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# Overview of Metastasis Locations in Breast Cancer Patients Based on Histopathological Type and Grading in Cut Meutia General Hospital Lhokseumawe in 2020-2021

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**A B S T R A C T**

Breast cancer is the most common type of cancer in women and is one of the most common causes of death. Breast cancer can develop into malignant when the cell invades surrounding tissue or metastasizes (spreads) to other organs of the body. Several examinations can be done to monitor the growth to malignancy of breast cancer, such as histopathology examinations. The purpose of this study is to find out the location of metastasis based on the type and grading of histopathology in breast cancer patients at Cut Meutia Lhokseumawe Hospital in 2020-2021. This study was a descriptive observational study using a cross-sectional design. The study sample was breast cancer patients who had metastases and met the inclusion and exclusion criteria of as many as 36 people. The incidence of breast cancer metastasis mostly occurs at the age of 36-45 (38.9%), the most histopathological type was invasive ductal carcinoma (83.3%), and the most histopathological grading was grade III (52.8%). The most common site of metastases in this study was bone (50%). Invasive ductal carcinoma and invasive lobular carcinoma tend to metastasize to the bone. Grade II tends to metastasize to the bone. While grade III tends to metastasize to the lungs.

## 1. Introduction

Breast cancer is a malignant neoplastic disease in parenchymal tissue that is found to have abnormal breast tissue growth that is infiltrative and instructive and can metastasize.[1] Breast cancer is the most common type of cancer in women and is one of the leading causes of death. Based on GLOBOCAN (Global Burden of Cancer) data 2020, breast cancer is still the leading cause of cancer incidence globally, with an estimated 2,261,419 million new cases, representing 11.7% of all cancer cases in the world with a death toll of about 684,996 people (6.9%). The incidence of breast cancer in Indonesia is ranked first in as many as 65,858 (16.6%) new cases, and it is one of the five types of cancer that causes the most deaths, with 22,430 deaths.

Data presented by the Directorate of Prevention and Control of Non-Communicable Diseases of the Ministry of Health 2020 revealed that the highest incidence rate for women was breast cancer which was 1.79 per 1000 population in 2018. The prevalence of breast cancer in Banda Aceh City, according to the Aceh Provincial Health Office in 2018, reported as many as 127,462 cases. The incidence of breast cancer based on medical record data from Cut Meutia Lhokseumawe Hospital in 2020-2021, there were 964 cases of breast cancer.[2-4]

Breast cancer can develop into malignant when the

cell invades surrounding tissue or metastasizes (spreads) to distant areas of the body. Breast cancer spreads when abnormal cells invade the surrounding healthy tissue. In most cases, breast cancer initially spreads to other parts of the affected breast, then to nearby lymph nodes. If cancer cells get into the lymphatic system, they can reach distant parts of the body. The most common locations for metastatic breast tumors include lungs, liver, bone, brain, and visceral.[5]

The high death rate from breast cancer is related to the incidence of metastasis. It is known that more than 90% of deaths in breast cancer are related to metastatic events and the complications that follow. It is estimated that 5-10% of patients already had metastasis at the time of the first diagnosis, and 20-40% get metastatic in the middle of the course of the disease and end up with a poor prognosis.

Several examinations can be done to monitor the growth to malignancy of breast cancer, such as radiological examinations (mammography, ultrasound, MRI) and anatomical pathology examinations (immunohistochemistry, cytology, and histopathology). Histopathology examination is the gold standard for the definitive diagnosis of breast cancer because it is one of the prognostic and predictive factors in assessing the risk and therapeutic decision-making of breast cancer. Breast cancer pathology examination currently has standards to include pathological data, including type and grading of histopathology.[6]

Data obtained based on the American Cancer Society 2020 stated the most common and frequent type of breast cancer histopathology is invasive ductal carcinoma which is about 70-80% of all breast cancers.7 Research conducted by Yang et al. found the most types of breast cancer histopathology were invasive ductal carcinomas 84.7%, followed by invasive lobar carcinomas 10.60%, and other types of carcinomas of other types 5.40%.[8]

