



The Relationship between Recurrence Rate and Molecular Subtypes of Breast Cancer in Patients with Locally Advance Breast Cancer (LABC) Post Mastectomy at RSUD Dr. Soetomo (Focus on Comparison of Luminal A and Luminal B)

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ABSTRACT

Background: Breast cancer is the highest prevalence of malignancy for women in Indonesia and important national health problem. 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).

Method: 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, the authors 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: According to this study, 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.

KEYWORD: breast cancer, Luminal A, Luminal B, *locally advanced breast cancer* (LABC), recurrence

INTRODUCTION

Breast cancer is a malignant tumor that arises from breast cells. Malignancy can arise from various breast tissues, ranging from the ductus to the breasts and glands that produce milk to connective tissue and lymph breast. Breast malignancy is a disease caused by various factors risk factor. There are risk factors that cause breast cancer cannot display such as gender, age, gene mutation (BRCA1, BRCA2, ATM, P53), family history, history of malignancy, benign tumor, to menopausal status. But apart from these factors, there are other risk factors that can still see such as activity, obesity, pregnancy, breastfeeding, therapy hormones, contraception, cigarettes and alcohol, use of bras, implants to diet and vitamins.

Regarding the association of subtypes with breast cancer recurrence. Several studies on gene expression indicate several subtypes of cancer breast, includes the two most important subtypes, namely Estrogen Receptor (ER) positive (Luminal A and Luminal B) and ER negative (Triple negative and Her2 positive). Several of these subtypes provide different prognoses and several options. 60% of breast cancer cases are luminal type. Therefore, in this study we aimed to determine the relationship between the recurrence rate and the molecular subtype breast cancer in locally advanced breast cancer (LABC) patients after mastectomy at Dr. Hospital. Soetomo (focus on the comparison of Luminal A and Luminal B)

MATERIAL AND METHOD

Study participants

The research design is associative test using a 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. Hospital. Soetomo Surabaya This study used secondary data from the medical records of the Oncology Polyclinic, RSUD Dr. Soetomo Surabaya in 2014 to 2019 who was diagnosed with locally advanced breast cancer who had undergone a mastectomy and had received additional therapy according to standard procedures.

Breast cancer staging

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 were complete in the medical record.

Breast cancer therapy

Definitive therapies used in this study were surgery (MRM, Radical Mastectomy, BCT), chemotherapy, radiation, hormones according to the stage of breast cancer based on the 2010 PERABOI protocol, and complete records in the medical record both the type of action, the operator and the type of chemotherapy regimen and hormonal therapy.

Neoadjuvant chemotherapy (NAC) was a treatment given before surgery for the treatment of breast cancer. Mastectomy is a surgery to remove all breast tissue on the chest wall. Disease free interval is the recorded time between the date of surgical therapy for breast cancer (thus no clinical finding of breast cancer) until confirmed signs and symptoms of local, regional recurrence or remote as evidenced by triple diagnoses recorded in the medical record. Recurrence is defined as the incidence of post-mastectomy recurrence that occurred at least the first 6 months after surgery and had received standard adjunctive therapy (chemotherapy, hormonal therapy and radiotherapy), was recorded from medical record.

Breast cancer subtype

Tumor subtype was determined based on post-mastectomy IHC examination recorded on the examination sheet by an Anatomical Pathologist, in the form of: Luminal A: If ER and, or PR is positive, HER-2 is negative and Ki-67 is low (<20%). Luminal B: ER positive, HER-2 negative and at least 1 of Ki67 “high” (≥20%) PR negative or low. Her2 Neu: HER-2 positive (non-luminal) HER-2 is overexpressed or amplified ER and PR is absent, any Ki-67. Triple Negative: ER and PR absent, HER-2 negative, with Ki-67.

RESULT**Subject characteristics**

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%). The characteristic of the study participants is shown in Table 1.

Table 1. The Characteristics of Research Subjects

	Characteristic	Frequency (%)
Subtype	Luminal A	107 (50 %)
	Luminal B	107 (50 %)
Histopathology	IDC	185 (86,4%)
	ILC	22 (10,7%)
	<i>Metaplastic carcinoma</i>	6 (2.8%)
	<i>Mucinous carcinoma</i>	1 (0.1%)
Lymphnode	<i>Negative</i>	99 (46,3%)
	<i>Positive</i>	115 (53,7%)
Angioinvasions	<i>Negative</i>	128 (59,8%)
	<i>Positive</i>	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%)

Association between subtypes and breast cancer subtype

In this study, the authors grouping the research subjects 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. Surgery performed by surgery resident as many as 69 people with luminal A and 73 people with luminal B. Of the 14 surgeries performed by seniors, 8 of them were luminal A. In lymphnodes involvement, out of 214 people only 115 involved the lymphnode and 61 people (53%) were luminal B. of 214 people only 86 had angioinvasion and 45 people were luminal A.

The author conducted a significance test with Chi Square to see the correlation between subtypes and recurrence. 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).

Tabel 2. Characteristic Analysis by Subtype

Characteristic	Subtype		<i>p</i> -value	OR	
	Luminal A	Luminal B			
	(N=107)	(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	Resident	69 (48.6%)	73 (51.4%)	0.792	-
	Outside Soetomo Hospital	30 (51.7%)	28 (48.3%)		
	Senior	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%)		

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).

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. 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. In addition, 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.

CONCLUSSION

The study concluded that 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.

Abbreviations

ER: Estrogen Receptor

PR: Progesterone Receptor

POSA: Poli Onkologi Satu Atap

LABC: Locally Advanced Breast Cancer

HR: Her-2 Receptor

EGFR: Epidermal Growth Factor Receptor

DCIS: Ductal Carcinoma In Situ

LCIS: Lobular Carcinoma In Situ

Conflicts of Interest:

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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