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Original Research Article

Retrospective Observational Assessment of the Grades of TB in Invasive Breast Carcinoma and Correlate it with Known Clinicopathological Parameters to Determine its Usefulness as a Prognostic Factor

Fauzia Perveen[1], C.P. Jaiswal[2]

[1]Tutor, Department of Pathology, Nalanda Medical College and Hospital, Patna, Bihar, India

[2]Associate Professor and HOD, Department of Pathology, Nalanda Medical College and Hospital, Patna, Bihar, India

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Corresponding author: Dr. C.P. Jaiswal
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Abstract

Aim: The aim of the present study was to assess the grade of TB in Invasive Breast Carcinoma and correlate it with known clinicopathological parameters to determine its usefulness as a prognostic factor.

Methods: This was a retrospective observational study carried out in Department of pathology at Nalanda Medical College and Hospital, Patna, Bihar, India with the available histopathological data of 50 cases of modified radical mastectomy for the period of one and a half year.

Results: Out of the 50 cases, most of the cases belonged to age groups 40-49 years and 50-59 years (30% each), followed by 22% cases of age group 60-69 years, 12% cases of age group 30-39 years and 6% cases of age group 20-29 years. Of these 50 cases, 35 cases (70%) were of invasive ductal carcinoma, 7 cases (14%) were of No specific type, and 2 cases each of lobular Ca, Mucinous Ca, Metaplastic Ca (4% each), 1 case of Ca with medullary features and Ca with neuroendocrine features (2% each). Maximum cases are of age group >45 years (76%), newly diagnosed (60%), lymph node negative (46%), Tumour size T2 (52%) and TNM stage III (46%). High tumour budding was seen in patients above the age of >45 years (66.66%) compared to age <45 years (42.10%). High tumour budding was seen in patients who had a newly diagnosed malignancy (53.34%) compared to those who were post chemotherapy (45%). 71.42% cases of Invasive carcinoma- NST showed high tumour budding while 28.58% cases showed low tumour budding. 48.58% cases of Invasive ductal carcinoma showed high tumour budding while 51.42% cases showed low tumour budding. 2 cases (100%) each of Lobular, Metaplastic and Medullary carcinoma showed Low tumour budding while 2 cases (100%) of Mucinous and and one case (100%) neuroendocrine carcinoma showed High tumour budding.

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.

Keywords: Invasive Breast Carcinoma, Tumour Budding, Prognostic Markers, Clinico-Pathological Parameters.

Introduction

Tumor budding is a pathologic phenomenon associated with many cancers. Although its specific definition differs from study to study, it generally consists of a small number of cells, usually up to five cells in the most commonly used definition, which have detached from the bulk of the tumor and are observed as isolated cells or small clusters of cells in histologic sections. Cancers in which tumor budding has been observed and studied include colorectal, gastric and esophageal, lung, head and neck, and also breast cancers. [1] Tumor buds may be observed in areas near the margins of tumors at the invasive tumor front and are called peritumoral buds, or inside the tumor mass and are thus called intratumoral buds. [2]

Tumor budding is believed to represent cancer cells caught in the process of invasion. [3] The metastatic process begins with detachment of cells from the tumor bulk, infiltration through surrounding tissues into small blood vessels, and travel through the circulation to remote locations where they extravasate and may eventually establish colonies of metastatic disease. Paramount in metastasis is the process of epithelial to mesenchymal transition (EMT) and the reverse process of mesenchymal to epithelial transition (MET). [4] These processes, sometimes collectively referred to as epithelial mesenchymal plasticity, are part of normal embryogenesis and physiologic wound healing, and have been usurped by cancer. During EMT, detached cancer cells partially or completely lose their epithelial characteristics, detach from neighboring epithelial cells and gain mesenchymal characteristics, including expression of mesenchyme-associated proteins, to become motile. In metastatic sites, the reverse process takes place when arriving cells, helped by cues in their new microenvironment, regain epithelial properties and re-establish connections with neighboring cells. [5]

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. [6] 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. [7] 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 invasive tumour front, called as peritumour buds, or inside the tumour mass and are called as intratumour buds. [8,9] 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. [10]

The aim of the present study was to assess the grade of TB in Invasive Breast Carcinoma and correlate it with known clinico-pathological parameters to

determine its usefulness as a prognostic factor.

