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Tumour budding is a predictor of lymph node metastasis in colorectal carcinoma

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Abstract
Context: Tumour budding score (TBS) implies poor prognosis in colorectal cancer (CRC). A higher score is associated with a higher rate of lymph node metastasis. Therefore, it influences the treatment modality in Stage 2 and pT1 CRC. The International Tumour Budding consensus conference (ITBCC) proposed use of x20 objective for scoring which is not frequently available in Indian Laboratories. Tata Memorial Centre (TMC) has proposed score groups for x40 objective which could be more feasible for reporting in India.
Aims: To establish the significance of reporting tumour budding routinely in CRC and assess the reproducibility of TMC proposed score groups for x40 objective.
Methods: 4 Hematoxylin and Eosin stained sections from the tumour were studied in 32 CRC cases. TBS was defined as the single worst field with highest number of Tumour buds using the x40 objective and scored as low=0 to 1, intermediate=2 to 4 and high= more than equal to 5. TBS was compared with nodal metastasis.
Results: TBS was low in 23 cases, intermediate in 6 cases and high in 3 cases. All 3 cases with high TBS showed nodal metastasis with 2 cases (66%) having nodal stage N2b. All 6 cases with intermediate TBS score also showed nodal metastasis. Of the 23 low TBS cases, 7 showed nodal metastasis with 5 cases having nodal stage N1a.
Conclusions: TBS using x40 objective is a reproducible method and is associated with higher risk of lymph node metastasis. It should be incorporated in routine reporting of all CRC cases.

Keywords: Surgical pathology, prognosis, ITBCC

Introduction

Incidence of Colorectal Cancer (CRC) worldwide is approximately 6 lakh cases. More than 60% cases occur in developed countries. In India, CRC is the 8th and 9th most common cancer in men and women respectively [1]. Histologically more than 98% of CRCs are adenocarcinomas [2]. Treatment varies from endoscopic resection to major colectomies along with chemoradiation therapy based on the pathological stage. The decision for surgery in Stage I is still a subject of debate [3]. Various histologic prognostic factors help assess the aggressiveness of the disease [4]. One of those factors tumour budding has received increasing recognition as an independent prognostic factor in CRC, especially as a predictor of lymph node metastasis in pT1 CRC and survival in stage II CRC [5]. The International Tumour Budding Consensus Conference (ITBCC) recommends counting Tumour Budding Score (TBS) in the single worst field using x20 objective.(6) But it is frequently not reported in Indian Laboratories as availability of x20 objective is uncommon. The Tata Memorial Centre (TMC) proposed TBS groups in CRC using x40 objective tries to eliminate this problem.(5) This study aims to establish the significance of reporting tumour budding routinely in CRC and assess the reproducibility of TMC proposed score groups for x40 objective. The incorporation of TBS can give the surgeon a significant factor to decide the treatment of early CRC cases.

Material and Methods

After institutional ethics committee approval, a retrospective and prospective, observational study was carried out on all resections of CRC received in the Department of Pathology, Bharati Hospital, Pune. The study was conducted from 1st July 2015 to 30th June 2019. All cases of Adenocarcinoma of colon were considered for the study. Patients having received neo-adjuvant chemotherapy before resection were excluded from the study.

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Demographic data was retrieved from hospital records. A total of four Hematoxylin and Eosin stained sections from the tumour were studied in each case. Tumour buds were defined as individual cells or clusters of 4 or less cells at the progressing border of tumour. Using the TMC proposed system, the single worst field with highest number of Tumour buds using the x40 objective were recorded. These were grouped into low (0-1), intermediate (2-4) and high (≥5) TBS considering the single worst field. The microscope used was MLXi Plus manufactured by Olympus Opto Systems with a field diameter of 0.65mm. Demographic details were obtained from test request forms. Gross parameters noted were site of tumor, size of tumor and presence of tumor perforation. Histological parameters including tumour grade, lymphovascular invasion (LVI), perineural invasion (PNI), lymph node status and presence of metastatic deposits were noted. The staging was done using AJCC TNM classification. Statistical analysis was done using SPSS software.
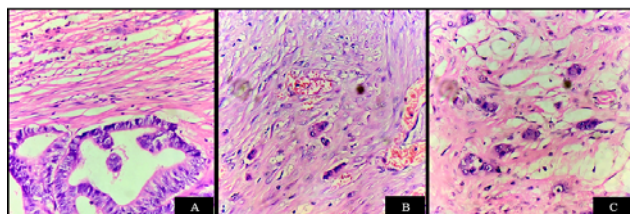

Fig 1: Tumour Budding Score using x40 objective. A: Low TBS (0-1), B: Intermediate TBS (2-4), C: High TBS (5 or more).

