The Correlation of Tumor Budding Index with Clinicopathology Parameters on Invasive Breast Carcinoma No Special Type

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Abstract-Background: Invasive breast carcinoma no special type (NST) is the most common type of cancer, making up about 40-75% of invasive breast cancers. Conventional histopathology prognostic indicators including histology type, tumor size, lymph node involvement, grade, hormone receptor expression, etc. still play an important role in the estimated prognosis in breast carcinoma. Tumors bud are an important step in tumor invasion and metastasis and have attracted interest as a marker of prognosis. Research on the role of tumor budding in breast cancer is still limited.

Research Objective: Analyzes the correlation between tumors budding and clinicopathology parameters that include tumor size, lymph node involvement, histological grade, LVI, and immunohistochemical profile in invasive breast carcinoma NST.

Material and Methods: This study is an analytical study with a cross sectional approach in 42 samples of paraffin block patients diagnosed histopathologically as invasive breast carcinoma NST. Then, a re-cutting of the paraffin block. Assessment of peritumoral tumor budding was categorized as ≤ 20 buds/10LPB (low grade) and > 20 buds/10LPB (high grade) with H&E staining and 400x enlargement. The correlations between tumor budding index and clinicopathology parameters in invasive breast carcinoma NST was statistically tested.

Result: The most age was 50-59 years, with an average age of 52.52 years. There is a significant association between tumor budding index and several clinicopathology parameters, such as grade, LVI, and immunohistochemical profile. As for tumor size and lymph node involvement did not show a significant association. The most widely found tumor budding index is high grade buds as much as 85.7%.

Conclusion: Reporting of tumor budding results in invasive breast carcinoma of NST can be one of the prognostic criteria that can be applied in routine examinations.

Keywords: tumor budding, invasive breast carcinoma NST, prognosis.

I. INTRODUCTION

Breast carcinoma ranked second most common in the world, with 2,088,849 new cases (11.6%) with a mortality rate of 626,679 (6.6%) reported in 2018.\textsuperscript{1,2,3} Breast carcinoma is the fifth leading cause of death from carcinoma in the world and the second most common cause of death from carcinoma in women in the United States, after lung cancer. About 1 in 8 women in the United States or about 12% have invasive breast cancer. According to the American Cancer Society in 2020, there are an estimated 276,480 new cases of invasive breast carcinoma and about 42,170 are expected to die by 2020 from breast carcinoma.\textsuperscript{4,5}

In Indonesia the prevalence of breast carcinoma based on data from Global Burden Cancer (GLOBOCAN) 2018, showed that breast carcinoma occupies the first most common carcinoma in women with 58,256 new cases (30.9%) and became the leading cause of death in women with 22,692 (11.0%). Based on data from Basic Health Research Data in Indonesia which until now there has been no update of data, the highest prevalence of breast carcinoma occurred in 2013 at 0.5‰, where D.I Yogyakarta Province has the highest prevalence of breast carcinoma, which is 2.4‰, while North Sumatra has a prevalence of breast carcinoma of 0.4‰.

Breast carcinoma is also still the first type of carcinoma found in Dharmais cancer hospital for the last 4 years until 2013, with the number of new cases (711-819 cases), and the number of deaths from carcinoma continues to grow (93-217 cases).\textsuperscript{7} Over the past 5 years, breast carcinoma case data was obtained at Haji Adam Malik Hospital, namely: in 2014 there were 1181 cases, in 2015 it was 969 cases, in 2016 it was 915 cases, and in 2017 it was 976 cases.\textsuperscript{8}

Breast carcinoma is a heterogeneous disease both clinically and pathologically. The heterogeneity of high breast carcinoma causes management to be not completely satisfactory.\textsuperscript{9} Although molecular and genomic assessments have emerged, conventional prognostic indicators of histopathology including histological type, tumor size, lymph node involvement, grade, hormone receptor expression, etc. still play an important role in the estimated prognosis of breast carcinoma.\textsuperscript{10,11}

