Original Article

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Prevalence of Tumor Budding and its Significance for Predicting Lymph Node Metastasis in Carcinomas at Tertiary Care Centre

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Submitted 25 February 2023 **Accepted** 15 December 2023 **Published** 29 December 2023

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Citation

"Paudel A, Karki S, Shah N, Shrestha B, Baral A. The Prevalence of Tumor Budding and its Significance for Predicting Lymph Node Metastasis in Carcinomas at Tertiary care Centre. JBPKIHS. 2023;6(2):18-22"

https://doi.org/10.3126/jbpkihs.v6i2.57704

Abstract

Background: "Tumor budding" basically means the presence of clusters of less than five malignant cells in the tumor stroma, located ahead of the invasive front of tumor. Various studies have been carried out regarding tumor budding, its significance in tumor metastasis involving head and neck, breast, gastrointestinal tract, pancreas and cervix and is now evolving in cancer reporting templates. We conducted this study in regards to growing importance of tumor budding in cancer metastasis with objectives to find out the prevalence of tumor budding in carcinoma and to know the association of tumor budding with lymph node, perineural and lymphovascular invasion.

Methods: All the resected specimen with regional lymph node were examined for presence or absence of tumor buds. It was graded as high/ low grade based on the number of buds. Association of the tumor buds with lymph node metastasis, lymphovascular and perineural invasion was calculated. The study was conducted from January 2019 to January 2020. Purposive sampling was used. Ethical clearance was ensured from the institutional review board before the start of study. All surgically resected specimen of carcinomas with regional lymph nodes were included in the study whereas autolysed specimen and patient who refused to give consent were excluded from the study.

Result: Total 37 cases of resected specimens of gastrointestinal tract, breast, head and neck were evaluated. The prevalence of tumor budding was 91.9%. In every instance where tumor budding existed, there was an observation of high-grade tumor bud. Tumor budding was strongly associated with lymph node invasion ($p = 0.005$). Significant value was not observed in the correlation of tumor budding with lymphovascular and perineural invasion.

Conclusion: Tumor budding holds an important role in predicting lymph node metastasis in carcinomas, highlighting its importance in the histopathological reports of resected specimen.

Keywords: Neoplasm invasiveness; Lymphatic metastasis; Lymph nodes; Prognosis

Declarations

Ethics approval and consent to participate: This study was conducted with prior ethical approval from Institutional Review Board of BPKIHS (IRC Code: IRC/1322/018). Informed consent was taken from all the patients prior to the enrollment.

Consent for publication: Not applicable.

Availability of data and materials: The full data set supporting this research will be made available upon request by the readers.

Competing interest: None

Funding: None.

Authors' contributions: AP: Concept, design, data collection, data analysis, statistical analysis, and interpretation, drafting of manuscript. SK: Concept, design, data analysis, statistical analysis, and interpretation. NS: Concept, design, data analysis, statistical analysis, and interpretation. BS: Manuscript review/ editing. AB: Manuscript review/ editing. All authors have read and approved the final manuscript.

Acknowledgements: I would like to acknowledge and thank my guide and co guides at BP Koirala institute of health sciences, Dharan, for their supervision and guidance during the progress and completion of this work.

BACKGROUND

Tumor budding is defined as single cells or clusters of less than five cells, located in the stroma at the invasive front of a tumor. As the burden of the cancer are increasing every day globally, research on various factors have been carried out to identify and establish the prognostic significance of these factors. Though factors like perineural invasion/ lymphovascular invasion, tumor differentiation, depth of invasion have already established itself as a prognostic significance, various study are being carried out since decades to establish tumor budding as an independent prognostic factor [1].

Tumor budding has received increasing attention by pathologists as a valuable prognostic factor. Studies on other organs like head and neck, breast, cervix, pancreas, esophagus and stomach are also being carried out so that the importance of tumor budding is not just limited to the colorectal carcinomas. Specifically, detection of tumor budding may allow the identification of patients at high risk for nodal metastasis [2].

Tumor budding, has been well researched in the past two decades as a poor prognostic factor for colorectal adenocarcinomas, breast, head and neck, cervix and pancreas but has been slow to be incorporated into routine pathology reporting. However, the most recent American Joint Committee on Cancer (AJCC) 8th edition, as well as the College of American Pathologists (CAP) guidelines for colorectal carcinoma reporting, are now including tumor budding as an optional reporting field [3 - 5].

Tumor budding can play a vital role for surgeon in therapeutic decision making. Its major role will be after the small biopsy where the presence of tumor budding will add for therapeutic significance predicting lymph node metastasis which in turn will indicate the need for large surgical resection and patient selection for adjuvant therapy. Similarly in its absence a smaller scale operation may be possible to avoid unnecessary resection. Thus, it will help to ovoid under and over surgical resection.

The purpose of the current study was to evaluate the potential clinical value of tumour budding in various carcinomas as a predictor of lymph node, lymphovascular and perineural invasion.

