Relationship between Clinicopathological Factors of Breast Cancer and Lymph Node Metastasis in Young Women

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KEYWORDS
Clinicopathological Factors, Breast Cancer, Lymph Node Metastasis, Young Women.

ABSTRACT
Aim : To determine the incidence of lymph node metastasis in breast cancer of young women and its relationship with clinicopathologic factors. Methods : The study used an analytic observational design and a cross-sectional approach. Bivariate analysis was performed with Fisher's exact probability test to determine the association of clinicopathologic factors with lymph node metastasis. Results: N1 lymph node metastases could be found in most of the young women breast cancer patients at 42.9%, followed by N3 and N2 at 11.4% and 8.6%, respectively. On the other hand, 37.1% of patients showed no lymph node metastasis. Fisher's exact probability test showed that of the six clinicopathological factors, only tumour size was associated with lymph node metastasis with a p-value of 0.031. Conclusion : The incidence rate of lymph node metastasis in breast cancer of young women was 42.9% for N1, 11.4% for N3, and 8.6% for N2. There was a significant association between tumour size and lymph node metastasis.

1. Introduction

Breast cancer is the most common cancer experienced by women.[1] For many years, breast cancer has had the highest incidence of all types of cancer in women worldwide.[2] World Cancer Research Fund International noted that throughout 2020, there were more than 2.26 million new cases of breast cancer in women worldwide.[3] This is equivalent to 47.8 new cases per 100,000 people.

Globocan recorded 396,914 new cancer cases in Indonesia in 2020. Of the total cases, breast cancer ranked first, with a total of 65,858 new cases, or equivalent to 16.6% of the total cancer cases. Patient deaths due to breast cancer totaled 22,430 (equivalent to 9.6%). This mortality rate is the second largest after lung cancer.[4]

Breast cancer is a disorder where epithelial cells experience uncontrolled growth and form tumors that can spread throughout the body.[5,6] This cell growth originates from the milk ducts or milk-producing lobules in the breast.[5] Cancer cells are characterized by uncontrolled division, causing abnormal growth (carcinoma in situ) and the ability to invade normal tissue locally (invasive cancer)[7] or metastasize to other organs.[5]

Breast cancer can metastasize both hematogenously and lymphogenously. Hematogenous metastasis can occur in the chest, liver, spine, and brain. Meanwhile, lymphogenous metastasis can spread to regional lymph nodes.[8]

Women with lymph node metastases in breast cancer have a greater proportion of breast cancer deaths.[9] Of all new cases of breast cancer, 32-36% of patients have metastasis to the lymph nodes at the time of diagnosis.[9] Among all age groups, women under 40 have the highest chance of developing lymph node metastasis.[9,10] Women under 40 were 1.55 times more likely to have lymph node metastases in breast cancer than women aged 60-69 years.[9] In line with these findings, other studies have also linked a statistically significant association between age and lymph node metastasis in breast cancer. Post-menopausal women have a '>3' lower risk of developing N than pre-menopausal women.[11]

Compared to older patients, breast cancers at a young age tend to be more aggressive, have more lymph node involvement, have a higher tumor grade with larger size, have more lymphatic and

vascular involvement, more advanced tumor stage with triple-negative, overexpression of human epidermal growth factor receptor 2 (HER2/neu), and fewer luminal A and B breast cancers.[12]

The relationship between clinicopathological factors of breast cancer and lymph node metastasis in young woman patients is an important need that has not been widely studied.[13] The findings of Courtney et al. suggest that clinicopathologic factors are significantly associated with breast cancer incidence and recurrence.[14] Individual factors (including the hormone receptor/HER2-positive) are also associated with outcomes in lymph node metastasis in breast cancer,[15] and recently there has been an increased appreciation of the clinicopathologic parameters that influence recurrence and mortality.[14]

Clinicopathological factors (age, tumor size, histopathological type, histopathological grade, lymphovascular invasion, and tumor subtype) would certainly be beneficial for determining surveillance, treatment strategies, possible prevention, and anticipating metastatic recurrence. Therefore, the objectives of this study were (1) to determine the incidence of lymph node metastasis in breast cancer of young woman patients and (2) to examine clinicopathologic factors associated with lymph node metastasis in young woman patients with breast cancer.

Methods

This research used an analytic observational design with a cross-sectional approach. The collected data were analyzed descriptively and presented in tabular form. The descriptive data analyzed included all variables studied from lymph node metastasis patients in young breast cancer. Bivariate analysis was conducted using Fisher's exact probability test to fulfill the second research objective. This test showed the relationship between clinicopathologic factors and lymph node metastasis.

