A Tertiary Care Hospital

Sanjay M[1], Amita K[2]

[1]Associate Professor, [2]Professor, Department of Pathology, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagmangala Taluk, Mandya, Karnataka 571448, India.

Corresponding Author:

Amita K, Professor, Department of Pathology, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagmangala Taluk, Mandya, Karnataka 571448, India.

E-mail: dramitay@gmail.com

Received on 25.10.2019

Accepted on 29.01.2020

Abstract

Background: Gastrointestinal tract malignancies (GIT) are on the rise and it is imperative to identify individuals at risk of developing relapse or metastasis and decide on management protocol consequently. Accurate risk assessment is pivotal to balance benefit versus overtreatment. Recently the tumour bud scoring has been included as a marker in cancers. The present study was planned to determine the association of tumour budding with various clinicopathology parameters in GIT malignancies. *Material & Methods:* This was a retrospective study conducted over a duration of two years including 40 cases. Tumour budding was counted in the maximum invasive area. Tumour budding was defined as the presence of single tumour cells or small clusters of up to five cells in the tumour stroma, Correlation between tumour budding and various clinicopathological characteristics were tested by chi-square test, with $p < 0.05$ significance. *Results:* There was a statistically significant association between grade of tumour budding and histologic type ($p < 0.048$), histologic grade ($p < 0.000$), lymph vascular invasion ($p < 0.000$), TNM staging ($p < 0.001$) and tumour interface (infiltrative versus expansile) ($p < 0.004$). *Conclusion:* Astandardized information about presence of tumour budding in routine histopathology reporting of GIT malignancies will help clinicians in adopting an effective modality of treatment for better patient care.

Keywords: Tumour budding; Gastrointestinal tract; Prognosis.

How to cite this article:

Sanjay M, Amita K. Tumour Budding As Prognostic Tool in Gastrointestinal Tract Malignancies: A Diagnostic Analytical Study at A Tertiary Care Hospital. Indian J Pathol Res Pract. 2020;9(1 Part II):200–205.

Introduction

Gastrointestinal tract (GIT) carcinomas are the leading cause of malignancy in developing countries. In today's era of personalized oncomedicine, it is imperative to identify individuals at risk of developing relapse or metastasis and decide on management protocol consequently. In traditional approach of tmour, lymph node and metastasis (TNM) system used for deciding treatment plan, early stage disease is subjected to aconservative

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0.

management protocol, while advanced stage diseases are taken up for multimodality therapy. Despite this, some early stage disease develops adverse outcomes.[1,2] Accurate risk assessment is pivotal to balance benefit versus overtreatment.[3] Hence, there is always a need to identify new prognostic factors that can predict such adverse events or identify high risk individuals. Recently, much emphasis has been placed on role of tmourhost microenvironment, especially the epithelial mesenchymal transition in tmour progression. The epithelial mesenchymal transition refers to the dissociation of tmour cells, stromal lysis and migration of tmourcells.[4–6] Tmour budding is one such correlate of epithelial mesenchymal transition wherein small clusters of tmour cells less thanfive are seen at the invasive front of tmour with aggressive biologic potential.[5] Since its documentation for first time in 1950 by Gabbert H et al.,[7] several researchers have attempted to standardize the scoring of tmour budding. Recently the tmour bud scoring has been included as a marker in colorectal cancers. However, literature on the role of tmour budding in GIT malignancies is scarce. Hence the present study was planned to determine the association of tmour budding with various clinicopathology parameters in GIT malignancies.

Materials and Methods

This was a retrospective study conducted over a duration of two years from June 2017 to May 2019. All the 40 consecutive cases of gastrointestinal tract (GIT) malignancies who had undergone surgical resection at Adichunchanagiri Institute of Medical Sciences, BG Nagara, were included in the study. Cases diagnosed of GIT malignancies at biopsy, those with concurrent malignancy at other sites or with previous history of malignancy were excluded from the study. The tmours were staged according to Tmour Node Metastasis staging system. Grading was performed as per organ specific standard guidelines. Computer system and case sheets from medical records department were screened for clinicodemographic information. Institutional ethical committee clearance was obtained.

All the surgically resected specimens were fixed in 10 % formalin, grossed as per the protocol and five-micron thin sections were obtained. The slides were stained withhaematoxylin and eosin stain (H & E stain). Two senior Pathologist with more than eightyears experience in histopathology and unaware of the final diagnosis and clinical data, independently reviewed the slides. Histologic typing was done as per WHO guidelines. Lymph vascular invasion was defined as presence of tmour cells in vessel wall, adherent to endothelium, covered by endothelium and protruding into the lumen. The pathologic staging was assigned as per the UICC guidelines.