Histopathological grading assessments that are often used are the Nottingham Grading System (NGS) which is made based on grading tubular formation, pleomorphism of the gland (nuclear pleomorphism), and the number of mitoses (mitotic count). The results of the NGS assessment are categorized into three degrees, namely low degrees (well-differentiated), moderately differentiated degrees, and high degrees (poorly differentiated). Grading of cancer describes the degree of aggressiveness of cancer. This is also supported by the results of research by Tariq et al., which also found grade II is the most common histopathological grading at 53.8%, followed by grade 3 at 44% and grade 1 at 1.8%.9 This study aimed to describe metastasis locations in breast cancer patients based on the histopathological type and grading in Cut Meutia General Hospital Lhokseumawe.

## 2. Methods

This study was descriptive observational research using a cross-sectional approach conducted from January to March 2022 at Cut Meutia Hospital in North Aceh. Data used in this study is secondary data obtained from medical records. A total of 36 patients were included in this study. The sampling technique in this study is purposive sampling. The inclusion criteria were all patients diagnosed with breast cancer at the Cut Meutia Hospital from January 2020 to December 2021, metastasized, and had complete and accessible medical records. This study has been approved by the ethical committee of medical research, Faculty of Medicine, Universitas Malikussaleh.

## 3. Results and Discussion

The age interval used is based on the Indonesian Ministry of Health in 2009. Table 1 shows that the majority of the age of patients experiencing the incidence of breast cancer that has metastasized is in the age interval of 36-45 years, namely as many as 14 patients (38.9%). The average age of patients who experience breast cancer metastasis is 46.5 years, with the most frequency at 44 years.

Table 1. Frequency distribution by age

| Age interval (years) | Frequency (n) | Percentage (%) |
|---|---|---|
| 26-35 | 5 | 13,9 |
| 36-45 | 14 | 38,9 |
| 46-55 | 11 | 30,6 |
| 56-65 | 4 | 11,1 |
| >65 | 2 | 5,6 |
| **Total** | **36** | **100,0** |

Age is one of the important risk factors for cancer due to increased exposure to valves and mutations. Age, when diagnosed, plays an important role in the survival of patients. Along with changes in age, there are also changes in organs that are at risk of causing a transformation into malignancy. The molecular and cellular effects of aging on normal breast tissue are accompanied by persistent developmental changes in the nipple epithelium, which usually occur between puberty and menopause.[10]

In a cohort study that links the age at diagnosis and metastasis, it was concluded that the older the age, the lower the risk of metastasis, but if metastasis occurs, the risk of death will be higher.[11] This may be related to the composition and remodeling of the extracellular matrix. These factors play a role in tumorigenesis and metastatic processes. The aging process can disrupt the extracellular matrix by reducing its matrix so that metastatic progression can be reduced.[12]

Based on the results of this study, data has been obtained on the picture of histopathological types based on the histological classification of breast tumors. Table 2 shows that the majority of histopathological types of breast cancer patients who have metastasized are invasive ductal carcinoma types, with a total of 30 people (83.3%).

Table 2. Histopathological type of breast cancer

| Histopathological type | Frequency (n) | Percentage (%) |
|---|---|---|
| Invasive ductal carcinoma | 30 | 83,3 |
| Invasive lobular carcinoma | 6 | 16,7 |
| **Total** | **36** | **100.0** |

Invasive ductal carcinoma is the most common type of breast cancer and the most common metastatic. This is related to the location of invasive ductal carcinoma that starts from the breast milk ducts and then penetrates the duct wall and develops in the breast fat tissue. This area is rich in the lymphatic system and blood flow, which facilitates the spread of cancer to other parts of the body.[13] Invasive lobular carcinoma does not show much change in the clinical appearance of morphology (the picture of tubular structure does not exist, mitosis is not very aggressive (infrequent), and the nucleus tends to be the same (uniform)), but the loss of cohesion between cells due to inactivation of E-cadherin causes the aggressiveness of this type of histopathology.