The research was conducted at Dr. Cipto Mangunkusumo General Hospital (RSCM). This location was chosen because it is a national referral hospital in Indonesia, with the hope that the population and samples taken from this hospital represent a more comprehensive picture of lymph node metastasis in breast cancer. Samples were taken from the population that met the inclusion criteria, including:

1. Breast cancer patients registered at the Polyclinic of the Oncology division of the Department of Surgery and received therapy at RSCM from September 1, 2018 to September 1, 2023;
2. Patients aged 19 to 39 years old;
3. The patient is woman;
4. Breast cancer patients with Stage I-III;
5. Histopathology and immunohistochemistry examination at RSCM;
6. The medical record data of patients with breast cancer contained information: date of birth (age), tumor size and existence (T), lymph node metastasis (N), histopathological type, histopathological grade, lymphovascular invasion, and tumor subtype..

The exclusion criteria include:

1. Breast cancer patients who experience recurrence (locoregional); And
2. Breast cancer patients with distant metastases.

Although this study collected patient data from 2018 to 2023, researchers only obtained electronic medical record data from 2020 to 2023 because in 2018-2019, there was a transition from conventional medical records to electronic medical records. From the available data, the number of breast cancer patients aged 19 to 39 years was 254 patients. Considering that many patients had entered stage 4, were referred back to the original hospital, no anatomical pathology examination results were found, immunohistochemistry examinations were performed outside the study site, and did not contain data needs according to the inclusion criteria, the researcher only found 35 patient

data that met the inclusion criteria (see Figure 1). Of all the subjects who met the inclusion criteria, it was found that all of them had undergone anatomical pathology examination so that it could be confirmed that the diagnosis used as data for this study was a pathological diagnosis.

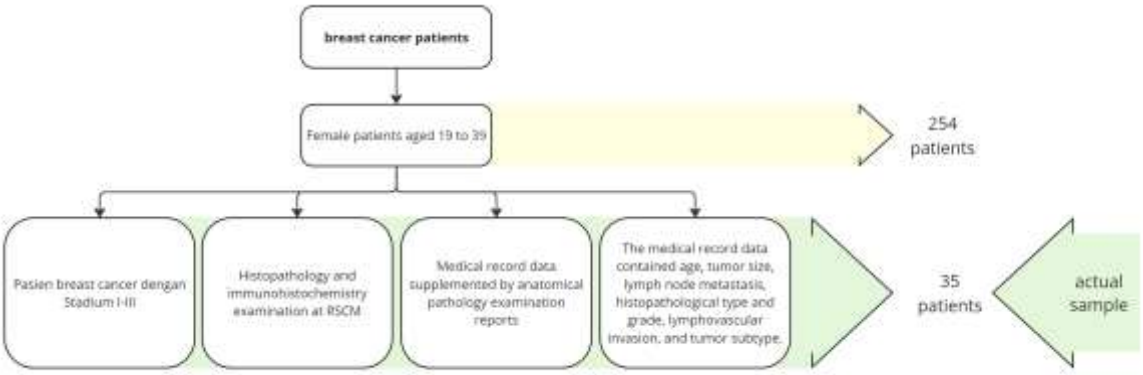

Figure 1. Sample Selection Process

Result

Incidence of Lymph Node Metastases in Breast Cancer in Young Woman Patients

Of the number of patients with lymph node metastases that have been pathologically examined, it was found that patients with N1 lymph nodes were 15 people (42.9%), N2 were 3 people (8.6%), N3 were 4 people (11.4%), and no lymph node metastases (N0) were found in 13 people (37.1%).

Table 1. Incidence rate of lymph node metastasis in breast cancer of young women patients

Variable	Amount	Percentage (%)
Lymph node metastases (N)		
N0	13	37.1%
N1	15	42.9%
N2	3	8.6%
N3	4	11.4%
Histopathological type		
NST	35	100.0%
Lymphovascular invasion		
No lymphovascular invasion	34	97.1%
Lymphovascular invasion is present	1	2.9%
Tumor subtype		
HR-/HER2+	4	11.4%
HR+/HER2-	9	25.7%
HR+/HER2+	4	11.4%
Luminal B HER2-	9	25.7%
Luminal B HER2+	6	17.1%
Triple Negative	3	8.6%
Tumor Size (T)		
T2	11	31.4%

T3	10	28.6%
T4	14	40.0%
Histopathological grade		
G1	0	0%
G2	11	31.4%
G3	24	68.6%

Table 1 explains that at the time of the study, the 35 subjects taken as a whole (100%) had the same histopathology type, namely No Special Type (NST). Only one patient (2.9%) had lymphovascular invasion, and the remaining 34 (97.1%) did not.

