

ASSOCIATION BETWEEN MOLECULAR SUBTYPES AND SITES OF METASTASIS IN BREAST CANCER

Faizal Makharim ¹, Sidho Hantoko ², Solimun ³, Hery Susilo ⁴, Imam Suseno Bayuadi ⁵, Wilma Agustina ⁶

^{1,3,4,5,6} Department of Surgery, Faculty of Medicine, Universitas Brawijaya / Saiful Anwar General Hospital, Malang, Indonesia

² Department of Surgery, Dr. Soepraoen is a Level II Army Hospital / Faculty of Medicine, Universitas Brawijaya, Indonesia

Corresponding Email : makharimfaizal@gmail.com

ABSTRACT

Background: Breast cancer is a leading cause of cancer-related mortality worldwide, with metastasis contributing significantly to poor outcomes. Molecular subtypes are known to exhibit different metastatic patterns; however, findings remain inconsistent. This study aimed to evaluate the association between molecular subtypes and metastatic sites in breast cancer. **Methods:** A cross-sectional analytical study was conducted at Saiful Anwar General Hospital, Malang, Indonesia, from July to December 2025. Metastatic site data were obtained from medical records, and molecular subtypes were determined by immunohistochemistry. Data were analyzed using the chi-square test, with $p < 0.05$ considered statistically significant. **Results:** A total of 94 patients were included. The lung was the most common metastatic site (58.5%), followed by bone (33.0%) and liver (4.3%). Luminal A was the predominant subtype (57.45%). Liver metastasis was significantly associated with molecular subtype ($p < 0.001$), whereas no significant associations were found for lung, bone, or other metastatic sites. **Conclusion:** Liver metastasis is significantly associated with breast cancer molecular subtypes.

Keywords: Breast Cancer, Molecular Subtype, Metastasis, Lung, Liver, Clinical Correlation

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and ranks fifth as a cause of cancer-related death. According to GLOBOCAN, an estimated 2.3 million new cases were reported globally. In the United States, breast cancer accounts for approximately 29% of all new cancer cases in women. It remains a leading cause of cancer-related death among women worldwide, responsible for 685,000 deaths in 2020, equivalent to 16%, or one in every six, of cancer-related deaths in women. In Indonesia, breast cancer is also the most frequently diagnosed cancer, with 65,858 new cases and 22,430 deaths reported in 2020. Moreover, 60–70% of patients with breast cancer in Indonesia are diagnosed at advanced stages (III and IV), resulting in poor quality of life, low survival rates, and an increasing financial burden.^{1,2}

The high mortality of cancer is partly attributable to metastasis. Metastasis occurs when a primary tumor spreads and develops into secondary tumors, reflecting the aggressive nature of cancer and its capacity for rapid dissemination. This often results in delayed or unsuccessful treatment and ultimately leads to high patient mortality. Therefore, patient prognosis is closely associated with metastasis. Breast cancer cells can spread to distant organs, particularly the lungs, liver, bones, and brain. These cells proliferate into metastatic nodules, which are responsible for death in most patients. The 5-year survival rate of patients with breast cancer who develop distant metastasis is less than 20%.^{3,4}

Breast cancer is classified into several molecular subtypes based on receptor expression in tumor tissue. Immunohistochemistry-based molecular subtyping is used to predict tumor response to hormonal therapy and anti-HER2 therapy (trastuzumab). Based on the St. Gallen Consensus (2013), breast cancer is classified into Luminal A, Luminal B (HER2-negative), Luminal B (HER2-positive), HER2-enriched, and triple-negative breast cancer (TNBC).^{5,6}

Breast cancer is a genetically and clinically heterogeneous disease. Conventional prognostic factors include immunohistochemical markers such as ER, PR, and HER2, together with clinicopathological variables including tumor size, tumor grade, and nodal involvement.⁷

Each subtype exhibits a distinct metastatic pattern. Bone, liver, lung, and brain are the most frequent sites of distant metastasis and are associated with poor survival outcomes. Bone metastasis is more common in luminal subtypes, whereas lung metastasis is more frequent in TNBC. HER2-positive subtypes are associated with a higher risk of liver metastasis.^{4,8,9}

Understanding the relationship between molecular subtypes and metastatic sites is important for improving breast cancer management, including screening strategies, treatment selection, and follow-up. However, previous studies have shown inconsistent results. Therefore, this study aimed to investigate this association.

METHODS

A. Research Design

This was an analytical observational study employing a cross-sectional design, in which data on the independent variable (molecular subtype of breast cancer) and the dependent variable (site of metastasis) were collected simultaneously at a single point in time (Figure 1).

B. Study Setting and Population

The study was conducted at the Surgical Outpatient Clinic of Saiful Anwar General Hospital, Malang, from July to December 2025. The study population comprised all patients with breast cancer and distant metastases treated at the hospital. The study sample consisted of patients who met the inclusion and exclusion criteria during the study period.