Tmour budding was counted in the maximum invasive area. Tmour budding was defined as the presence of single tmour cells or small clusters of up to five cells in the tmour stroma, adjacent to large circumscribed areas of tmour cells. The buds were counted at 40x magnification in ten hotspots (densest area). The tmour budding was categorized as low, intermediate andhigh-grade tmour budding as follows; low grade – <4 tmour buds/10 HPF, intermediate 5 to 9/10 HPF and high grade – >10/10 HPF. Continuous variables were expressed as mean ± standard deviation, median, and minimum and maximum, while categorical variables were expressed as frequency and percentage.

Correlation between tmour budding and various clinicopathological characteristics were tested by chi-square test, with $p < 0.05$ significance.

Results

Among the 40 cases of GIT malignancies, age range was from 25 to 88 years with maximum cases being more than 60 years old. Females outnumbered males, with female to male ratio being 4:1. Demographic details are shown in (Table 1). The most frequent site of involvement was colon (18/40), followed by stomach (16/40), appendix, oesophagus and tongue (two in each case). Most tmours were 1 to 3 cm in size (40%). Most common histologic type was adenocarcinoma in 55%, followed by signet ring cell carcinoma in 20%, intestinal type of adenocarcinoma 4%, squamous cell carcinoma 4% and tubular carcinoma 2% of cases. 50% of tmours were well differentiated whereas poorly differentiated and moderately differentiated tmours accounted for 30% and 20% of all cases respectively. Lymph vascular invasion was seen in 55% (22/40) cases. Median number of lymph nodes isolated was 12 (range 07–20). Low tmour budding was seen in (20/40) 50%, high tmour budding in 40% (16/40) and intermediate tmour budding in (4/40) 10% cases. Tmour infiltrating lymphocytes were seen in 70% (28/40) cases. Perineural invasion was noted in 30% (12/40) of cases.

Association of various demographic and morphologic characteristics with different grades of budding is depicted in (Table 1).

Table 1: Shows demographic and clinicopathologic variables

Demographic characteristics	Frequency	Percentage (%)
Age in years		
25–40	5	12.5
41–50	7	17.5
51–60	9	22.5
>60	19	47.5
Sex		
Male	8	20.0
Female	32	80.0
Size of Tmour		
1–3 cms	16	40.0
4–5 cms	10	25.0
≥6cms	14	35.0
Histological Type		
Adenocarcinoma	22	55.0
Signet ring adenocarcinoma	8	20.0
Tubular adenocarcinoma	2	5.0
Intestinal type adenocarcinoma	4	10.0
Squamous cell carcinoma	4	10.0
Grading		
Well differentiated	20	50.0
Moderately differentiated	8	20.0
Poorly differentiated	12	30.0
Lymph vascular invasion		
Absent	22	55.0
Present	18	45.0
Tmour Budding		
Low	20	50.0
Intermediate	4	10.0
High	16	40.0
Tmour infiltrating lymphocytes		
Present	28	70.0
Absent	12	30.0
Perineural Invasion		
Present	12	30.0
Absent	28	70.0
TNM Staging		
T1 & T2	18	45.0
T3 & T4	22	55.0
Tmour Interface		
Expansile	14	35.0
Infiltrating	26	65.0
Proximal Margin		
Involved	12	30.0
Uninvolved	28	70.0
Distal Margin		
Involved	14	35.0
Uninvolved	26	65.0

There was no statistically significant association between different grades of tmour budding and demographic and morphologic characteristics like age ($p < 0.2$), gender ($p < 0.859$), type of procedure ($p < 0.124$), size of tmour ($p < 0.381$), number of lymph nodes ($p < 0.307$), tmour infiltrating lymphocytes ($p < 0.48$) and perineural invasion ($p < 0.327$). There was a statistically significant association between grade of tmour budding and histologic type ($p < 0.048$), histologic grade ($p < 0.000$), lymph vascular invasion ($p < 0.000$), TNM staging ($p < 0.001$) and tmour interface (infiltrative versus expansile) ($p < 0.004$).