Materials and Methods

This was a retrospective observational study carried out in Department of pathology at Nalanda Medical College and Hospital, Patna, Bihar, India with the available histopathological data of 50 cases of modified radical mastectomy for the period of one and a half year. 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 was 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.

Results

Table 1: Age distribution and types of carcinoma

Age groups in years	**N%**
20-29 years	3 (6)
30-39 years	6 (12)
40-49 years	15 (30)
50-59 years	15 (30)
60-69 years	11 (22)
Types of carcinomas	
Invasive ductal carcinoma	35 (70)
Invasive Carcinoma- NST	7 (14)
Lobular Ca	2 (4)
Mucinous Ca	2 (4)
Metaplastic Ca	2 (4)
Ca with medullary features	1 (2)
Ca with neuroendocrine features	1 (2)

Out of the 50 cases, most of the cases belonged to age group 40-49 years and 50-59 years (30% each), followed by 22% cases of age group 60-69 years, 12% cases

of age group 30-39 years and 6% cases of age group 20-29 years. Of these 50 cases, 35 cases (70%) were of invasive ductal carcinoma, 7 cases (14%) were of No specific type, and 2 cases each of lobular Ca, Mucinous Ca, Metaplastic Ca (4% each), 1 case of Ca with medullary features and Ca with neuroendocrine features (2% each).

Table 2: Clinicopathological characteristics of 40 cases of breast carcinoma

Clinicopathological Parameters		N	%
Age	<45 years	12	24
	> 45 years	38	76
Treatment status	Post chemotherapy	20	40
	Newly diagnosed	30	60
Lymph node status	Positive	21	42
	Negative	23	46
	Unknown	6	12
Invasion	Lymphovascular	35	70
	Dermal	15	30
Tumour size	T1	6	12
	T2	26	52
	T3	9	18
	T4	9	18
TNM staging	I	7	14
	II	20	40
	III	23	46

Maximum cases are of age group >45 years (76%), newly diagnosed (60%), lymph node negative (46%), Tumour size T2 (52%) and TNM stage III (46%).

Table 3: Correlation of tumour budding with clinicopathological parameters

Clinicopathological Parameter		High tumour budding	Low tumour budding	Total
Age (n=50)	<45	8 (66.66)	4 (33.34)	12
	>45	16 (42.10)	22 (57.90)	38
Treatment status (n=50)	Post chemotherapy	9 (45)	11 (55)	20
	Newly diagnosed	16 (53.34)	14 (46.66)	30
Types of carcinomas	Invasive ductal carcinoma	17 (48.58)	18 (51.42)	35
	Invasive Carcinoma- NST	5 (71.42)	2 (28.58)	7
	Lobular Ca	0	2 (100)	2
	Mucinous Ca	2 (100)	0	2
	Metaplastic Ca	0	2 (100)	2
	Ca with medullary features	0	1 (100)	1
	Ca with neuroendocrine features	1 (100)	0	1

Tumour budding was evaluated in all 50 cases. High tumour budding was seen in 25 cases (50%) and low tumour budding was seen in 25 cases (50%). High tumour budding was seen in patients above the age of >45 years (66.66%) compared to age <45 years (42.10%). High tumour budding was seen in patients who had a newly diagnosed malignancy (53.34%) compared to those who were post chemotherapy (45%). 71.42% cases of Invasive carcinoma- NST showed high tumour

budding while 28.58% cases showed low tumour budding. 48.58% cases of Invasive ductal carcinoma showed high tumour budding while 51.42% cases showed low tumour budding. 2 cases (100%) each of Lobular, Metaplastic and Medullary carcinoma showed Low tumour budding while 2 cases (100%) of Mucinous and one case (100%) neuroendocrine carcinoma showed High tumour budding.