Tumor subtypes can be said to be very diverse. The most common tumor subtypes were HR+/HER2- and Luminal B HER2-, each with 9 patients (or 25.7%). The next order was Luminal B HER2+ in 6 patients (17.1%), HR-/HER2+ in 4 patients (11.4%), HR+/HER2+ in 4 patients (11.4%), and 3 patients (8.6%) with Triple Negative subtype (TNBC).

Tumor size was also quite diverse. There were 11 patients (31.4%) with T2 tumor size, 10 patients (28.6%) with T3 tumor size, 14 patients (40.0%) with T4 tumor size, and no patients with T1 tumor size. In histopathological variables, 24 patients (68.6%) with G3, 11 patients (31.4%) with G2, and no patients with G1 were found.

Table 2. Stage of breast cancer in young woman patients

No	TNM levels	Amount	Stadiums	Amount	Percentage
1	T2N0M0	7	**IIA**	7	20.0%
3	T3N0M0	3	**IIB**	5	14.3%
4	T2N1M0	2			
5	T3N1M0	3	**IIIA**	5	14.3%
6	T3N2M0	1			
7	T2N2M0	1			
8	T4N1M0	10	**IIIB**	14	40.0%
9	T4N0M0	3			
10	T4N2M0	1			
11	T3N3M0	3	**IIIC**	4	11.4%
12	T2N3M0	1			

Based on the AJCC *Cancer Staging Manual* 7th edition,[16] a combination of tumor size (T), lymph node metastasis (N), and distant metastasis (M) were reviewed to determine the stage of breast cancer. As detailed in Table 2, it was found that the majority of patients were at stage IIIB with 13 people (37%), followed by 8 patients with stage IIA (23%), 5 patients with stage IIB (14%), 5 patients with stage IIIA (14%), and 4 patients with stage IIIC (11%).

Relationship between clinicopathologic factors of breast cancer and lymph node metastasis in young female patients

Using crosstabulation and Fisher's Exact test, bivariate analysis was conducted to determine the association of clinicopathological factors with lymph node metastasis. Because Fisher's Exact test requires data in a 2 x 2 contingency table,[17] all data in this study were clustered into 2 categories (high and low). Lymph node metastasis was categorized into N0 and N1-N3. Age was grouped into 19-29 years and 30-39 years. Tumor size was categorized into T1-T2 and T3-T4. Histopathological grade was categorized into G1-G2 and G3. Lymphovascular invasion was categorized into negative and positive. The tumor subtype was categorized into HER2- and HER2+. There was no categorization for histopathological type as all samples were NST. The details of the findings based on this grouping can be seen in Table 3.

Table 3. Bivariate analysis of the relationship between clinicopathological factors and lymph node metastases

Clinicopathological Factors	**Lymph Node Metastasis (N)**		***p-value**
	N0	**N1-N3**	
Age			0.664
19-29	3 (50.0%)	3 (50.0%)	
30-39	11 (37.9%)	18 (62.1%)	
Tumor Size			0.031
T1-T2	8 (66.7%)	4 (33.3%)	
T3-T4	6 (26.1%)	17 (73.9%)	
Histopathological type			*unknown*
NST	14 (40.0%)	21 (60.0%)	
Histopathological grade			1.00
G1-G2	4 (36.4%)	7 (63.6%)	
G3	10 (41.7%)	14 (58.3%)	
Lymphovascular invasion			0.400
Negative	13 (38.2%)	21 (61.8%)	
Positive	1 (100.0%)	0 (0.0%)	
Tumor subtype			0.08
HER2-	11 (52.4%)	10 (47.6%)	
HER2+	3 (21.4%)	11 (78.6%)	

p-value is the result of analysis using **Fisher's exact test*

DISCUSSION

Incidence of Lymph Node Metastases in Breast Cancer in Young Woman Patients

Behring et al. and Moosavi et al. stated that women under 40 years old have the highest chance of lymph node metastasis in breast cancer.[9,10] This research complements their findings and provides additional information on the variation of lymph node metastasis in young patients. As can be seen in Table 1, N1 lymph node metastases were found in most of the young breast cancer patients at 42.9%, followed by N3 and N2 at 11.4% and 8.6% respectively. On the other hand, 37.1% of patients showed no lymph node metastasis.

