Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 270–276

OPEN ACCESS

Original Article

Breast Cancer Metastases Based on Molecular Subtypes at RSUD Dr. H. Abdul Moeloek Lampung

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.904

Accepted: January 06th, 2023
Approved: August 08th, 2023

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Abstract

Background : Breast cancer is the most common cancer in Indonesia and is a leading cause of cancer-related deaths in the country. Metastases are responsible for most deaths among breast cancer patients. Breast cancer is typically classified into four subtypes based on immunohistochemistry: luminal A, luminal B, HER2+, and TNBC. The objectives of this study was to determine the association between the metastatic pattern of breast cancer and their molecular subtypes at RSUD Dr. H. Abdul Moeloek Lampung.
Methods : This study was an observational analytic study with a cross-sectional design. The sample comprised 81 individuals who had suffered from breast cancer and were recorded in the medical records section of RSUD Dr. H. Abdul Moeloek Lampung between 2013–2021 and met the inclusion and exclusion criteria. The association between breast cancer subtypes and the incidence and metastase sites were tested using the Chi-Square test.
Results : This study found a significant association between breast cancer subtypes and the incidence of metastases ($p < 0.05$). The TNBC subtype had a more frequent rate of metastases (34.5%) than the other subtypes (31% luminal B, 20.7% luminal A, and HER2+ 13.8%). The study also revealed a relationship between ER status and the incidence of metastases ($p < 0.05$). The luminal A subtype tends to metastasize to the liver, luminal B tends to metastasize to the bone, HER2+ tends to metastasize to the lung and liver, and TNBC tends to metastasize to the lung. However, no significant association was found between breast cancer subtypes and metastatic sites.
Conclusion : There was a significant association between breast cancer subtypes and the incidence of metastases, but not with the metastatic sites.

Keywords : breast cancer; molecular subtypes; metastases

INTRODUCTION

According to the World Health Organization (WHO) data in 2019, cancer was ranked as the top cause of death before age 70 in 112 countries, and 23 other countries ranked third or fourth. Based on data from GLOBOCAN in 2020, breast cancer is the most common cancer in women worldwide. In addition, breast cancer is also the major cause of cancer deaths worldwide, with a total of 685.000 deaths or 29% of total breast cancer cases.[1]

In Indonesia, breast cancer is ranked first with the most cancer cases and has become the leading cause of cancer death. Aligned with the data, data from the Dharmais Cancer Hospital in 2018 also mentions that breast cancer is cancer with the highest incidence rate among other types of cancer.[2] The number of new cases of breast cancer is estimated at 68.585 cases (16.6%) of the total 396.914 new cases of cancer in Indonesia. The number of deaths due to breast cancer is estimated to reach more than 22 thousand people or 32% of total breast cancer cases.[3]

Death in breast cancer patients is mainly caused by metastasis. Patients diagnosed with breast cancer have a 30% metastasis rate of all cancer patients.[4] Patients with metastatic breast cancer have a survival rate of 27%, much lower than patients with localized breast cancer.[5] The process of metastasis in breast cancer patients is related to the high heterogeneity of breast cancer.

Breast cancer is grouped into four subtypes based on the immunohistochemistry test (IHC) of the hormone receptors, namely estrogen receptor (ER) and progesterone receptor (PR), as well as the protein, namely human epidermal growth factor receptor-2 (HER2).[6] The four subtypes are Luminal A (ER positive, PR positive, HER2 negative and Ki-67<20%), Luminal B (ER positive and PR positive, HER2 positive or negative, and Ki-67 >20%), HER2+ (ER negative, PR negative, and HER2 positive), and Triple Negative Breast Cancer (TNBC) (ER negative, PR negative, and HER2 negative).[7]

Hormone receptor (HR) status is closely related to breast cancer treatment and prognosis. Patients with positive HR are known to be more responsive to hormone therapy and have a better prognosis than patients with negative HR. However, breast cancer is a disease with high heterogeneity at the molecular level from its various subtypes. This heterogeneity can certainly influence the response to therapy given and the prognosis. Heterogeneity in breast cancer includes differences in metastatic sites, number of metastases, and differences in prognosis between patients with primary breast cancer and metastases from different subtypes.[8]