Table 3. Histopathological grading

| Histopathological *Grading* | Frequency (n) | Percentage (%) |
|---|---|---|
| Grade II | 17 | 47,2 |
| Grade III | 19 | 52,8 |
| **Total** | **36** | **100.0** |

The majority of histopathological grading of metastatic breast cancer patients was in grade III, which was 19 patients (52.8%), followed by grade II with 17 patients (47.2%) (Table 3). Histopathological grading is defined as an assessment of the morphology of cells suspected of being part of the tumor tissue. Grade III indicates that cancer has a poor degree of differentiation with rapid and uncontrolled cell growth and spread and is also not similar to the original cell, so breast cancer recurrence is likely to occur. Grade III also shows many mitoses, pleomorphic cell nuclei, and changes in the tubular appearance tend to disappear. This is related to the weaker bonds between epithelial cells so that they do not form a tubular pattern.

Decreased intercellular adhesion increases the tumor's ability to metastasize. Decreased intercellular adhesion accompanied by lymphovascular invasion indicates a higher level of tumor aggressiveness and increases the likelihood of tumor metastases. At a high degree of histopathology, numerous mitoses, nuclear pleomorphisms, and glandular and tubular formations were found. Nuclear changes in these tumors are caused by the high rate of mitosis compared to normal cells. The tubular appearance tends to disappear at a poor degree of differentiation. This is due to the weaker bonds between epithelial cells so that they do not form a tubular pattern.[14]

Bonding between cells in tissues is mediated by a transmembrane protein called E-cadherin. The function of E-cadherin is lost in almost all epithelial cancers caused by the inactivation of the e-cadherin gene. The E-cadherin–catenin complex plays an important role in intercellular adhesion. A decrease in this function is associated with the occurrence of such metastases. The degree of histopathology can determine the level of aggressiveness of cancer, where the more aggressive cancer, the more likely it is to metastasize.[15]

There is a correlation between the pattern of metastatic spread and the degree of histopathology. This explains the poor prognostic value of the high histopathological grade, as metastases from grade III are more common at sites associated with a poorer prognosis. Distant metastases are associated with a higher degree of histopathology. Research conducted by Purushotham et al. showed that the higher the histological grade of breast cancer, the higher the risk of developing metastases because the high histologic grade is also positively correlated with the proliferation and metastatic capacity of tumor cells.[16]

Table 4. Metastases location

| Metastases locations | Frequency (n) | Percentage (%) |
|---|---|---|
| Bone | 18 | 50,0 |
| Lung | 11 | 30,6 |
| Liver | 5 | 13,9 |
| Brain | 2 | 5,6 |
| **Total** | **36** | **100.0** |

This study showed the location of the most breast cancer metastases was metastases to the bones of as many as 18 people (50.0%) (Table 4). Breast cancer tends to metastasize to the bones, brain, liver, and lungs. The percentage of breast cancer patients with metastasis is about 30-60% metastasize to the bones, 21-32% to the lungs, 15-32% to the liver, and 4-10% to the brain (39). Bones are the most commonplace of metastasis. In total, 60% to 75% of breast cancers are diagnosed as bone metastases at the beginning of the prognosis.[17]

The second most common site for metastatic spread is the lungs. This happens because the lungs have a higher expression of *chemokine ligand* 12 (CXCL12) than other organs, while breast cancer very much expresses chemokine receptor 4 (CXCR4). Organs that have higher expression of CXCL12 are associated with being common sites of distant metastatic target organs. The CXCR4-CXCL12 interaction encourages the migration of cancer cells to

the target organ of distant metastatic breast cancer.[18]

Table 5. Metastases location based on the histopathological type

| **Histopathological type** | **Metastases location** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lung | | Bone | | Liver | | Brain | |
| | n | % | n | % | n | % | n | % |
| Invasive Ductal Carcinoma | 10 | 33,3 | 15 | 50,0 | 3 | 10,0 | 2 | 6,7 |
| Invasive Lobular Carcinoma | 1 | 16,7 | 3 | 50,0 | 2 | 33,3 | 0 | 0,0 |
| **Total** | 11 | 30,6 | 18 | 50,0 | 5 | 13,9 | 2 | 5,6 |

The description of the location of metastases based on histopathological type is described as follows, and invasive ductal carcinoma tends to metastasize to bone (50.0%), lung (33.3%), liver (10.0%), brain (6.7%), and invasive lobular carcinoma has a tendency to metastasize to bone (50.0%), liver (33.3%), lung (16.7%).