Relationship between clinicopathologic factors of breast cancer and lymph node metastasis in young female patients

Age

Previous researchers recorded mixed findings regarding the relationship between age and lymph node metastasis in breast cancer. Research by Behring et al. and Moosavi et al. stated that there is a significant relationship between age and lymph node metastasis in breast cancer.[9,10] They stated that women under the age of 40 had the highest chance of lymph node metastasis in breast cancer when compared to the higher age group (above 40 years). Meanwhile, Nouh et al., Ivković-Kapicl et al., and Chakraborty et al. found that there was no association between age and lymph node metastasis in breast cancer.[18–20]

Although there have been findings that age below 40 years has the highest chance of lymph node metastasis in breast cancer, there was not enough evidence to see an association between the age variation of woman patients aged below 40 years and lymph node metastasis in breast cancer. The p-value of age generated from Fisher's exact test was 0.664 or greater than 0.05 (see Table 3). Thus, the finding of this study is that there is no significant association between age and lymph node metastasis in breast cancer of young women. This study's conclusions align with the results of Nouh et al., Ivković-Kapicl et al., and Chakraborty et al., who stated that there is no association between age and lymph node metastasis in breast cancer.[18–20]

Tumor Size

Previous studies have suggested that tumor size is associated with lymph node metastasis in breast cancer.[20–22] Chakraborty et al. even stated that tumor size is one of the best predictive factors for lymph node involvement in breast cancer.[20] In line with the findings of previous researchers, this study also found that there is a significant relationship between tumor size and lymph node metastasis in breast cancer in young woman patients, as evidenced by the p-value of tumor size generated from Fisher's exact test of 0.031 (see table 3).

Histopathological Type

Mustafa et al. examined the relationship between histopathologic type and lymph node metastatic involvement in the United States. He found that histopathologic type had no significant impact on the frequency of lymph node metastases based on univariate analysis with a P-value of 0.08.[23] This research could not identify the relationship between histopathologic type and lymph node metastasis in breast cancer because no histopathologic type variants other than NST were found (see Tables 1 and 3).

Histopathological Grade

Hermansyah et al. found a relationship between histopathological grade and lymph node metastasis with a p-value of 0.001.[24] Similarly, Zheng-Jun et al. and Cserni et al. also revealed a positive relationship between histopathological grade and the number of metastasized lymph nodes.[25,26] Unlike the previous researchers, this research did not find an association between histopathological grade and lymph node metastasis. After Fisher's exact test analysis, it was found that the p-value of histopathological grade was greater than 0.05.

Lymphovascular Invasion

Only 2.9% of patients had lymphovascular invasion (see Table 1). Thus, it certainly cannot be stated that there is an association between lymphovascular invasion and lymph node metastasis. Moreover, table 3 shows the results of Fisher's exact test analysis with a p-value of 0.4. The findings of this study are certainly different from Chakraborty et al. and Rezaianzadeh et al. who stated that lymphovascular invasion acts as one of the significant independent prognosis factors in line with lymph nodes.[20.27]

Tumor Subtypes

This research conducted Fisher's exact test analysis on the tumor subtype variable and produced a p-value of 0.08 (see Table 3). Therefore, it can be said that there is no association between tumor subtype and lymph node metastasis. Thus, the results of this research are in line with the findings of Chua et al.[28] and Gajdos et al.[29] which showed no significant relationship for estrogen (ER) or progesterone (PR) status, and the study of Chakraborty et al.[20] who found no association between hormone receptor status and lymph node metastasis in breast cancer .

Based on the above, it can be said that of the six clinicopathological factors, only tumor size is significantly associated with lymph node metastasis in young woman patients. In young women with breast cancer, tumor size has been found to have a significant association with lymph node

involvement.[20,29,30] This relationship is especially evident in younger patients, where high tumor size is more common.[30] The larger size of these tumors is often accompanied by other aggressive features, such as a higher likelihood of negative estrogen receptors, further increasing the risk of lymph node involvement.[30]

Conclusions

The incidence rates of lymph node metastasis in breast cancer of young woman patients were 42.9% for N1, 11.4% for N3, and 8.6% for N2. Of the six clinicopathological factors, only tumor size was significantly associated with lymph node metastasis in young woman patients.

Recommendations

Since tumor size has a significant association with lymph node metastasis, this can be the basis for managing tumor size to reduce the incidence of lymph node metastasis in young woman breast cancer patients.

Considering that this study was conducted from 2018 to 2023, during which time there was a transition from conventional medical records to electronic medical records, which caused data not to be obtained in 2018 and 2019, research on the same topic is needed in the future to avoid incomplete data due to the transition period of medical records.

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