Relationship between Molecular Subtype, Degree of Differentiation, and Lymph Node Metastasis with Survival of Breast Cancer Patients at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Breast cancer has the highest incidence of all cancers in women worldwide. A molecular subtype of breast cancer, degree of differentiation, and lymph node metastasis are prognostic and predictive factors of breast cancer. This study aims to explore the relationship between molecular subtype, degree of differentiation, and lymph node metastasis with overall survival and disease-free survival of breast cancer patients at Dr. M. Djamil General Hospital Padang. **Methods:** This study was an analytic observational study with a retrospective cohort approach using secondary data from 68 subjects. The test variables in this study were the molecular subtype of breast cancer, the degree of differentiation, and lymph node metastasis which were obtained from secondary data and medical records. Another test variable is patient survival, namely overall survival (OS) and disease-free survival (DFS). Data analysis with the help of SPSS software in univariate, bivariate, and multivariate. **Results:** Patients with lymph node metastases were 7.94 times more likely to experience an event (death) (HR=7.94 95% CI: 0.91–78.2). Patients with lymph node metastases were 10.2 times more likely to experience an event (recurrence) (HR=10.2 95% CI: 1.03–101.1). **Conclusion:** Lymph node metastases are the factors most related to survival (overall survival and disease-free survival) of breast cancer patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

1. Introduction

Breast cancer has the highest incidence of all cancers in women worldwide. It is estimated that about one in eight women in the United States (US) are at risk of developing breast cancer. In 2018, more than 266,000 new cases of breast cancer were expected in women in the US.[1,2] Data from the Global Burden of Cancer (GLOBOCAN) released by the World Health Organization (WHO) states that the incidence of breast cancer in 2020 was 2,261,419 cases, with 684,996 deaths in 2020. Deaths from cancer are expected to continue to increase to more than 13,000. 1 million in 2030. In Indonesia, breast cancer is the largest contributor to cancer cases, with incidents of 65,858 and deaths of 22,430 people in 2020.[3] Data sourced from the Dharmais Cancer Hospital in 2018 shows that the most cases of cancer are breast cancer at 19.18%, cervical cancer at 10.69%, and lung cancer at 9.89%. The types of cancer that often occur in women,

namely breast and cervix, are the biggest contributors to all types of cancer.[4] Indonesia Health Profile 2020 stated that there were 190 suspected cases of breast cancer during 2018-2020 in West Sumatra from the results of early detection examinations.[5]

In order to quickly and accurately screen breast cancer, many diagnostic methods are based on imaging and molecular biotechnology. Immunohistochemical examination (IHC) is an additional method for diagnosing breast cancer. Currently, CPI is the best diagnostic method for assessing estrogen receptor (ER) and progesterone receptor (PR) in breast cancer. Immunohistochemistry can screen and diagnose breast cancer patients by evaluating the levels of biomarker proteins. A molecular subtype of breast cancer, degree of differentiation, and lymph node metastasis are prognostic and predictive factors of breast cancer. Previous studies revealed that the molecular subtype determines the incidence of lymph node metastases, the degree of cancer cell differentiation, and the survival of breast cancer patients.[6-11] This study aims to explore the relationship between molecular subtype, degree of differentiation, and lymph node metastasis with overall survival and disease-free survival of breast cancer patients at Dr. M. Djamil General Hospital Padang.

2. Methods

This study was an analytic observational study with a retrospective cohort approach. This study uses secondary data obtained from the medical record installation of Dr. M. Djamil Padang, Indonesia. A total of 68 subjects were included in this study, where the study subjects met the inclusion criteria in the form of female patients aged > 18 years who were diagnosed with breast cancer and had undergone Modified Radical Mastectomy surgery and patients had complete medical records that had been examined for IHK (ER, PR, HER2, Ki67). This study was approved by the medical and health research ethics committee at Dr. M. Djamil General Hospital, Padang, Indonesia (No. LB.02.02/5.7/496/2022).

The test variables in this study were the molecular subtype of breast cancer, the degree of differentiation, and lymph node metastasis which were obtained from secondary data and medical records. Another test variable is patient survival, namely overall survival (OS) and disease-free survival (DFS). Data analysis was performed with the help of SPSS version 25 software. Univariate analysis was performed to present the frequency distribution of study subject data. Bivariate and multivariate analyzes were performed for survival analysis with Cox Proportional Hazard Regression, with a p-value <0.05.