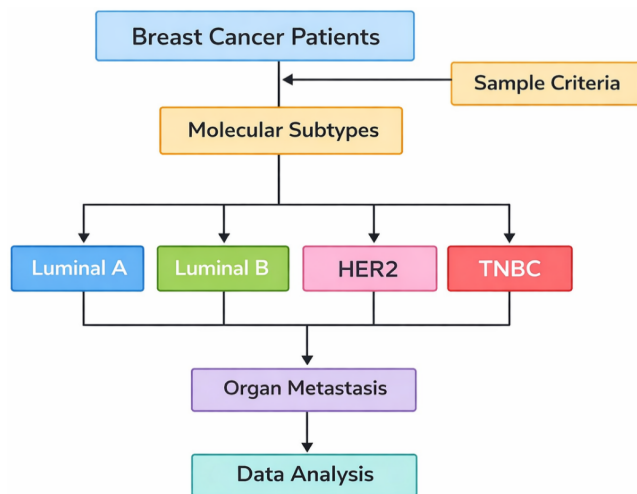


Figure 1: Breast cancer subtyping and metastasis analysis process. HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

C. Eligibility Criteria and Sampling

The inclusion criteria were patients diagnosed with breast cancer between July and December 2025 who had undergone molecular subtype examination and had documented distant metastasis. The exclusion criteria were locoregional recurrence, incomplete medical records (including missing data on age at diagnosis, marital status, tumor size, histological grade, ER, PR, HER2 status, Ki-67 or molecular subtype, as well as metastasis status and site), and other malignancies.

The minimum sample size was calculated using a comparative test formula for categorical variables in a contingency table with 12 degrees of freedom, a significance level (α) of 5%, and a statistical power of 80%. Based on literature data regarding metastasis distribution, a chi-square value of 35.699 and an effect size of 0.2987 were obtained, resulting in a minimum required sample size of 100 breast cancer patients with distant metastases. Quota sampling was applied, in which eligible subjects were recruited consecutively until the required sample size was approached.

D. Variables and Operational Definitions

The independent variable in this study was the molecular subtype of breast cancer, whereas the dependent variable was the site of metastasis. Molecular subtypes were determined based on the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 obtained from immunohistochemical examination. These were subsequently classified into Luminal A (ER and/or PR positive, HER2 negative, Ki-67 <20%), Luminal B (ER and/or PR positive, HER2 negative, Ki-67 >20%), HER2-enriched (HER2 positive with ER and/or PR either positive or negative), and triple-negative breast cancer (TNBC) (ER, PR, and HER2 negative).

The site of metastasis was defined as the spread of cancer cells from the primary tumor to distant organs, confirmed by supporting diagnostic examinations documented in the

medical records. These included brain metastasis (head CT scan), lung metastasis (chest radiography or thoracic CT scan), liver metastasis (abdominal ultrasonography or CT scan), bone metastasis (plain radiography, CT scan, or MRI), and metastasis to other organs. All variables were measured on a nominal scale. The research instruments included patients' medical records, observation sheets, and data collection forms.

E. Research Procedure and Ethical Considerations

The research procedure began with obtaining ethical clearance (No. 400/059/K.3/102.7/2025) from the Ethics Committee of the Faculty of Medicine, Universitas Brawijaya, as well as permission from Saiful Anwar General Hospital, Malang. After approval was obtained, medical records were reviewed to identify eligible patients based on the inclusion and exclusion criteria. Data collected included patient characteristics (age at diagnosis and marital status), tumor characteristics (tumor size, histological grade, ER, PR, HER2, and Ki-67 status or molecular subtype), and metastasis data (status and site). The data were then coded, entered into Microsoft Excel, and subsequently analyzed using SPSS software. Ethical principles were upheld by ensuring patient confidentiality and prioritizing patient welfare throughout the study.

F. Statistical Analysis

Data were analyzed descriptively and presented as frequency distributions and percentages. Bivariate analysis was performed using the chi-square test to assess the association between molecular subtype and site of metastasis, provided that the test assumptions were fulfilled (sample size >40, no cells with an observed frequency of zero, and no more than 20% of cells with expected counts <5). If these assumptions were not met, Fisher's exact test was applied. A p-value of <0.05 was considered statistically significant.

RESULTS

A. Characteristics of the Study Population

A total of 94 female patients with metastatic (stage IV) breast cancer were included in this study. The baseline characteristics of the study population are presented in Table 1. Most patients were aged >40 years (89.9%), whereas 10.1% were aged <40 years. More than half of the patients reported a history of hormonal contraceptive use (57.4%). Regarding molecular subtypes, Luminal A was the most common subtype (57.4%), followed by Luminal B (23.4%), triple-negative breast cancer (TNBC) (13.8%), and the HER2-enriched subtype (5.3%). Overall, the study population was predominantly composed of older patients with luminal-subtype breast cancer.

