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Original Research Article

Evaluation of prognostic role of tumour budding in breast carcinoma and its correlation with known clinicopathological parameters

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ABSTRACT

Background: Tumour budding (TB) consists of a small group of cells (upto 5) which have detached from the tumour bulk. TB has been studied in many malignancies including head and neck, colorectum, oesophagus, etc. However there are very few studies to determine its role in Breast cancer. This study was designed to study the role of tumour budding as a prognostic factor in Breast cancer.

Objectives: To study the grade of TB in Invasive Breast Carcinoma and correlate it with known clinicopathological parameters to determine its usefulness as a prognostic factor.

Materials and Methods: In this retrospective observational study, 40 cases of modified radical mastectomy from July 2019 to December 2020 were evaluated for the tumour budding. Ethical clearance was not required as it was a secondary data collection study which did not relate to patient's privacy, clinical examination or treatment. Significance and correlation was studied between the grade of TB and known clinicopathological parameters using Chi-square test.

Results: Out of the 40 cases evaluated, 20 cases (50%) were of High grade TB (>/=10/10HPF), while 20 cases (50%) were of Low grade TB (<10/10HPF). Majority patients were of age group 40-60 years (60%), with primary carcinoma (52.5%) and invasive ductal type (72.5%). Higher TB was observed with Lymphnode positive cases (p=0.002), in higher TNM stage (p=0.006) and with lymphovascular invasion (p=0.000).

Conclusion: As higher grade tumour budding was associated with positive lymphnode status, higher tumour stage and presence of lymphovascular invasion, it can be considered as an indicator of poor prognosis in cases of breast carcinoma especially in resource poor institutes which are not equipped with sophisticated IHC and Molecular markers.

1. Introduction

Breast carcinoma is very common in perimenopausal, menopausal and post-menopausal patients. Early diagnosis and prognosis is very important for proper management of the patient for the clinician as well as for the society. Many prognostic factors like molecular factors, hormone receptors and proliferative markers are under investigation and have been applied in daily clinical practice. However they are not easily available in routine laboratory setups. Newer markers are still in research and one of them is tumour budding.[1] Tumour budding consists of a small group cells (upto 5 cells) which have detached from the tumour bulk. Tumour budding cells have a cancer stem cell character because of their potential for migration and redifferentiation, locally and at sites of metastasis. They are a group of cells with the ability of self renewal.[2] Tumour budding has been studied in many malignancies which include head and neck, lung, gastric, oesophageal and colorectal cancers. They are usually seen in areas near the margin of the tumour at the

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invasive tumour front, called as peritumour buds, or inside the tumour mass and are called as intratumour buds.[3,4] Tumour budding can be studied in Hematoxylin and Eosin sections as well as immunohistochemistry methods using CK stain. However, H&E staining is sufficient to identify tumour budding but when there is significant inflammatory infiltration, IHC methods are utilized for tumour budding identification.[5]

2. Materials and Methods

This is a retrospective observational study carried out in the histopathology section of a tertiary care referral institute with the available histopathological data of 40 cases of modified radical mastectomy from July 2019 to December 2020. Ethical approval for this study was not required by our institute as it was a secondary data collection study which did not relate to patient's privacy, clinical examination or treatment. The slides were retrieved from the archives and all the tumour sections were examined. Inter-observer agreement was tested between two independent observers and discordance between the observers were resolved by simultaneous review and this data was used to do further statistical analysis.

Evaluation of the tumour buds was done as follows:

1. The invasive front of invasive breast carcinoma was identified in scanner power (4x objective).
2. Tumour buds were searched in low power (10x objective).
3. Details of tumour buds were examined under high power (40x objective).
4. The possibility of mimickers of tumour buds like inflammatory cells, multinucleated giant cells, fibroblasts, endothelial cells, smooth muscle cells and artifacts were excluded by examining under high power (40x objective).
5. Nuclear and cytoplasmic characteristics of tumour bud cells were compared with those of the invasive tumour cells by examining under high power (40x objective).
6. Number of tumour buds counted in 10 high power fields were documented.
7. Tumour budding was classified into High tumour budding (Tumour buds > 10 per 10 HPF) and low tumour budding (Tumour buds </= 10 per 10 HPF).

Other clinicopathological variables like age, treatment status, tumour type, lymph node status, TNM stage and presence of lymphovascular or dermal invasion was documented. Association between tumour budding and histopathological parameters and clinical details were analysed by statistical methods.