3. Results

Table 1 shows that the majority of patients are aged ≥ 40 years (91.2%), high school graduates (45.6%), year of diagnosis 2021 (54.4%), clinical stage II (58.8%), histopathologic NST (75%) and had no history of hormonal contraception (63.2%). Most breast cancer patients were in the HER2 type subtype (39.7%), then followed sequentially, namely Luminal B HER2 Positive (23.5%), Luminal B HER2 Negative (14.7%), TNBC (13.2%), and the least is luminal A (8.8%). In the degree of differentiation variable, most of the patients were in grade II (66.2%), then grade III (29.4%), and the least was grade I (4.4%). Furthermore, it can be seen that most of the patients had lymph node (LN) metastases (82.4%).

Table 1. Characteristics of research subjects.

Variable	Frequency	Percentage %
Age		
< 40 years	6	8.8
≥ 40 years	62	91.2
Education		
Not schooling	4	5.9
Graduated from junior high school	18	26.5
Graduated from high school	31	45.6
Graduated from college	15	22.2
Years of diagnosis		
2020	14	20.6
2021	37	54.4
2022	17	25.0
Clinical stage		
Stage II	40	58.8
Stage III	28	41.2
Histopathological		
NST	51	75.0
Non-NST	17	25.0
History of hormonal contraception		
No	43	63, 2
Yes	25	36.8
Molecular subtype		
Luminal A	6	8.8
Luminal B HER2 negative	10	14.7
Luminal B HER2 positive	16	23.5
HER2 type	27	39.7
TNBC	9	13.2
Degree of differentiation		
Grade I	3	4.4
Grade II	45	66.2
Grade III	20	29.4
LN metastases		
No	12	17.6
Yes	56	82.4

Table 2. Relationship between molecular subtypes and overall survival (OS) and disease-free survival (DFS) in breast cancer patients at Dr. M. Djamil General Hospital Padang.

Variable	OS			DFS		
	HR	95% CI	Sig.	HR	95% CI	Sig.
Molecular subtype						
Luminal A	1					
Luminal B HER2 negative	0.78	0.04 – 13.73	0.869	0,61	0,03 – 10,98	0,738
Luminal B HER2 positive	0.19	0.01 – 3.66	0.276	0,49	0,04 – 5,902	0,576
HER2 type	0.59	0.06 – 6.20	0.661	1,27	0,13 – 12,74	0,839
TNBC	3.30	0.34 – 32.44	0.305	6,27	0,56 – 66,94	0,129
Degrees of differentiation						
Grade 1 & II	1					
Grade III	0.53	1.73 – 1.62	0.264	0.91	0.37 – 2.24	0.843
LN metastases						
No	1					
Yes	7.94	0.81 – 78.2	0.076	10.20	1.03 – 101.1	0.047

Table 2 shows that the dominant variable affecting overall survival in breast cancer patients at Dr. M. Djamil General Hospital Padang is an LN metastatic variable. Patients with lymph node metastases were 7.94 times more likely to experience an event (death) than patients with no lymph node metastases after controlling for molecular subtype and degree of differentiation (HR=7.94 95% CI: 0.91–78, 2). Furthermore, the dominant variable influencing disease-free survival in breast cancer patients at Dr. M. Djamil Padang is an LN metastatic variable. Patients with lymph node metastases were 10.2 times more likely to experience an event (recurrence) than patients with no lymph node metastases after controlling for variable molecular subtype and degree of differentiation (HR=10.2 95% CI: 1.03–101, 1).

4. Discussion

In this study, it was found that the dominant variable that affected overall survival and disease-free survival in breast cancer patients at Dr. M. Djamil Padang is an LN metastatic. Patients with lymph node metastases are 7.94 times more likely to die within 3 years and 10.2 times more likely to relapse within 3 years compared to patients without lymph node metastases. These results were supported by previous studies, which stated that LN eradication could reduce the incidence of distant recurrence and death in patients. Other studies have also stated that regional recurrence in lymph nodes is associated with worse DFS and OS. LN is an inhibitor of the spread of cancer cells to more distant organs.[12-16]

However, in the presence of tumor cell metastases in the LN, this effect will reverse, where the LN will become a source of tumor cell spread along the LN drainage channel, thus allowing the systemic spread of tumor cells. This is what causes the high rate of recurrence and death in patients regardless of the role of molecular subtype and also tumor grading. Different results were found in other studies where it was stated that p53 and ER status had a more role in influencing the death of breast cancer patients compared to the number of lymph nodes that experienced metastases.

p53 mutations are not only associated with resistance to therapy in the primary tumor but are also associated with poorer survival in TNBC (Triple-Negative Breast Cancer) patients.[17-20]

5. Conclusion

Lymph node metastases are the factors most associated with survival (overall survival and disease-free survival) of breast cancer patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

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