Table 1. Population Characteristics

Variable	n	(%)
Age		
>40 years	80	89.89
<40 years	9	10.11
Hormonal Contraceptive Use		
Yes	54	57.45
No	35	42.55
Subtype		
TNBC	13	13.83
Luminal A	54	57.45
Luminal B	22	23.4
HER2	5	5.32

HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

B. Distribution of Metastatic Sites

The distribution of metastatic sites is summarized in Table 2. No cases of brain metastasis were observed in this cohort (0%). The lung was the most frequent site of metastasis, occurring in 55 patients (58.5%), followed by bone metastasis in 31 patients (33.0%). Metastasis to other organs was identified in 27 patients (28.7%), whereas liver metastasis was relatively rare, being observed in only 4 patients (4.3%). Within the “other organ” category, metastases included involvement of the contralateral breast (23.7%), contralateral supraclavicular lymph nodes (2.15%), and contralateral infraclavicular lymph nodes (2.15%). Overall, these findings indicate that the lung and bone are the predominant metastatic sites in this population, whereas brain metastasis was not observed.

Table 2. Breast Cancer Metastasis

Metastasis		n	(%)
Brain	Yes	0	0
	No	94	100
Lung	Yes	55	58.5
	No	39	41.5
Liver	Yes	4	4.3
	No	90	95.7
Bone	Yes	31	33
	No	63	67
Other Organs	Yes	27	28.7
	No	67	71.3
Contralateral breast		23	23.7
Contralateral supraclavicular lymph nodes		2	2.15
Contralateral infraclavicular lymph nodes		2	2.15

C. Association Between Molecular Subtypes and Metastatic Sites

Lung metastasis was most frequently observed in the Luminal A subtype (33.0%), followed by Luminal B (13.8%), TNBC (7.4%), and HER2 (4.3%); however, this distribution was not statistically significant ($p = 0.778$). A statistically significant association was found between molecular subtype and liver metastasis ($p < 0.001$). Liver metastasis was observed in the Luminal B (1.1%), TNBC (1.1%), and HER2 (2.1%) subtypes, whereas no cases were identified in the Luminal A

subtype. Bone metastasis occurred most commonly in patients with Luminal A (21.3%), followed by Luminal B (7.4%) and TNBC (4.3%), with no cases observed in the HER2 subtype; this association was not statistically significant ($p = 0.407$). Similarly, metastasis to other organs was most frequent in the Luminal A subtype (17.0%), followed by Luminal B (7.4%) and TNBC (4.3%), with no statistically significant association identified ($p = 0.539$). No cases of brain metastasis were detected across any molecular subtype in this study. The association between molecular subtypes and metastatic sites was analyzed using the chi-square test, as shown in Table 3.

Table 3. Analysis of the Relationship Between Subtype and Breast Cancer Metastasis

Organ	HER2	Luminal A	Luminal B	TNBC	p-value
	n (%)	n (%)	n (%)	n (%)	
Lung	4 (4.3%)	31 (33.0%)	13 (13.8%)	7 (7.4%)	0.778
Liver	2 (2.1%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	<0.001
Bone	0 (0.0%)	20 (21.3%)	7 (7.4%)	4 (4.3%)	0.407
Other Organs	0 (0.0%)	16 (17.0%)	7 (7.4%)	4 (4.3%)	0.539

Analysis performed using the chi-square test. HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

DISCUSSION

This study demonstrates that the lung is the most common site of distant metastasis across all investigated molecular subtypes of breast cancer, including HER2-positive, Luminal A, Luminal B, and triple-negative breast cancer (TNBC). Although lung metastasis appeared descriptively predominant across all subtypes, statistical analysis revealed no significant association between molecular subtype and the occurrence of lung metastasis. These findings suggest that the lung functions as a relatively universal target organ for metastasis in breast cancer, regardless of hormone receptor or HER2 expression status. This pattern is consistent with epidemiological reports identifying bone, lung, liver, and brain as the most frequent sites of distant metastasis in breast cancer.^{4,10}

The absence of a statistically significant relationship between molecular subtype and lung metastasis may be attributed to the complex and multifactorial nature of the metastatic process, which is not governed by a single determinant such as molecular subtype alone. The lung is considered a relatively non-specific metastatic site, as nearly all breast cancer subtypes possess the capacity for hematogenous dissemination, with the lung serving as one of the first capillary beds encountered in the systemic circulation. Furthermore, the influence of molecular subtype may be overshadowed by other dominant clinical factors, including disease stage, tumor size, lymphovascular invasion, and response to systemic therapy. Methodological limitations, such as the limited sample size and unequal subtype distribution, may also have reduced the statistical power to detect significant associations.^{11,12}