Tumor buds are an important step in tumor invasion and metastasis and in recent years have attracted interest as a marker of prognosis in colorectal cancer, head and neck squamous cell carcinoma, breast cancer, esophageal cancer, gastric cancer, and cervical cancer. Tumor buds are the presence of a single tumor cell or small group of tumors on the front of the invading tumor.\textsuperscript{12,13} The number of cells in tumor budding based on the
International Tumor Budding Consensus Conference (ITBCC) amounted to less than five tumor cells or up to 4 cells. Tumor buds are associated as part of epithelial mesenchymal transition (EMT), in which tumor cells have the ability to migrate with loss of adhesion and polarity between cells as well as invasion that are characteristic of mesenchymal cells. EMT and its reverse process, mesenchymal epithelial transition (MET), are physiological processes that play a role during embryonic development, wound healing and tissue repair. Aberrant EMT activation is considered a hallmark of cancer metastasis.14,15

Tumor buds are associated with tumor aggressiveness and have shown a correlation with a poor prognosis. This can be assessed by the staining of hematoxylin-eosin (H&E) which is routinely used and does not require other expensive additional equipment.14,16 However, research on the role of tumor budding in breast cancer is still limited. Assessment of tumor budding is still relatively new in Indonesia, especially in Medan, where research on the role of tumor budding in the breast is still limited and the significant prognostic strength of tumor budding in other cancers is the background to detect its role in breast carcinoma. Therefore, on this occasion, the authors wanted to examine the correlation of tumor budding index with various clinicopathology parameters in invasive breast carcinoma NST.

II. MATERIALS AND METHODS

This research is an analytical study with a cross sectional approach conducted at the Anatomical Pathology Laboratory of the Faculty of Medicine, University of North Sumatera and the Anatomical Pathology Unit of Haji Adam Malik Medan General Hospital. This research was conducted from November 2020 to September 2021, after receiving approval from the Health Research Ethics Committee of the Faculty of Medicine, University of North Sumatera.

This study sample is a paraffin block from patients who have been diagnosed histopathologically as an invasive breast carcinoma NST that meets the criteria for inclusion and exclusion. Samples are taken using consecutive sampling techniques. Inclusion criteria include adequate clinical data on medical records (age, tumor size, lymph node involvement, and immunohistochemistry profile) as well as representative slide or paraffin preparations, derived from postoperative tissue results diagnosed histopathologically as invasive breast carcinoma NST with H&E staining. The exclusion criteria for the study are incomplete medical record data and unrepresentative slides or blocks of paraffin that cannot be reprocessed. Each sample is recut and colored with H&E.

Tumor buds are tumor cells that are detached from the body of the main tumor, describing the presence of a single and undifferentiated cancer cell. The assessment of tumor budding assessed is at peritumoral, referring to studies that have been conducted by Kumarguru, where the number of tumor buds is categorized as follows, when ≤ 20 buds/10 HPF (low grade buds) and ≥20 buds /10 HPF (high grade buds).48 The grading system refers to the 2019 WHO classification for breast tumors.24 Association tumor budding index with clinicopathology parameters in invasive breast carcinoma NST was statistically tested.

III. RESULT

In this study, 42 samples of invasive breast carcinoma NST were obtained at the Laboratory of Anatomical Pathology, Faculty of Medicine, University of North Sumatera and Anatomical Pathology Unit of Haji Adam Malik Medan General Hospital. The most age is 50-59 years, with an average age of 52.52 years. Tumor size was more in T2 as many as 21 cases (50.0%). Lymph nodes were found in 29 cases (69.0%). LVI was found in 28 cases (66.7%), grade was found to be most in grade 3 at 20 cases (47.6%), and immunohistochemistry profile was found in Luminal A at 14 cases (33.3%). Tumor budding most found high grade buds by 85.7% (Table 1).