Several previous studies have explored the relationship between molecular subtypes of breast cancer and metastatic patterns in breast cancer patients but with varied results. A study conducted in Indonesia found that the breast cancer subtype was closely related to the incidence of metastasis but not to the location of the metastasis.[9] Several studies conducted in other countries found the opposite result, the subtype of breast cancer had a close relationship with the location of the metastasis.[10–12] Other studies even found a close relationship between breast cancer subtypes and patient survival.[13] The differences in results in these various studies encourage the need to continue to explore the relationship between breast cancer subtypes and metastasis patterns, especially in local populations in Indonesia, considering its importance in the treatment plan and prognosis of breast cancer. Unfortunately, until now, there is no research data regarding the relationship between breast cancer subtypes and metastasis patterns in Lampung. Therefore, it is necessary to conduct research on the pattern of breast cancer metastasis based on molecular subtypes at RSUD Dr. H. Abdul Moeloek Lampung.

RESEARCH METHODS

This research is an observational analytical study with a cross-sectional design. The research was carried out in the medical records section of RSUD Dr. H. Abdul Moeloek Lampung Province during October–December 2022. The target population in this study is all breast cancer cases that have been recorded and have been diagnosed clinically, pathologically, and with other supporting examinations from January 1st, 2013 – December 31th 2021 and have complete medical record data, have been followed up and allowing the data to be used for this research. The sample used is the entire population that meets the inclusion and exclusion criteria. The inclusion criteria used are patients diagnosed with breast cancer who have conducted immunohistochemistry tests (IHC) for breast cancer (ER, PR, HER2, and Ki-67) and those experiencing metastases and non-metastases. The exclusion criteria are patients with incomplete IHC test results and HER2 results showing 2+ or borderline results. Sampling methods used a consecutive sampling technique, where the entire population that met the inclusion and exclusion criteria within that period was used as the sample for this study. The total sample that met the inclusion and exclusion criteria was 81 breast cancer patients. This number meets the minimum sample size based on the sample size formula for unpaired categorical analytical research, 81 samples. This research has passed ethical review from the Health Research Ethics Committee, Faculty of Medicine, University of Lampung, with No. 4183/UN26.18/PP.05.02.00/2022.

The data collected consists of demographic data and pathological characteristics such as grade, type of cancer, subtype, metastasis status, and results of ER, PR, HER2, and Ki-67 examinations of samples recorded in the medical record. The data that has been obtained is then cleared from duplicate and incomplete data. The

relationship between sample characteristics and the incidence of metastasis and the relationship between breast cancer subtype and the incidence and location of metastasis was tested using the Chi-Square test with a significance level of 95%.

RESEARCH RESULTS

Sample Characteristics

During the study period, the target population was 186 breast cancer patients. One hundred five patients did not meet the inclusion and exclusion criteria, such as patients conducting the IHC test, incomplete IHC data, and borderline HER2 results, leaving only 81 patients who met the inclusion and exclusion criteria.

The results of this study indicate that breast cancer is more commonly diagnosed in patients aged ≥50 years. When first diagnosed, most breast cancer patients are at high grade (III). 14 Invasive ductal carcinoma and luminal B subtype are the most common breast cancers. Metastases were found in 35.8% of samples, and the lung was the most common location for metastases (Table 1).

TABLE 1
Characteristics of breast cancer patients

Characteristics		Frequency	%
Age	<50 years	37	45.7
	≥50 years	44	54.3
Grades	Low (I–II)	18	22.2
	High (III)	63	77.8
Type	*Invasive ductal carcinoma*	73	90.1
	Invasive lobular carcinoma	3	3.7
	Mixed invasive carcinoma	5	6.2
Subtype	Luminal A	17	21
	Luminal B	41	50.6
	HER2-enriched	9	11.1
	TNBC	14	17.3
Metastatic Status	Metastasis	29	35.8
	Non Metastatic	52	64.2
Metastasis Location	Brain	1	3.4
	Lungs	11	37.9
	Heart	9	31
	Bone	7	24.1
	Other	1	3.4
Estrogen Receptor (ER) Status	Negative	27	33.3
	Positive	54	66.7
Progesterone Receptor (PR) Status	Negative	32	39.5
	Positive	49	60.5
HER2 status	Positive	34	42
	Negative	47	58
Ki-67 Status	>20%	64	79.1
	<20%	17	20.9