3. Results

A total of 40 cases of invasive breast carcinoma were included in the study.

Out of the 40 cases, maximum cases were of age group 40-49 yrs and 50-59 yrs (30% each) followed by 12.5% cases of age group 30-39 yrs and 5% cases of age group 20-29 yrs.

Of these 40 cases, 29 cases (72.5%) were of invasive ductal carcinoma, 6 cases (15%) were of No specific type, and 1 case each of lobular Ca, Mucinous Ca, Metaplastic Ca, Ca with medullary features and Ca with neuroendocrine features (2.5% each).

Clinicopathological characteristics of the 40 cases are summarized in Table 2. Maximum cases are of age group >45 yrs (75%), newly diagnosed (57.5%), lymph node negative (45%), Tumour size T2 (52.5%) and TNM stage III (45%).

Tumour budding was evaluated in all 40 cases. High tumour budding was seen in 20 cases (50%) and low tumour budding was seen in 20 cases (50%). High tumour budding was seen in patients above the age of >45 years (70%) compared to age <45 years (43.3%). High tumour budding was seen in patients who had a newly diagnosed malignancy (52.1%) compared to those who were post chemotherapy (47%). 66.6% cases of Invasive carcinoma-NST showed high tumour budding while 33.3% cases showed low tumour budding. 48.2% cases of Invasive ductal carcinoma showed high tumour budding while 51.7% cases showed low tumour budding. 1 case (100%) each of Lobular, Metaplastic and Medullary carcinoma showed Low tumour budding while 1 case (100%) each of Mucinous and neuroendocrine carcinoma showed High tumour budding. High tumour budding was seen with positive lymph nodes (82.3%) compared to negative lymph nodes (22.2%). High tumour budding was seen with increasingly larger tumour size and TNM staging.

Table 1: Percentage age distribution

AGE	N=40	% Distribution
20-29 yrs	02	5
30-39 yrs	05	12.5
40-49 yrs	12	30
50-59 yrs	12	30
60-69 yrs	09	22.5

4. Discussion

Tumour budding is one of the mechanisms of cancer invasion and metastasis. Nowadays it is increasingly recognised as a strong adverse prognostic factor. It has been studied in detail in colorectal cancer and has now been included in the specific guidelines for the management of colorectal cancer.[1,6,7] There are very few studies in literature regarding tumour budding in breast carcinoma. In this study we have evaluated the significance of tumour budding in breast carcinoma and its correlation with the clinicopathological parameters such as age, treatment

Table 2: Clinicopathological characteristics of 40 cases of breast carcinoma

Clinicopathological Parameter		N=40	% Distribution
Age	<45 years	10	25
	>45 years	30	75
Treatment status	Post treatment	17	42.5
	Primary	23	57.5
Lymph node status	Positive	17	42.5
	Negative	18	45
	Unknown	5	12.5
Invasion	Lymphovascular	4	10
	Dermal	9	22.5
Tumour size	T1	5	12.5
	T2	21	52.5
	T3	7	17.5
	T4	7	17.5
Tnm staging	I	5	12.5
	II	16	40
	III	18	45
Type of carcinoma	Invasive carcinoma – nst	06	15
	Invasive ductal carcinoma	29	72.5
	Lobular carcinoma	01	2.5
	Mucinous carcinoma	01	2.5
	Metaplastic carcinoma	01	2.5
	Ca with medullary features	01	2.5
	Ca with neuroendocrine features	01	2.5

Table 3: Correlation of tumour budding with clinicopathological parameters

Clinicopathological Parameter		High tumour budding	Low tumour budding	Total
Age (n=40)	<45	7(70)	3(30)	10
	>45	13(43.3)	17(56.6)	30
Treatment status (n=40)	Post chemotherapy	8(47)	9(53)	17
	Newly diagnosed	12(52.1)	11(47.8)	23
Type of carcinoma (n=40)	Invasive Carcinoma- NST	4(66.6)	2(33.3)	6
	Invasive Ductal Carcinoma	14(48.2)	15(51.7)	29
	Lobular Carcinoma	0(0)	1(100)	1
	Mucinous Carcinoma	1(100)	0(0)	1
	Metaplastic Carcinoma	0(0)	1(100)	1
	Carcinoma with Medullary features	0(0)	1(100)	1
	Carcinoma with Neuroendocrine features	1(100)	0(0)	1