Table 4: Clinicopathological correlation with tumour budding

Clinicopathological Parameter		High tumour budding	Low tumour budding	Total
Lymph Node Status (n=50)	Positive	16 (76.20)	5 (23.80)	21
	Negative	6 (26.08)	17 (73.92)	23
	Unknown	2 (33.34)	4 (66.66)	6
Tumour Size (n=50)	T1	2 (33.34)	4 (66.66)	6
	T2	12 (46.15)	14 (53.84)	26
	T3	6 (66.66)	3 (33.34)	9
	T4	5 (55.55)	4 (44.44)	9
TNM Staging (n=50)	I	2 (28.58)	5 (71.42)	7
	II	5 (25)	15 (75)	20
	III	16 (69.56)	7 (30.44)	23

High tumour budding was seen with positive lymph nodes (76.20%) compared to negative lymph nodes (26.08%). High tumour budding was seen with increasingly larger tumour size and TNM staging.

Discussion

Carcinoma of the breast is the second largest cause of mortality from cancer among women in India. [11] Breast lumps and other constitutional symptoms were the most common clinical presentations. [12] Cancer patients' prognosis is affected by a number of variables, including age, tumor kind, grade and stage, and the presence or absence of a hormone receptor. It is the goal of all of these methods to ensure that the proper therapy is given to the right patients. [13] Improved breast cancer detection and treatment have contributed to a drop in mortality over the last several decades. Biomarkers and other prognostic criteria need to be given much more consideration.

Tumor budding is one of these prognostic indicators. Detachment from neoplastic glands at the invasive front of the tumor means a limited number of cancer cells that are separated from the main tumor mass. [14] Peri-tumoral buds and intra-tumoral buds are the terms used to describe tumor buds that are positioned on the outside of a tumor mass and those that are located inside the tumor mass. [12]

Tumor budding has been highly recommended as a crucial step in the treatment of invasive breast cancer. [15] Various additional malignancies, such as colorectal carcinoma, gastric adenocarcinoma, and esophageal squamous cell carcinoma, have been suggested to have tumor budding as a potential prognostic marker. [16,17] As has been demonstrated in several studies, colorectal cancer tumor buds have a role in stage II. Patients with tumor buds had a worse overall survival rate than those who did not have tumor buds. [16]

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 status, lymph node status, tumour size, TNM staging and lymphovascular and dermal invasion. Salhia et al., [18] B.N Kumarguru et al.

[19] and the present study used high power (40X) objective to count the tumour buds. In contrast, Liang et al. [20] and Radhika Agarwal et al. [21] 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 25 (50%) cases and low grade in 25 (50%) cases. This was in close approximation with Radhika Agarwal et al. [21] [High grade 47.5% and low grade 52.5%] and B.N Kumarguru et al. [19] [High grade 60% and low grade 40%].

In another study that included localized breast cancers across the sub-type spectrum, higher tumor budding (> seven buds per a 200× power field in a slide with the maximal invasive margin) was observed in about two thirds of patients, while the remaining one third displayed low tumor budding (seven or fewer buds per 200× power field in a slide with the maximal invasive margin). High tumor budding as well as tumor size, nodal status and the presence of lymphovascular invasion were independently associated with OS.20 Immunohistochemical studies showed that tumor bud cells had increased vimentin expression and decreased E-cadherin expression compared with the center of the tumor, suggesting that they had undergone an EMT. [22]

Another series with early breast cancer patients across sub-types, but mostly consisting of luminal cancers, showed that high tumor budding was associated with lymphatic invasion and positive lymph node disease. [18] A series of 146 ductal carcinoma patients with operable disease was evaluated for both tumor budding, defined as less than five cells per bud, as well as for the presence of buds of five or more tumor cells not forming glands, termed “poorly differentiated clusters”. [23]

However, the majority of patients will still have residual disease after neoadjuvant chemotherapy, independent of their cancer subtype. [24] In addition, there are no predictive markers for the response of patients to neoadjuvant treatment besides tumor subtype. Thus, in this scenario, tumor budding could be an additional predictive marker to consider in order to better predict tumor responses to treatment, should further studies confirm its predictive value.

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.

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