TABLE 2
Relationship between patient characteristics and the incidence of metastasis

Characteristics		Metastasis		Non Metastatic		*p*
		n	%	n	%	
Age	<50 years	12	41.4	25	48.1	0.56
	≥50 years	17	58.6	27	51.9	
Grades	Low (I–II)	9	31	9	17.3	0.15
	High (III)	20	69	43	82.7	
Type	*Invasive ductal carcinoma*	26	89.7	47	90.4	0.18
	Invasive lobular carcinoma	2	6.9	1	1.9	
	Mixed invasive carcinoma	1	3.4	4	7.7	
Estrogen Receptor (ER) Status	Negative	14	48.3	13	25	0.03
	Positive	15	51.7	39	75	
Progesterone Receptor (PR) Status	Negative	15	51.7	17	32.7	0.93
	Positive	14	48.3	35	67.3	
HER2 status	Positive	8	27.6	26	50	0.05
	Negative	21	72.4	26	50	
Ki-67 Status	< 20%	6	20.7	11	21.2	0.96
	> 20%	23	79.3	41	64.2	

TABLE 3
Relationship between breast cancer subtypes and the incidence of metastasis

Subtype	Metastasis		Non-metastatic		*p*
	n	%	n	%	
TNBC	10	34.5	4	7.7	0.01
Luminal B	9	31	32	61.5	
Luminal A	6	20.7	11	21.2	
HER2+	4	13.8	5	9.6	

TABLE 4
Relationship between breast cancer subtype and metastatic location

Subtype	Metastasis Location					*p*
	Brain	Lungs	Liver	Bone	Other	
Luminal A	0	2	4	0	0	0.39
Luminal B	0	3	2	4	0	
HER2+	0	2	2	0	0	
TNBC	1	4	1	3	1	

TABLE 5
Time to breast cancer metastasis

Subtype	Metastasis (Year 2)						
	1	2	3	4	5	6	7
Luminal A	2	0	1	0	1	1	1
Luminal B	2	1	5	0	0	0	1
HER2+	1	2	0	0	0	1	0
TNBC	4	1	4	0	1	0	0

Relationship between patient characteristics and metastatic events

In this study, a significant relationship was found between ER status and the incidence of metastasis ($p<0.05$). However, other characteristics, such as age, grade, type of cancer, PR status, HER2, and Ki-67, were not significantly related to the incidence of metastasis ($p>0.05$) (Table 2).

Relationship between Breast Cancer Subtypes and Metastatic Incidence

In this study, breast cancer with the TNBC subtype had the highest rate of metastasis, and the lowest was the HER2+ subtype. The results of the Chi-Square test showed a significant relationship between the breast cancer subtype and the incidence of metastasis ($p<0.05$) (Table 3).

Relationship between Breast Cancer Subtypes and Metastasis Locations

The results of this study show that the lung organ is the most frequent location of metastasis in TNBC subtype breast cancer. The luminal A subtype has the most metastases in the liver, while the luminal B subtype has the most bone metastases. HER2+ subtype breast cancer is found to metastasize to the lungs and liver with the same frequency. The Chi-Square test results did not show a significant relationship between breast cancer subtype and metastasis location (Table 4).

Time of Breast Cancer Metastases

The time of breast cancer metastases is calculated from the initial diagnosis until the time metastases occur, identified through the results of radiological examinations (chest x-ray, ultrasound, and CT scan). Breast cancer with the TNBC subtype experienced more metastases in the first year than other subtypes (Table 5).