METHODS

A prospective cross - sectional hospital based study at BPKIHS was carried out with 37 surgically resected specimen of carcinoma over a period of one year from January 2019 to January 2020. Purposive sampling was used. Ethical clearance was ensured from the institutional review board before the start of study (IRC code: IRC 1322/018). All surgically resected specimen of carcinomas with regional lymph nodes were included in the study whereas autolysed specimen and patient who refused to give consent were excluded from the study.

Prevalence of tumor budding, its grade and significance for lymph node metastasis, lymphovascular and perineural invasion was analysed. Collected data was entered in Microsoft office excel 2007. Data was analysed by using SPSS 11.5 (Statistical package for social sciences). For Descriptive statistics percentage (%), proportion, ratio, mean and standard deviation was calculated. For inferential statistics Fisher exact test was used.

For assessing and counting of tumor budding:
The prepared slide was examined with Nikon Eclipse E600 microscope under 2x, 4x, 10x, 20x and 40x objective lens. Tumor budding was defined as a single cell or clusters of < 5 cell at the invasive tumor front. All tumor block was first examined at low magnification and the most representative block with highest number of budding foci was chosen for the analysis. Then number of buds was counted in 10 High Power Field (40x) magnification. High grade budding was defined as an average of 10 or more buds across 10 high power field and less than 10 buds across 10 high power field was defined as low grade. For the vascular invasion, tumor cells present within the vessel, confirmed by the presence of endothelial lining was taken as positive. Lymph node positive was taken as presence of tumor cell within the lymph nodes slides. Perineural invasion was taken as presence of tumor within the perineural space. Multiple pathologists evaluated the slides and result were blinded. Where there was discrepancy common consensus was made [3].

RESULTS

Of the total 37 cases, 34 of the cases showed tumor budding with a prevalence of 91.9 %. Prevalence of tumor budding in Gastrointestinal Tract (GIT), head and neck and breast was 95.9 %, 71.4% and 100% respectively. All the cases with tumor budding showed high grade tumor budding.

Of the total 34 cases where tumor budding was observed, lymph node invasion was seen in 30 cases. The three cases without tumor budding did not exhibit lymph node invasion as well. There was significant relation of tumor budding with lymph node invasion (p value = 0.005).

Lymphovascular invasion was seen in 17 cases with tumor budding. In one case, there was evidence of lymphovascular invasion with absence of tumor budding. Significant relation was not observed between tumor budding and lymphovascular invasion (p value > 0.99). Similarly, 13 cases with tumor budding showed perineural invasion. Significant relation was not observed between tumor budding and perineural invasion (p value = 0.28).

DISCUSSION

Our study showed 91.9% tumor budding in carcinoma. Various studies have shown prevalence of tumor budding from 61.8% to 100% **(Table 1)**. Nevertheless, the prevalence of tumor budding in our study falls within these range. Accounting prevalence as per organ system, prevalence of tumor budding in GIT was 95.9 % which is concordant with other studies [8 - 13]. However, tumor budding in head and neck tumor decreased is only 71.4% which shows slight discordant with the study done by Manjula et al [6]. In breast, prevalence of tumor budding was found to be 100% which is concordant with the study done by Liang et al where the prevalence of tumor budding was also 100% [7].

All the cases where tumor budding was present were of high grade. We did not find cases showing low grade tumor budding. This could be due to the fact that the maximum number of cases were at advanced stage of presentation. We did not select a single hotspot but counted across 10 high power field with maximum number of tumor buds. The discrepancy in grade of tumor budding in our study compared with other studies can be attributed to the heterogeneity in values which arises from the unavailability of established histologic cutoff. We have compared the tumor budding grade in our study with various studies in **Table 2.**

Table 1: Prevalance of tumor budding across various studies

Series	Year	Total no. of cases (n)	Specimen	Prevalence or tumor buds (%)
Our study	2019	37	GIT/ Head and neck/ Breast	Overall prevalence: 91.9 GIT: 95.6 Breast: 100.0 Head and neck: 71.4
Hase et al [8]	1970 - 1985	663	Colon-rectum	100.0
Kazama et al [9]	1990 - 2001	56	Colorectum (T2)	61.8
Wang et al [10]	1990 - 2004	128	Colorectum (T3)	100.0
Graham et al [11]	2016	553	Colorectum	78.0
Pai et al [12]	2010 - 2014	116	Colorectum (T1)	100.0
Bektas et al [13]		73	Colorectum	100.0
Satabongkoch et al [14]	2006 - 2012	129	Cervix	100.0
Karamitopoulou et al [15]	2013	117	Pancreas	100.0
Manjula et al [6]	2014	33	Oral cancers	100.0