From a biological perspective, lung metastasis in breast cancer occurs through a multistep process involving phenotypic transformation of primary tumor cells via epithelial–

mesenchymal transition (EMT), which enhances migratory and invasive capabilities and facilitates entry into the systemic circulation. Circulating tumor cells are then mechanically trapped within the pulmonary capillary network owing to its extensive vascular architecture. In addition to these mechanical factors, primary tumors can establish a pre-metastatic niche in the lung through the secretion of pro-inflammatory cytokines, angiogenic factors such as vascular endothelial growth factor (VEGF), and extracellular vesicles that modify the pulmonary microenvironment prior to tumor cell arrival. These changes promote vascular permeability, endothelial activation, and immune cell recruitment, thereby facilitating tumor cell adhesion, extravasation, and subsequent proliferation within lung tissue.^{13–15}

In contrast to lung metastasis, this study identified a statistically significant association between molecular subtype and liver metastasis, although the overall incidence of liver metastasis was relatively low. This finding indicates that liver metastasis is not evenly distributed across subtypes but is instead concentrated in specific groups. Previous studies have similarly reported that HER2-positive and Luminal B subtypes exhibit a higher propensity for liver metastasis than Luminal A. Large population-based studies by Gong et al. and Yang et al. have also demonstrated that patients with HER2-positive breast cancer, irrespective of hormone receptor status, have a higher prevalence of liver metastasis than those with other subtypes.^{16,17}

Biologically, liver metastasis represents a highly selective process influenced by complex interactions between the primary tumor, circulating tumor cells, and the hepatic microenvironment. Primary tumors secrete mediators such as VEGF, transforming growth factor- β (TGF- β), and tissue inhibitor of metalloproteinase-1 (TIMP-1), which contribute to the formation of a pre-metastatic niche in the liver through activation of Kupffer cells and liver sinusoidal endothelial cells. This environment becomes conducive to tumor cell implantation. Following arrival in the liver, successful colonization is determined by interactions with hepatocytes, hepatic stellate cells, sinusoidal endothelial cells, and local immune components, collectively creating an angiogenic and immunosuppressive milieu that supports metastatic growth.¹⁸

Within this context, the observed subtype-specific tendency toward liver metastasis can be explained by the concept of metastatic organotropism, which refers to the ability of cancer cells to preferentially adapt to and colonize specific organs. HER2-positive and Luminal B subtypes are characterized by more aggressive biological behavior and the expression of molecules that facilitate hepatic colonization, including the CXCR4/CXCL12 chemokine axis, activation of non- β -catenin Wnt signaling pathways, and increased angiogenic signaling and hypoxia response. Additionally, the high vascular supply and relatively tolerogenic immune environment of the liver provide favorable conditions for the survival and proliferation of tumor cells with these characteristics.^{19,20}

The findings of this study are also consistent with prior research demonstrating that molecular subtypes of breast

cancer are associated with distinct patterns of distant metastasis and prognosis. Large-scale analyses by Guo et al. and Zhang et al. have reported that HER2-positive and TNBC subtypes are more likely to develop visceral metastases, including to the lung and liver, whereas hormone receptor-positive/HER2-negative subtypes more commonly metastasize to bone. However, overlapping metastatic patterns across subtypes have also been reported, which may explain why differences in certain metastatic sites, particularly the lung, do not consistently reach statistical significance across studies. Additional studies have indicated that Luminal A tends to metastasize to bone and liver, HER2-positive to lung and liver, and TNBC to lung and brain, although these findings are not entirely consistent across all populations. Such variability may be influenced by differences in population characteristics, sample size, study design, and the definition and recording of metastatic patterns, including single versus multiple metastatic sites.^{21–24}

LIMITATIONS

Several limitations of this study should be considered when interpreting the findings. The cross-sectional design captures data at a single time point and therefore does not allow causal inference or evaluation of the temporal dynamics of metastatic progression. The use of quota sampling and reliance on secondary data from medical records may have introduced selection bias and limited data completeness, potentially affecting the representativeness of the findings. Furthermore, the single-center setting at Saiful Anwar General Hospital, Malang, and the restricted study period limit the generalizability of the results to broader populations. Variations in diagnostic methods and clinical practices over time may also have influenced data consistency.

CONCLUSION

Lung metastasis is the most common metastatic site across all molecular subtypes of breast cancer, with no significant differences observed between subtypes. In contrast, a significant association was found between molecular subtype and liver metastasis, particularly among the Luminal B and TNBC subtypes. These findings underscore the importance of recognizing subtype-specific metastatic patterns, especially in the liver, to refine screening protocols, inform adjuvant therapy decisions, and enhance follow-up strategies. Ultimately, this knowledge may contribute to improved treatment outcomes and a better quality of life for patients with breast cancer.

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