DISCUSSION

Breast cancer is a very heterogeneous type of cancer. Based on the type of hormone receptor, this cancer is classified into four subtypes: luminal A, luminal B, HER2+, and TNBC. This study discovered that the breast cancer subtype had a significant relationship with the incidence of metastasis (Table 3). This finding aligns with several previous studies, which also found a significant relationship between breast cancer subtypes and metastasis.[15,16] This can be caused by the high heterogeneity of breast cancer, where each subtype has a different type of gene and, of course, will express different proteins. These gene and protein expression differences will influence each subtype's metastasis patterns.[15]

In this study, TNBC was the subtype that experienced the most metastases, followed by luminal B, luminal A, and HER2+ subtypes. These results align with previous studies' results, which also found that TNBC is the subtype with the highest frequency of metastasis and distant metastasis compared to other subtypes.[9,17,18] Several factors cause patients with the TNBC subtype to have a higher metastasis rate than other subtypes. First, TNBC does not have a specific therapeutic target, so TNBC is more challenging to treat.[19] This condition will certainly increase the potential for TNBC to metastasize. Second, TNBC is known to have a higher proliferation rate than other subtypes.[20] High cell proliferation will increase the opportunity for tumor cells to leave their initial location and spread to other organs via the bloodstream and lymphatic system. Third, TNBC has a unique microenvironment that is different from other subtypes. The microenvironmental conditions in TNBC allow interaction with various cells around it, thus enabling it to trick the immune system and spread cancer cells to other organs.[21]

The most common metastatic location for breast cancer is the lung, liver, bone, and brain. Another location is the contralateral breast. These results align with the results of other research conducted at RSUP Dr. Sardjito for the 2013–2018 period, who found that the lung was the most common location for breast cancer metastases, namely 12.7%, followed by bone (12.3%), pleura (8.8%), liver (5.5%), and brain (1.9%).[18]

This study found no significant relationship

between breast cancer subtype and metastatic location (Table 4). These findings align with previous research at RSUP Dr. M. Djamil Padang, who also did not find a significant relationship between breast cancer subtype and metastasis location.[9] However, several other studies reported different results, which showed that breast cancer subtype had a significant relationship with metastasis location.[10–12] This difference in results can be caused by differences in the research's location. Sample characteristics such as different races and ethnicities can also influence research results. Another factor that can cause differences in research results is the limited and different number of samples in each study.[22]

This study also found a relationship between ER status and the incidence of metastasis. The metastatic group had a higher frequency of negative ER status than the non-metastatic group (48.3% vs. 25%). These results align with previous research, which found that cancer with negative ER had a higher frequency of metastasis than ER positive (26.1% vs. 25.2%).[18] The results of this study are in accordance with the theory, which states that breast cancer with hormone receptors (26.1% vs 25.2%). ER or PR) positive are often less aggressive, low stage, and have a low risk of metastasis and recurrence, so this type of tumor has a good prognosis.[14]

The results of this study also show that most breast cancers with the TNBC subtype metastasize in the first to third year after the diagnosis of breast cancer is made. In the second year, breast cancer with the HER2+ subtype has the highest frequency of metastases compared to other subtypes. Breast cancer that is slow to metastasize is the luminal A and luminal B subtypes. The results of this study are in accordance with the theory, which states that breast cancer with the TNBC subtype has the fastest onset of metastasis (<0.5 years) compared to other subtypes. The luminal subtype has a late onset of metastasis.[7]

This study is the first study to examine the relationship between molecular subtypes of breast cancer and metastasis patterns in local community populations in Lampung Province. This research has several limitations, including that the sample in this study only came from RSUD Dr. H. Abdul Moeloek Lampung, so we cannot provide a complete picture of the distribution of breast cancer subtypes and metastasis patterns in Lampung Province. Another limitation is that this study used a cross-sectional design, so the course of cancer from initial diagnosis to data collection was not observed. Apart from that, the number of samples used was still small due to the small number of breast cancer patients at RSUD Dr. H. Abdul Moeloek, who could carry out a complete IHC test.

CONCLUSION

Breast cancer subtype was significantly associated with the incidence of metastasis but not with the location of metastasis. The breast cancer subtype that most frequently metastasizes is the TNBC type, with the most common location of metastasis is the lung. Therefore, screening for metastases in breast cancer patients with the TNBC subtype, especially at the most common metastatic locations, is necessary as an early detection effort of breast cancer metastases.

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