The Relationship between Recurrence Rate and Molecular Subtypes of Breast Cancer in Locally Advance Breast Cancer (LABC) Post Mastectomy: Focus on Comparison of Luminal A and Luminal B

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A B S T R A C T

Background: Breast cancer is the highest prevalence of malignancy for women in Indonesia and important national health problem. Estimated 2 million women developed breast cancer in 2018 with a mortality rate of 14.1 in every 100,000 women. Regarding the relationship between subtypes and breast cancer recurrence Several studies on gene expression have shown several subtypes of breast cancer, including the two most important subtypes, estrogen receptor (ER) positive (Luminal A and Luminal B) and ER negative (Triple negative and Her2 positive). Based on the explanation above, currently there is no data in Soetomo Hospital that discusses the role of breast cancer subtypes as a prognostic factor in determining the recurrence rate in locally advanced breast cancer. **Methods:** The research design is an associative test using a retrospective cohort observational analytical study design, associating the relationship between tumor subtypes with recurrence in locally advanced breast cancer patients after mastectomy and has received additional therapy according to standard procedures at Dr. Soetomo Surabaya This study used secondary data from the medical records of the Oncology Polyclinic, RSUD Dr. Soetomo Surabaya from 2014 to 2019. **Results:** The research subjects who have been selected according to inclusion criteria are 214 people, with the proportion in the population of luminal A and luminal B subtypes of 107 people each. Based on this study, it was found that the subtype was positively correlated with recurrence in LABC patients who had undergone mastectomy with a significance value of $p = 0.000$ ($p < 0.05$; 99% CI). **Conclusion:** There is a relationship between the recurrence rate and the molecular subtype of breast cancer in locally advanced breast cancer (LABC) patients after mastectomy at Dr Soetomo Hospital.

1. Introduction

Breast cancer is the highest prevalence of malignancy for women in Indonesia and important national health problem. Estimated 2 million women developed breast cancer in 2018 with a mortality rate of 14.1 in every 100,000 women.[1,2,3] Regarding the relationship between subtypes and breast cancer recurrence Several studies on gene expression have shown several subtypes of breast cancer, including the two most important subtypes, Estrogen Receptor (ER) positive (Luminal A and Luminal B) and ER negative (Triple negative and Her2 positive). Based on the explanation above, currently there is no data in Soetomo Hospital that discusses the role of breast cancer subtypes as a prognostic factor in determining the recurrence rate in locally advanced breast cancer.[2,4,5]

Cancer recurrence was defined as the return of cancer after treatment and after a time during which the cancer could not be detected. In a previous study it was reported that 40% of breast cancer patients had postoperative recurrence. Clinical and histopathological factors have been investigated to influence breast cancer risk. Clinical factors include age, tumor location, clinical stage, clinical tumor size, nodal status, adjuvant systemic therapy, operator, and hospital type. While the histological factors are the results of histopathological examination of tumors

such as tumor size, tumor subtype and lymph node status.[2,6] In Chung et al's study, it was found that age, tumor size, lymph node status, histopathological gradation, and hormonal receptors had an effect on survival and recurrence rates. In a bivariate study conducted in 2015 and at Dr. Soetomo proved that only tumor size, hormonal status and positive angioinvasion affected recurrence, while age and histopathological gradation did not affect breast cancer recurrence rate. Meanwhile, in 2017 a study was also conducted on 240 breast cancer patients with retrospective data from 2011-2016 and it was proven that the status of the KGB gland and hormonal status were not predictive factors of distant recurrence.[7,8,9]

2. Methods

The research design is associative test using retrospective cohort observational analytic study design, associating the relationship between tumor subtypes and recurrence in locally advanced breast cancer patients after mastectomy and has received additional therapy according to standard procedures at Dr. Soetomo hospital, Surabaya. This study used secondary data from the medical records of the Oncology Polyclinic in 2014 to 2019 who was diagnosed with locally advanced breast cancer, had undergone a mastectomy and had received additional therapy according to standard procedures.

Operational definitions used in this study are as follows; locally advanced breast cancer (LABC) or locally advanced breast cancer with characteristics of skin ulcers, tumors attached to the chest wall, satellite nodules, palpable supraclavicular lymph node enlargement or stage IIIa IIIA breast cancer (T0N2M0, T1N2M0, T2N2M0, T3N1M0 , T3N2M0) and IIIb (T4N0M0, T4N1M0, T4N2M0) obtained from physical examination (tumor size was calculated using a caliper) and radiological records. Definitive therapy includes surgical procedure, chemotherapy, x-ray therapy, hormone therapy according to the stage of breast cancer based on PERABOI 2010 protocol.

3. Results

The study assessed the recurrence rate with molecular subtypes of breast cancer in post-mastectomy locally advanced breast cancer (LABC) patients looking at clinical pathological factors, operators and adjunctive therapy after mastectomy on the occurrence of locoregional and distant recurrence. From the research subjects, there were 107 Luminal A subtypes (50%) and 107 Luminal B subtypes (50%). The most histopathological types were infiltrating ductal carcinoma of NOS as many as 185 people (86.4%), infiltrating lobular carcinoma as many as 22 people (10.7%), metaplastic carcinoma as many as 6 people (2.8%) and mucinous carcinoma as many as 1 person (0.1%).