Table 4: Clinicopathological correlation with tumour budding

Clinicopathological Parameter		High tumour budding	Low tumour budding	P value
Lymph Node Status (n=40)	Positive	14(82.3)	3(17.6)	p=0.002
	Negative	4(22.2)	14(77.7)	
	Unknown	2(40)	3(60)	
Tumour Size (n=40)	T1	2(40)	3(60)	p= 0.66
	T2	10(47.6)	11(52.3)	
	T3	4(57.1)	3(42.8)	
	T4	5(71.4)	2(28.5)	
TNM Staging (n=40)	I	1(20)	4(80)	p=0.006
	II	5(29.4)	12(70.5)	
	III	14(71.4)	4(28.5)	
INVASION (n=4)	Lymphovascular	1(100)	0(0)	p=0.000

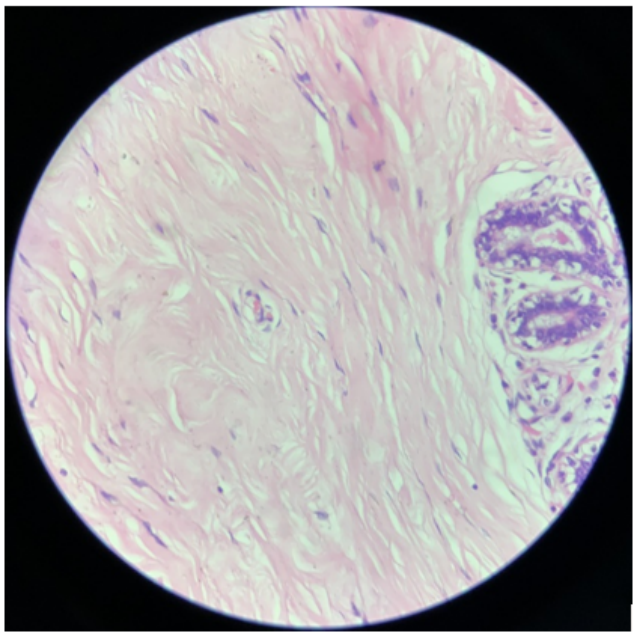

Fig. 1: Low grade tumor budding in invasive ductal Ca (H&E, 40x magnification)

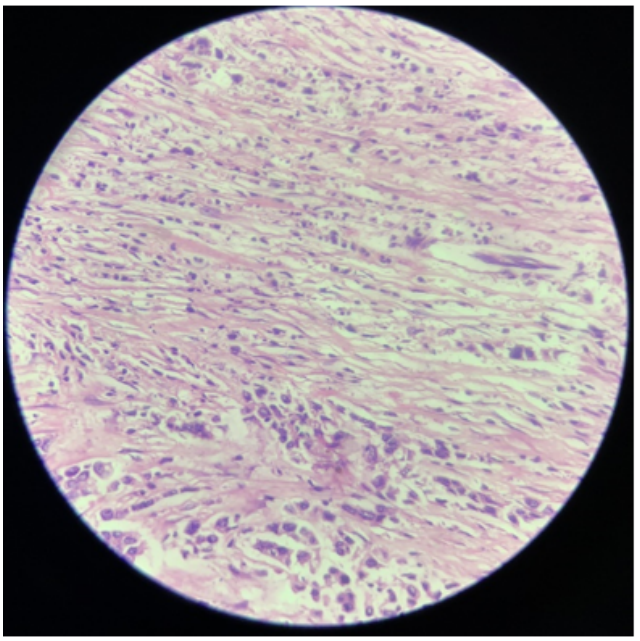

Fig. 2: High grade tumor budding in Invasive Lobular Ca (H&E, 40x magnification

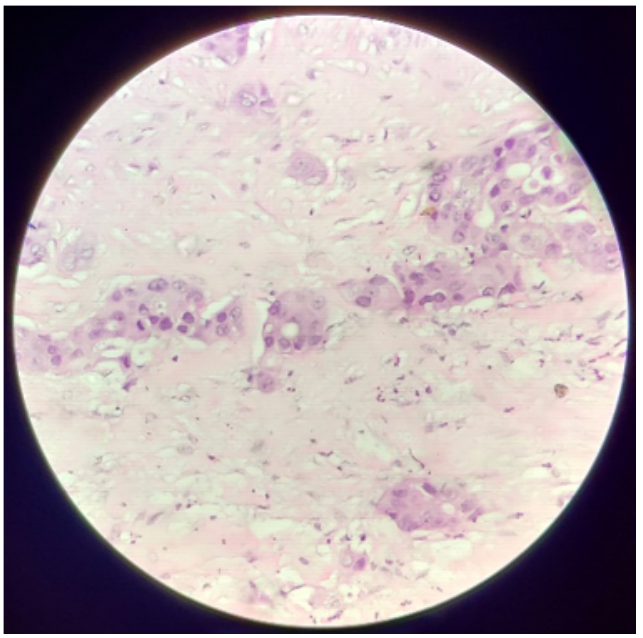

Fig. 3: High grade tumor budding in invasive ductal Ca (H&E, 40x magnification)