Bone metastases are the most common site of metastatic breast cancer. This is due to the rich blood flow in the bone marrow and blood flow from the breast flowing through the vertebral plexus, which will significantly increase the risk of cancer metastases to the bone.[19] Bone is considered a site of growth-stimulating factors, including fibroblast growth factors, platelet-derived growth factors, and bone morphogenetic proteins. These factors, released and activated in bone, can stimulate tumor cell growth and act as sites for metastases formation.

The second most frequent site of metastases in IDC was the lung (33.3%). While in the ILC group, it was to the liver (33.3%). Patients in the ILC group tended to have larger tumors and lower histopathological grades than in the IDC group. The higher the degree of histopathology, the worse the location of metastases and vice versa. Bone has a better prognosis than the lung. IDC patients can metastasize to more locations such as the brain, liver, and lungs than ILC patients.

Compared to IDC, ILC is more difficult to detect with standard imaging techniques such as mammography and PET-Scan. Therefore, there are fewer metastatic sites in ILC than in IDC. However, ILC was more detectable in older patients and at a more advanced stage than IDC. Compared with stage/grade-matched IDC, patients with ILC show relatively slow recurrence.[20]

Table 6. Metastases location based on histopathological grading

| **Histopathological Grading** | **Metastases Location** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lung | | Bone | | Liver | | Brain | |
| | n | % | N | % | n | % | n | % |
| Grade II | 3 | 17,6 | 11 | 64,7 | 3 | 17,6 | 0 | 0,0 |
| Grade III | 8 | 42,1 | 7 | 36,8 | 2 | 10,5 | 2 | 10,5 |
| **Total** | 11 | 30,6 | 18 | 50,0 | 5 | 13,9 | 2 | 5,6 |

The description of location of metastases based on histopathological grading is described as follows: grade II (medium grade or moderately differentiated) tends to metastasize to bone (64.7%) while grade III (high grade or poorly differentiated) tends to metastasize to the lung (42.1%). Distant metastases are associated with a higher degree of histopathology. 21 As the degree of histopathology increases, the mitotic picture becomes more active and clearer. In other words, the proliferative activity of malignant cells is higher. Patients with bone metastases have a better prognosis and generally have a longer duration of

survival than patients with other metastatic sites. The median survival of patients with bone metastases is approximately two years, and 20% of these patients live more than five years compared with patients with brain, liver, or lung metastases.[22]

Breast cancer patients with pulmonary metastases have a median survival rate of only 22 months after treatment, suggesting a poor prognosis. It has been reported that 60-70% of breast cancer patients who eventually die are diagnosed with lung metastases. Despite the various treatments available for lung metastases, such as radiotherapy, chemotherapy, or targeted therapy, the survival rate for lung metastases patients remains very low. Patients with lung metastases have a shorter survival time than patients with bone metastases and longer survival than patients with liver disease or brain metastases.[23]

## 4. Conclusion

The age range in breast cancer patients who have metastasized is 36-45 years. The location of metastases in breast cancer patients at the Cut Meutia Hospital, Lhokseumawe, in 2020-2021 is bone, invasive ductal carcinoma amounting to 30 people (83.3%). The histopathological grading was grade III. All types of breast cancer in this study tend to metastasize to bone. The description of location of metastases based on histopathological grading is described as follows: grade II (medium grade or moderately differentiated) tends to metastasize to bone (64.7%). Meanwhile, grade III (high grade or poorly differentiated) tends to metastasize to the lung (42.1%).

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