GIT: Gastrointestinal Tract

Table 2: Grading of tumor budding across various studies

SN	Series	Year	No. of cases (n)	Specimen	High grade(%)	Low grade (%)	Methodology
1	Our study	2019	37	GIT/ Head-neck/ Breast	100.0		400x across 10f ield. ≥ 10 High grade/ less low grade
2	Hase et al [8]	1970 - 1985	663	Colon - rectum	74.4	25.6	If predominant buds present high grade
3	Kazama et al [9]	1990 - 2001	56	Colorectum (T2)	-	-	Grading not done/ IHC used to see tumor buds
4	Wang et all [10]	1990 - 2004	128	Colorectum (T3)	45.0	55.0	200x; High grade if more than 50% of area were positive for buds
5	Graham et al [11]	2016	553	colorectum	32.0	46.0	≥10 or more buds across 200x.
6	Pai et al [12]	2010 - 2014	116	Colorectum (T1)	20.0	80.0	High grade if ≥ 5 tumor buds across 0.95mm2
7	Bektas et al [13]		73	Colorectum	54.8	45.2	200x single filed - if ≥ 10 or more buds.
8	Satabongkoch et al [14]	2006 - 2012	129	Cervix	12.0	88.0	≥ 1 5 or more per 10 hpf (400x)
9	Morodomi et al [16]	2014	33	Oral cancers	63.0	37.0	500x2500 micrometer2- 0 - 4 negative, 5 - 14 mildly positive, 15 or more strongly positive.

GIT: Gastrointestinal Tract

Among 37 resected specimens of carcinoma, tumor budding was seen in 34 cases. Thirty out of 34 cases showed presence of lymph node metastasis (p value = 0.005).

Out of 23 cases of gastrointestinal tract tumor 95.9% cases tumor budding were seen and lymph node invasion was seen in 82% which was statistically significant (p value = 0.005). A total of 423 lymph node were examined and 192 of the lymph nodes were from the specimen of the gastrointestinal tract. Out of 192 lymph nodes, 75 of the lymph nodes were positive for lymph node invasion. According to the study done by Hase et al [8] lymph node invasion was seen in 37% of cases and was significantly associated with tumor budding (p value = 0.005). In a study done by Klazama et al et al [9] lymph node invasion was present in 57% of cases and was significantly associated with tumor budding (p value = 0.004). Percentage of lymph node invasion is comparatively higher in our cases as we have included all (T1-T4) stages **(Table 3).**

All the seven cases of invasive ductal carcinoma NST (no special type) included in our study had tumor budding and lymph node metastasis which is comparable with the study done by Liang et al [7].

In our study there were seven cases of head and neck squamous cell carcinomas. In five cases tumor budding were observed and lymph node invasion were seen in four of those cases. The remaining one case with tumor budding did not exhibit lymph node invasion. We were not able to determine the statistical significance due to less number of data. Similar study done by Manjula et al (33 oral squamous carcinoma), tumor budding was seen in all cases and lymph node metastasis was present in 18 cases, the relation was statistically significant (p = 0.014) [6]. Thus, the importance of tumor budding in predicting lymph node metastasis is equally important in every organ system.

The incidence of lymphovascular invasion varied from 18 to 56% in various studies [15-19]. Incidence in our study is 45.9% which falls within these range. Very few cases have reported the incidence of perineural invasion ranging from 4.6% to 23% [16-18]. However, incidence of perineural invasion in our case is 35%, which is slightly higher than the published literature **(Table 4).** Association of tumor budding with that of lymphovascular and perineural invasion did not show statistical significance in our case. This could be possibly due to small sample size. Study done by Manjula et al [6] was similar in regarding the study population and there was a significant association of tumor budding with lymphovascular and perineural invasion. Statistical analysis was performed considering only high intensity tumor buds. Grading in this study was done selecting a single high-power field.

Our study spanned only one year and involved a limited sample size. The cases were selected from a single center, emphasizing that a large scale study would provide a representation of the population.

Table 3: Review of tumor budding with lymph node invasion involving GIT

SN	Series	No. of cases (n)	Tumor budding (%)	Lymph node invasion (%)	p value
1	Our study	23	95.0	82.0	0.005
2	Hase et al [8]	663	100.0	37.0	0.005
3	Kazama et al [9]	56	61.8	57.0	0.004
4	Bektas et al [13]	83	100.0	50.0	0.001

GIT: Gastrointestinal Tract

Table 4: Review of tumor budding with lymphovascular and perineural invasion

SN	Series	Site	No of cases (n)	Tumor budding (%)	Lymphovascular Invasion (%)	Perineural Invasion (%)
1	Our study	GIT /head and neck/ Breast	37	91.9	45.9	35.0
2	Hase et al [8]	colorectum	633	100.0	41.0	23.0
3	Kazama et al [9]	colorectum	56	61.0	38.0	Not performed
4	Wang et al [10]	colorectum	128	100.0	37.5	4.6
5	Bektas et al [13]	colorectum	73	100.0	37.0	Not performed
6	Liang et al [7]	Breast	190	100.0	23.8	Not performed
7	Satabongkoch et al [14]	cervix	129	100.0	56.5	Not performed
8	Manjula et al [6]	oral	33	100.0	18.0	21.0

GIT: Gastrointestinal Tract

CONCLUSION

Tumor budding holds an important role in predicting lymph node metastasis in carcinomas, highlighting its importance in the histopathological reports of resected specimen.

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