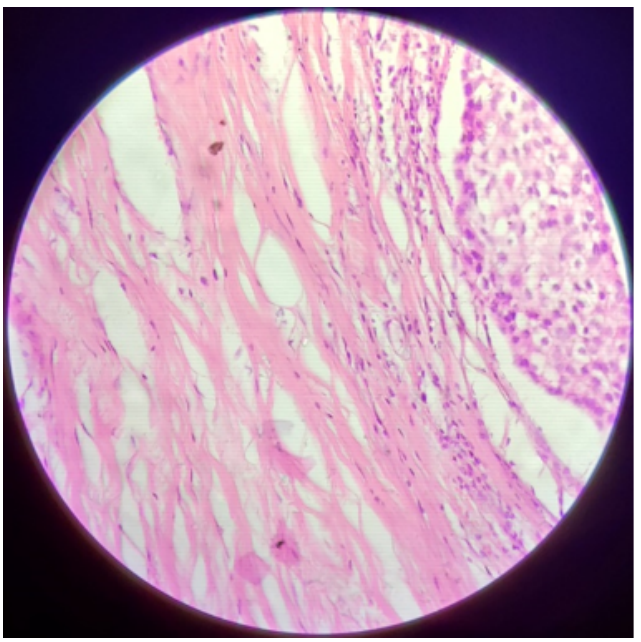

Fig. 4: Low grade tumor budding in Invasive breast Ca-NST (H & E, 40x magnification)

status, lymph node status, tumour size, TNM staging and lymphovascular and dermal invasion.

Salhia et al.,[8] B.N Kumarguru et al.[7] and the present study used high power (40X) objective to count the tumour buds. In contrast, Liang et al.[9] and Radhika Agarwal et al.[4] used the 20X objective. It may be suggested that it would be better if the tumour buds were confirmed under 40X objective to exclude their mimickers (inflammatory cells, fibroblast etc.) on H&E stained sections.

In this study, Tumour budding was high grade in 20 (50%) cases and low grade in 20 (50%) cases. This was in close approximation with Radhika Agarwal et al.[4] [High grade 47.5% and low grade 52.5%] and B.N Kumarguru et al.[7] [High grade 60% and low grade 40%].

Specimens with high grade budding were significantly associated with presence of lymph nodes positivity (p=0.002), higher pathological stage (p=0.006) and presence of lymphovascular invasion (p=0.000). This was in concordance with the study done by Liang et al.[9] Salhia et al.,[8] Radhika Agarwal et al.,[4] Niputu Sriwidyani et al.,[1] Renuka IV et al.[10] and B.N. Kumarguru et al.[7]

Tumour budding showed increasing association with presence of larger tumour size however was not statistically significant (p=0.61). This could be due to a smaller sample size of the study.

5. Limitations of the Study

Because of the COVID-19 situation and ours being a tertiary care COVID-19 institute, the number of patients in our study were less compared to other studies. Hormone receptor (ER, PR, Her -2neu) status and IHC markers (CK, E-Cadherin, MMP-9) were not possible in all cases as our institute is a tertiary care government setup and we don't get a regular supply of IHC reagents. It may be suggested that bigger and well equipped centres can do simultaneous H&E and CK correlation to differentiate the mimickers of tumour budding. Perineural invasion was studied in a lot of studies but our findings were not statistically significant to be included in the study.

6. Conclusion

High tumour budding was significantly associated with higher age, lymphovascular invasion, lymph node metastasis, TNM tumour staging. Hence, from the above study we conclude that high tumour budding can be considered as an indicator of poor prognosis in cases of breast carcinoma. However, there are insufficient studies to support our theory and more research in this field may be useful in incorporating tumour budding as a new parameter in the reporting protocols of breast carcinoma especially in resource poor institutes which are not equipped with sophisticated IHC and molecular markers.

7. Source of Funding

None.

8. Conflict of Interest

None.

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