Table 1. Characteristic of the study sample based on age, tumor size, lymph node involvement, LVI, histological grade, and immunohistochemistry profile in invasive breast carcinoma NST

![Figure 1. Low grade buds (H&E, 400X). B. High grade buds (H&E, 400X).](image)

In this study, it was assessed the correlation between tumor budding index and tumor size in invasive breast carcinoma NST. The study showed a not significant correlation between tumor budding index and tumor size (p-value=0.079) (Table 2).

Table 2. The correlation between tumor budding index and tumor size in invasive breast carcinoma NST

The study also assessed the correlation between tumor budding index and lymph node involvement in invasive breast carcinoma NST. The study showed not significant correlation...
between tumor budding index and lymph node involvement (p-value=0.647) (Table 3).

Table 3. The correlation between tumor budding index and lymph node involvement in invasive breast carcinoma NST.

<table>
<thead>
<tr>
<th>No.</th>
<th>Lymph node</th>
<th>Tumor budding</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Low grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>grade budding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Low grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>grade budding</td>
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<td></td>
<td></td>
<td>High grade</td>
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<td></td>
<td>Total</td>
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</table>

In this study, it assessed the correlation between tumor budding index and grading in invasive breast carcinoma NST. Studies have shown a significant correlation between tumor budding index and grading (p-value=0.0001) (Table 4).

Table 4. The correlation between tumor budding index and grading in invasive breast carcinoma NST.

<table>
<thead>
<tr>
<th>No.</th>
<th>Grade</th>
<th>Tumor budding</th>
<th>p-value*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low grade budding</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>High grade budding</td>
<td></td>
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<td></td>
<td>Total</td>
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</tbody>
</table>

In this study, it assessed the correlation between budding tumor budding index and LVI in invasive breast carcinoma NST. Studies have shown a significant association between budding tumor budding index and LVI (p-value=0.011) (Table 5).

Table 5. The correlation between tumor budding index and LVI in invasive breast carcinoma NST.

<table>
<thead>
<tr>
<th>No.</th>
<th>LVI</th>
<th>Tumor budding</th>
<th>p-value*</th>
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<tbody>
<tr>
<td></td>
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<td>Low grade budding</td>
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<td></td>
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<td>High grade budding</td>
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<td>Total</td>
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</tbody>
</table>

In this study, it assessed the correlation between tumor budding index and immunohistochemistry profile in invasive breast carcinoma NST. The study showed a significant association between the tumor budding index and the immunohistochemistry profile (p-value=0.00627) (Table 6).

Table 6. The correlation between tumor budding index and immunohistochemistry profile in invasive breast carcinoma NST.

<table>
<thead>
<tr>
<th>No.</th>
<th>Immunohistochemistry profile</th>
<th>Tumor budding</th>
<th>p-value*</th>
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<tbody>
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<td></td>
<td></td>
<td>Low grade budding</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>High grade budding</td>
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<td>1</td>
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IV. DISCUSSION

In this study the number of samples diagnosed as invasive breast carcinoma NST was 42 samples, the most patients aged 50-59 years, with an average of 52.52 years, the youngest age 31 years and the oldest age 75 years. Salhia et al. in 2015 it was found that invasive breast carcinoma NST occurred at the average age of patients at diagnosis was 61 years with an age range of 32-91 years. Gujam et al. in 2015 stated that invasive breast carcinoma NST occurred in women aged >50 years about 70%. Sriwidayani et al. in 2016 found that the average age of patients aged 48.6 years with an age range in his study of 23-74 years.

patients is 53.14 years, with an age range of 24-77 years. This study found that the age of breast carcinoma suffers is at an advanced age that occurs in women over 50 years. Reportedly a young patient in this study, which is 31 years old.

Invasive breast carcinoma NST, can be caused by various causes, including due to unhealthy lifestyle and genetic factors. In a less healthy lifestyle, combined with lack of physical exercise and a family history increases the risk of breast carcinoma. Therefore, of these risk factors, supporting the reason breast carcinoma can occur at a young age.