Discussion

Carcinogenesis is a multistep process with several molecular changes occurring at each step. One of the critical and earliest steps defining tmour progression is the epithelial mesenchymal transition, i.e., invasion of tmour cells into the surrounding stroma which is reflected at morphology as tmour budding. Studies have linked tmour budding to epithelial mesenchymal transition wherein the TB acquire fibroblastic morphology capable of undergoing migration. At the molecular level, both tmour budding and EMT phenotype show reduced expression of Beta catenin and E Cadherin.[8]

Early in 1950's, pathologists for the first time recognized "sprouting" seen at the invasive front of the tmour and presumed that it reflected an aggressive behaviour.[9] Later in 1980's, researchers described the presence of dissociated cells at invasive front.[10] Since then few studies have attempted to analyse the role of tmour budding as a prognostic marker, albeit with discrepancies in the criteria's used. It was only in 2016, when ITBC laid down guidelines for standard reporting of tmour budding.[11,12] Prognosticpotential of tmour budding has been reported in colorectal, oesophageal, pancreatic, gastric, breast, lung and laryngeal carcinoma.[13–16]

GIT malignancies are one of the leading causes of cancer related mortality in India. Several prognostic factors have been identified that directs management and overall outcome of the disease. Identification of additional prognostic markers with potential clinical impact is imperative for delivering personalized treatment. To have a clinical realm, the prognostic markers should be easy to assess, cost effective, less time consuming and reproducible. Counting and grading of tmour budding used in the present study, as per ITBC guidelines, met all the above criteria.

In the present study, there was significant association between grades of TB and histologic types. There are few studies investigating tmour budding in gastric adenocarcinoma. Che k et al., in their study, included all cases of gastric adenocarcinoma, irrespective of the histologic type and observed a significant association between tmour budding and other prognostic factors.[17] Some authors opine that signet ring carcinomas are primarily high-gradetmours and hence tmour budding should not be applied to these subtypes. However, in a study by Gabbert et al, involving 445 patients with gastric carcinoma.[13] Tmour buddingemerged as an independent prognostic marker in all the histologic subtypes. Yama et al. reported tmour budding to be significantly associated with histologic subtypes of lung cancer.[15] These findings suggest a variation in pathogenetic process of tmour budding in different histologic subtypes.

In the present study, the analysis as per grade revealed that tmour budding was significantly associated with tmour grade. 100% of Grade 3 tmours showed high grade tmour budding, 90% of Grade 1 tmours showed low grade tmourbudding Sevda et al. reported significant correlation between tmour grade and tmour budding.[18] Contrary to this, Mehta et al. did not find any such correlation. They proposed that such correlation may be false, since, in high grade tmours, single cells may be falsely counted as tmour budding.[19]

Gendi S et al. and Mehta et al. did not report any correlation between tmour budding and T stage of the disease.[19,20] However, Fukumoto et al. observed that tmour budding is an important prognostic factor for predicting prognosis in stage.[21] In stage pT1 colorectal carcinomas, presence of tmour budding has been incorporated as an important risk factor, with presence of high-gradetmour budding, in addition to other high-risk factors, necessitating surgical intervention.[22] Similarly, in Stage II colorectal cancers, high grade tmour budding implicates initiation of adjuvant therapy. Promisingly, in colorectal and oesophageal carcinomas, TB has emerged as a potential predictive marker of response to neoadjuvant therapy.[23] Tmours with low grade tmour buddingrespond to EGFR therapy and have non progressive disease, while presence of high grade tmour budding predicts non responsiveness to EGFR therapy.

Roh et al. reported an association between tmour size and tmour budding. In a cohort of 56 patientswith oesophageal carcinoma.[24] In the present study, there was no significant association

between tmour size and grade of tmour budding.

In the present study, analysis of tmour budding and TIL did not reveal any significant association. This was in contrast to the findings reported by Lang-Schwarz C et al., who observed that the presence of tmour infiltrating lymphocytes correlated with low tmour budding and consequently good prognosis.[25]

Since tmour budding has been reported to be a significant prognostic marker in colorectal, gastric, oesophageal, lung and laryngeal carcinoma, it can be considered as an unequivocal prognostic marker, irrespective of the cell type. 18 out of 22 (81.81%) tmours with low grade tmour budding did not show LV invasion whereas, 88.8% of tmours with high-gradetmour budding showed LV invasion. Roh et al. reported significant association between LV invasion, high stage and high tmour budding.[23] Similar association of tmour budding with LV invasion, lymph node metastasis and survival has been documented by various authors.

Conclusion

Assessment of tmour budding can be easily done under H & E stain which is very cost effective and reproducible. A standardized information about presence oftmour budding in routine histopathology reporting of GIT malignancies will help clinicians in adopting an effective modality of treatment for better patient care.