Table 1. Characteristics of research subjects

	Characteristic	Frequency (%)
Subtype	Luminal A	107 (50 %)
	Luminal B	107 (50 %)
Histopathology	IDC	185 (86,4%)
	ILC	22 (10,7%)
	Metaplastic carcinoma	6 (2.8%)
	Mucinous carcinoma	1 (0.1%)
Lymphnodes	Negative	99 (46,3%)
	Positive	115 (53,7%)
Angioinvasion	Negative	128 (59,8%)
	Positive	86 (40,2%)
Local Recurrence	Local	52 (32,5%)

	Regional	20 (12,5%)
	Distant Metastases	88 (55%)
Location of distant metastases	Bone	24 (25%)
	Brain	5 (5,2%)
	Lung	49 (51%)
	Liver	18 (18,8%)

In this study, the patients were grouped based on Luminal A and Luminal B. Based on the results of data analysis, 28 people with luminal A and 14 with luminal B. Age less than 40 years with luminal A was 79 people and 93 people with luminal B. As many as 69 people with luminal A and 73 people with luminal B were performed surgical procedures. Of the 14 surgical procedures, eight of them were luminal A. In lymphnodes involvement, out of 214 people only 115 involved the lymphnode and 61 people (53%) were luminal B.

Based on statistical analysis, it was found that the subtype was positively correlated with recurrence in LABC patients who had undergone mastectomy with a significance value of p= 0.000 (p<0.05; 99% CI).

Table 2. Characteristic analysis based on subtype

Characteristic		Subtype		p-value	OR
		Luminal A (N=107)	Luminal B (N=107)		
Age	≤ 40 y.o	28 (66.7%)	14 (33.3%)	0.016	2.354
	> 40 y.o	79 (45.9%)	93 (54.1%)		
Operator	By fellowship student	69 (48.6%)	73 (51.4%)	0.792	-
	Outside Soetomo Hospital	30 (51.7%)	28 (48.3%)		
	By surgeon	8 (57.1%)	6 (42.9%)		
Lymphnodes Involvement	Yes	54 (47%)	61 (53%)	0.337	1.302
	No	53 (53.5%)	46 (46.5%)		
Angioinvasion	Yes	45 (52.3%)	41 (47.7%)	0.577	0.856
	No	62 (48.4%)	66 (51.6%)		

4. Discussion

The research result the most frequent age was >40 years as many as 172 subjects (80.4%) and age <40 years as many as 42 subjects (19.6%). Breast cancer cases are reinforced by data that the most breast cancer age group is 30-40 years old and the average age is 48.8 years. The same result also reported in a study by Tovar (2014) in Spain, the median age was 50 years. This is in accordance with age as a risk factor for breast cancer cases, reinforced by data that 78% of breast cancers occur in patients aged over 50 years and only 6% in patients younger than 40 years. This is in accordance with the findings in a study by Anwar et al., who stated that there were more breast cancers with the luminal type (750) compared to the non-luminal type (554).[10-12]

The results of this study based on the subtype category in breast cancer were divided into two groups, luminal A and luminal B subtypes, each of which consisted of 107 people. In this study, the recurrence rate for luminal B was 58.1% (93 subjects) and luminal A was 41.9% (67 subjects). In a 2016 study, Li reported that the luminal B subtype is a very common type, accounting for approximately 40% of all breast cancer subtypes. In this study, it was found that 48.1% of patients with recurrence and metastasis had one of the luminal B subtypes. This is in accordance with data in Zhi-Hua Li (2016) that luminal type B is the type that

has the most recurrence rates in breast cancer. Luminal B is reported to have low expression of hormone receptors, high expression of cell proliferation, and higher grading than luminal type A.[13-15]

In addition, there is a gene HER-2 (Human Epidermal Growth Factor Receptor-2) that plays a role in breast cancer recurrence at a high degree higher. This is because at a higher degree of differentiation there is a faster progression of gene mutations. The higher degree of differentiation is influenced by the HER-2 gene because it is a gene that triggers cell growth and proliferation. At a high degree of differentiation, the HER-2 gene is usually positive, this causes an increased risk of recurrence.[16-19]

Recurrence is also caused by mutations in genes that regulate normal cell regulation in breast tissue because their balance is disturbed, these genes are DNA repair or BCL2, apoptotic regulatory genes and tumor suppressor inhibitory genes. This study has several limitations such as not observing the other factors such as comorbidities, Vit levels. D, With these limitations, further research is needed to be able to do further research with the identification of risk factors that are more diverse and broad and a larger number of samples to be able to further examine the recurrence rate of breast cancer patients after mastectomy.[20-25]

5. Conclusion

There is a relationship between the recurrence rate and the molecular subtype of breast cancer in locally advanced breast cancer (LABC) patients after mastectomy at Dr Soetomo Hospital.

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