Results
A total of 32 cases were included in the study. Age ranged from 31 years to 85 years with a mean age of 59 years. 21 were males and 11 were female with a male to female ratio of 1.9: 1. 11 were right sided cases and 21 were left sided with rectum being the most common site comprising of 11 (34.3%) cases. The greatest tumor dimension ranged from 2.5cm to 11 cm with an average size of 5.92cm. All cases were diagnosed as Adenocarcinoma histologically. TBS score was low in 23, intermediate in 6 and high in 3 cases.

There were 3 Grade 1 adenocarcinoma cases. 29 were Grade 2 and none of the cases were Grade 3. All grade 1 CRCs had a low or intermediate TBS whereas 3 cases of Grade 2 CRCs had a high TBS. This association was not significant statistically.

9 (28%) out of 32 cases showed presence of LVI. Of the 9 cases with LVI 5 cases (55%) showed an intermediate or high TBS where out of 23 cases without LVI only 4 cases (17%) showed an intermediate or high TBS. This associated did not have any statistical significance.

Only 3 (9.4%) out of 32 cases showed presence of PNI. 2 out of 3 (67%) cases with PNI had an intermediate or high TBS where only 4 out of 29 cases (24%) without PNI showed an intermediate or high TBS. This association again did not have statistical significance.

The T stage was T1, T2, T3 and T4 in 2, 8, 12 and 10 cases respectively. All TBS intermediate and high cases were T stage 3 or more except 1.

The nodal stage was 0, 1 and 2 in 16, 10 and 6 cases respectively. The associated of T stage and TBS score was statistically significant with a p value of …. No cases without lymph node metastasis had an intermediate or high TBS which was statistically significant with a p value of <0.001. The TNM stage was I, II, and III in 8, 8 and 16 cases respectively.

Table 1: Correlation of various parameters with TBS

Tumour Budding Score	Tumour Budding Score				
	Low	Intermediate	High	Total	p value
Grade					
1	2	1	0	3	0.643
2	21	5	3	29	
3	0	0	0	0	
LVI					
seen	4	3	2	9	0.074
not seen	19	3	1	23	
PNI					
seen	1	1	1	3	0.184
not seen	22	5	2	29	
T Stage					
1	2	0	0	2	
2	7	1	0	8	
3	9	2	1	12	0.677
4a	4	3	2	9	
4b	1	0	0	1	
Nodal stage					
0	16	0	0	16	
1a	5	1	0	6	
1b	1	1	0	2	<0.001
1c	0	1	1	2	
2a	0	1	0	1	
2b	1	2	2	5	
TNM Stage					
I	8	0	0	8	
II	8	0	0	8	0.012
III	7	6	3	16	

Discussion

TBS has been rapidly gaining importance in the management of carcinomas of head and neck, esophagus, breast, lung and colon as a prognostic marker. Guidelines for management in CRC based on the TBS have been recommended in 3 scenarios. The first one being surgical resection for T1 adenocarcinomas, second in deciding on the adjuvant therapy for Stage II CRCs, and lastly in making a decision regarding neoadjuvant treatment on preoperative biopsies of CRC [5]. The significance of TBS as a prognostic marker in CRC has been well documented but the recommended guidelines for reporting TBS have only been recently described by the ITBCC [6]. Although a consensus has been made regarding the guidelines for reporting TBS, the availability of 20x objective is a rarity in an Indian setting. There are no internationally established guidelines for using the 40x for TBS. The TMC proposed scoring system for TBS using 40x objective eliminates this issue [5].

The reporting was done using routine H and E staining. IHC staining using epithelial markers is considered superior but it is not recommended in routine practice [6].

Although, the percentage of cases with LVI was greater in high and intermediate TBS compared to low TBS but it was not statistically significant. Graham *et al*. in their study showed that there were LVI in 45/179 (25%) cases with high TBS and 16/122 (13%) cases with low TBS. However, reporting in their study was done using x40 microscope [7].

There was significant correlation of nodal stage with TBS score. Only 1 case with low TBS had a nodal stage of more than N1b whereas all cases with high TBS had nodal stage of more than N1c. Hence we found that TBS using 40x also showed significant association with lymph node metastasis. Roy *et al*. in their study have shown significant association of TBS using x40 objective with overall survival in CRC [5].

In pT1 cases where simple polypectomy is the surgical treatment high TBS becomes significant as further resection becomes necessary in view of possible lymph node metastasis [6]. Numerous studies have documented the prognostic implication of TBS in Stage II CRCs where it affects the decision regarding neoadjuvant therapy. An intermediate and high TBS warrants a neoadjuvant therapy in these cases [8].

Conclusions

TBS using x40 objective is a reproducible method and intermediate and high TBS is associated with higher risk of lymph node metastasis. TBS should be incorporated in routine reporting of all CRC cases. Further larger studies may be implicated to formulate an internationally accepted standard protocol to use x40 objective for reporting TBS in CRC.

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