References

1. Raja S, Rice TW, Goldblum JR, et al. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg 2011;142:1403–11.
2. Barbour AP, Jones M, Brown I, et al. Risk stratification for early esophageal adenocarcinoma: Analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 2010;17:2494–502.
3. Koelzer VH, Langer R, Zlobec I, et al. Tumor budding in upper gastrointestinal carcinomas. Front Oncol. 2014;4:1–12.
4. Zlobec I, Lugli A. Epithelial mesenchymal transition and tumor budding in aggressive colorectal cancer: Tumor budding as oncotarget. Oncotarget 1;2010:651–61.
5. Prall F. Tmour budding in colorectal carcinoma. Histopathology 50;2007:151–62.
6. Kalluri R, Weinberg RA. The basics of epithelial–mesenchymal transition. J. Clin. Invest 2009;119:1420–428.
7. Gabbert H, Wagner R, Moll R, et al. Tumor dedifferentiation: an important step in tumor invasion. Clin Exp Metastasis 1985;3:257–79.
8. Berg KB & Schaeffer DF. Tumor budding as a standardized parameter in gastrointestinal carcinomas: More than just the colon. Modern Pathology 2018;31:862–72.
9. Imai T. The growth of human carcinoma: Amorphological analysis. Fukuoka Igaku Zasshi 1954;45:13–43.
10. Cho SJ and Kakar S. Tumor Budding in Colorectal Carcinoma: Translating a Morphologic Score Into Clinically Meaningful Results. Archives of Pathology & Laboratory Medicine 2018;142:952–57.
11. Lugli A, Kirsch R, Ajioka Y et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299–311
12. Kakar S, Shi C, Berho ME, et al. Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum (V4.0.0.1). College of American Pathologists (CAP) website. http://www.cap.org/cancerprotocols. Accessed December 20, 2017
13. Gabbert HE, Meier S, Gerharz CD, Hommel G. Tumor-cell dissociation at the invasion front: A new prognostic parameter in gastric cancer patients. Int. J. Cancer 1992;50:202–07
14. Ohike N, Coban I, Kim GE, et al. Tumor budding as a strong prognostic indicator in invasive ampullary adenocarcinomas. Am. J. Surg. Pathol 2010;34:1417–24.
15. Yamaguchi Y, Ishii G, Kojima M, et al. Histopathologic Features of the Tumor Budding in Adenocarcinoma of the Lung: Tumor Budding As an Index to Predict the Potential Aggressiveness Journal of Thoracic Oncology 2010;5:1361–68.
16. Ekmekci S, Kucuk U, Kokkoz S, et al. Tumor budding in laryngeal carcinoma. Indian J PatholMicrobiol 2019;62:7–10.
17. Che K, Zhao Y, Qu X, et al. Prognostic significance of tumor budding and single cell invasion in gastric adenocarcinoma. Onco Targets Ther 2017;10:1039–47.
18. Sevda SB, Gülsün IM, Ibrahim MC, et al. Tumor Budding in Colorectal Carcinomas. Turkish journal of pathology 2012;28:61–66
19. Mehta A, Goswami M, Sinha R. Histopathological Significance and Prognostic Impact of Tumor Budding in Colorectal Cancer. Ann Clin Lab Sci 2017;47:129–35.
20. El-Gendi S, Al-Gendi A. Assessment of tumor budding in colorectal carcinoma: Correlation with b-catenin nuclear expression. Journal of the Egyptian National Cancer Institute 2011:23:1–9
21. Fukumoto K, Kikuchi E, Mikami S, et al. Tumor budding, a novel prognostic indicator for predicting

stage progression in T1 bladder cancers. Cancer Sci 2016;107:1338–44

22. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 2018;23:1–34
23. Miyata H, Yoshioka A, Yamasaki M, et al. Tumor budding in tumor invasive front predicts prognosis and survival of patients with esophageal squamous cell carcinomas receiving neoadjuvant chemotherapy. Cancer 2009;115:3324–34.
24. Roh MS, Lee JI, Choi PJ. Tumor budding as a useful prognostic marker in esophageal squamous cell carcinoma. Dis Esophagus 2004;17:333–7.
25. Lang-Schwarz C, Melcher B, Haumaier F, et al. Budding and tumor-infiltrating lymphocytes - combination of both parameters predicts survival in colorectal cancer and leads to new prognostic subgroups. Hum Pathol 2018;79:160–167.