The size of the tumor is more in T2, which is as much as 50.0%. Research by Liang et al. in 2013 reported that tumor size was highest at T2 (69.8%). Masilamani et al. in 2019 reported tumor size at T2 (49.8%). In this study, tumor size showed no statistical association with tumor budding. Differences in outcomes in this study may be attributed to differences in the study population and these results also suggest a lack of public awareness to get early checked for breast carcinoma. Delays in diagnosis and treatment of patients who are late result in patients usually coming already in an advanced condition. Differences in the size of this tumor may be related to microenvironment of a tumor.

Lymph node involvement is one indicator of poor prognosis in the majority of breast carcinoma studies, including in this study, which reported that most invasive breast carcinomas of NST accompanied by lymph node involvement, which is as much as 69.0%. The differences from this study may be due to differences in the study's population.

In this study, 47.6% of the study sample was grade 3. The results of this study are in line with research conducted by Gujam et al. in 2015, where they reported as much as 40% of invasive breast carcinoma NST is grade 3. Research by Sriwidayani et al. in 2016 also obtained results in line where grading is most found in grade 3 as much as 50%. Agarwal et al. in 2019 reported that the most common grade 3 cases were 82%. This is likely due to lack of awareness people to do early detection so that breast carcinoma is found at a high grade.

In this study, LVI was found to be 66.7%. The remaining 14 samples were not found LVI (33.3%). The results of this study are in line with research conducted by Sriwidayani et al. in 2016, where they found LVI as much as 75.71%. Whereas, in research conducted by Renuka et al. in 2019 found LVI as much as 74%. After statistical test analysis, a significant association was found between the tumor budding index and LVI in this study. The results of this study are not much different from previous studies. Even the results of a meta-analysis conducted by Lloyd et al. in 2020 also showed a significant association between budding tumors and LVI.0 The association of high grade buds with the presence of LVI can be considered an indicator of poor prognosis factors in breast carcinoma. This image can be helpful in therapy and decision-making and can be incorporated into reporting on invasive breast carcinoma NST.

Based on the results of immunohistochemical profile examination, the most luminal A subtypes were obtained in this study, which was 33.3%, then consecutively luminal B like HER2 positive (21.4%), non luminal (21.4%), luminal B like HER2 negative (19.1%), and the least is TNBC (4.8%). Salhia et al. in 2015 reported the most luminal A, which was 62.2%. Masilamani et al. in 2019 also reported the most luminal A.
which was 39.3%.53 Li et al. in 2017 has shown that tumors budding are significantly associated with decreased disease-free survival in breast carcinoma patients. Assessment of budding tumors can provide useful information for treatment management in breast carcinoma, especially in breast carcinoma ER(+) /HER2(-) and so that it can be used in routine reporting.50,63 Differences in results in this study may be attributed likely due to differences in the study population.

In this study, the most tumors budding were high grade buds as much as 85.7%, compared to low grade buds only as much as 14.3%. Salhia et al. (2015) reported that the most tumors budding were high grade buds, which was 79.7%.46 Masilamani et al. (2019) reported that the most tumors budding were high grade buds, which is as much as 80.4%.53 Prognostic value of tumor budding in breast carcinoma has been evaluated in a number of studies. In recent years tumor budding research began to develop and was introduced as a possible tool for identifying poor clinical outcomes in patients and finding budding tumors as independent predictors.48,60

V. CONCLUSION

After the study was conducted, we underlined some of the following conclusions:

1. Patients with invasive breast carcinoma NST occur mostly at the age of 50-59 years with the average age of patients is 52.52 years, where the youngest age is 31 years and the oldest age is 75 years.
2. The largest index of tumors budding is high grade buds.
3. Most invasive breast carcinomas of NST are accompanied by the involvement of lymph nodes, which is as much as 69.0%. There is no significant association between budding tumor index and lymph node involvement.
4. It found that 47.6% was grade 3. There is a significant correlation between budding tumor index and histopathological grading.
5. There was an LVI of 66.7%. There is a significant correlation between budding tumor index and LVI.
6. Obtained the most luminal subtype A in this study then consecutive luminal B like HER2 positive, non luminal, luminal B like HER2 negative and the least is TNBC.

REFERENCE


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