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Histopathological Aspects as Predictor of Recurrency of Locally Advanced Breast Cancer

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Abstract

The histopathological aspect of breast cancer has been established as one of the important prognostic factors of recurrence. This study aimed to determine whether histopathological examination can be used as a predictor of the incidence of recurrence in locally advanced breast cancer patients. This was a cohort retrospective observational study with a correlative analytical approach. Subjects of this study were breast cancer patients who have undergone mastectomy and/or received additional therapy at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, between January 2017 and September 2019. Data were collected through medical records and anatomical histopathology data. Subjects were divided based on their recurrency status. A total of 62 breast cancer patients were included in the study with 31 recurrent patients and 31 non-recurrent patients. A total of 29 patients in the recurrent group (93.5%) had lymphovascular invasion. Histopathology grading showed a difference in both groups, in which recurrent group patients were mostly (74.2%) in the high histopathological grade while 51.6% of samples in non-recurrent group were categorized as moderate histopathological grade. Complete histopathological margins were found in both recurrent and non-recurrent groups for 54.8% and 87.1% respectively. There is a correlation between histopathologic grading, lymphovascular invasion, and incision margin with the recurrence of a locally advanced stage breast cancer. It can be concluded that some histopathological aspects can be used as a predictor of recurrence in locally advanced breast cancer.

Keywords: Breast cancer, histopathology, recurrency

Introduction

Breast cancer is the fifth leading cause of cancer death in the world with 685,000 deaths annually.[1] The International Agency for Research on Cancer (IARC) based on the latest Global Burden of Cancer Study (GLOBOCAN) data in 2020, reported that the number of new cases diagnosed with breast cancer is 2.26 million (11.7%) cases of the total new cases of cancer diagnosed in the world.[2] Breast cancer in Indonesia also shows the same statistics as the world, ranking first with 65,858 new cases (30.8%) of all cancers in Indonesian women.[3]

Locally advanced breast carcinoma (LABC) is an advanced breast cancer that has not metastasized in other organs.[4] People with LABC have a high risk of experiencing recurrence of the disease and death caused by such recurrence and metastatic disease. Given its advanced presentation, LABC is associated with poor survival. The median survival of LABC across previous studies ranged between 28 and 66 months, and the five-year overall survival (OS) is reported to be between 40% and 75%. Disease-free survival (DFS) is reported to be around five-year locoregional recurrence rate (LRR) is 7–9%. Based on the 2018 National Cancer Database epidemiological data, the 15-year overall survival rate for stage IIIA breast cancer is 50% and stage

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IIIB is 23%.[5,6]

Recurrency is a condition of disease symptoms that reappear after previously being treated and declared cured, so there has to be a disease-free interval. Predictors of recurrence in breast cancer include age, clinical stage, lymph node involvement, histopathology, tumor grading, and breast cancer subtypes. More than 50% of breast cancer cases diagnosed in Indonesia are advanced stage.[7]

Breast cancer recurrence is 7-11% of the total incidence of breast cancer in the last 10 years.[8] This incidence increases mortality from breast cancer. In previous studies, it was found that local recidivist patients had a 5-year survival rate of 44% if local recurrency occurred within 3 years of therapy. The 5-year survival rate will be better if local recidivist cases occur more than 3 years after the incident, which is 87%.[7] In another study, it was found that the percentage of patients with local recurrence that occurred less than 2 years from the initial therapy would experience distant metastasis as much as 92%, while the percentage of patients who had local recurrence with an interval of more than 5 years experienced metastatic as much as 22%[7]

Three known factors can be used as prognostic factors in cases of breast cancer, namely: tumor size, primary lymph node status, and histopathology gradings.[9] Histopathology aspects have been established as one of the important prognostic factors and are associated with the patient's long-term survival. Histopathological examination is a gold standard for breast cancer diagnosis. Traditional histopathology depends largely on the experiences of histopathological doctors, which is labour-intensive and error-prone. Thus, it is urgent to develop an automatic and reliable computer-aided system on histopathological images to help cancer diagnosis and prognosis. There are many studies in related problems, such as detecting cancer cells in the tissue, classifying and grading breast cancer histochemical scoring, mitotic nuclei analysis, and so on. [10] Failure of initial therapeutic response in high-grade carcinoma is higher than low-grade carcinoma. The frequency of recurrence in high-grade carcinoma is also higher.[11]

In individual studies that are large enough to make comparisons, borderline and malignant phyllodes tumors are more likely to recur than benign phyllodes tumors after local excision alone. For example, Treves and Sunderland reported that 15% (3/21), 44% (4/9), and 80% (4/5) of patients with benign, borderline, and malignant tumors, respectively, developed in-breast recurrences after local excisions. In Zurrida's series, 9% (10/107), 44% (4/9), and 33% (1/3) of benign, borderline, and malignant phyllodes patients developed in-breast recurrences. Due to the heterogeneous nature of breast cancer and the clinical course of primary breast cancer varies for each patient, the authors aim to examine the relationship between aspects of histopathology and recurrence in breast cancer.

Methods

This study is an observational retrospective study with a case-control study design which is then analyzed with correlative analysis. Sample size were calculated with WHO sample size determination in health studies as reference and 30 samples were determined to be the minimal number of samples needed in this study. Samples are collected using the purposive sampling method according to the inclusion criteria. The inclusion criteria were breast cancer patients who have had mastectomy and/or additional therapy by the standard procedures of the oncology surgery division of Dr. Hasan Sadikin Hospital Bandung, the patient must also have complete documentation in the medical record, including the histopathology test result to be included in this study from January 2017 to September 2019, and the patients were all those who had undergone first-line chemotherapy with a partial response. The exclusion criteria in this study were incomplete medical records from January 2017 to September 2019, the medical records not found or lost, and the samples were all those who had undergone first-line chemotherapy and did not have a partial response.

Subjects in this study are categorized into the recurrent and non-recurrent groups where the potential association of suspected risk factors is examined by comparing both groups within 2 years of observation. In this study, we do not focus on how long the patient's diagnosis of breast cancer before recurrent, we focus on the patient who underwent mastectomy and/or received additional therapy at RSUP Dr. Hasan Sadikin Bandung between January 2017 and September 2019 based on the recurrence status. This study has the risk that medical record data is lost during data collection. The research has received a letter of approval from the Health Research Ethics Committee of Dr. Hasan Sadikin

Table 1 Characteristics of Subjects

Characteristic		Total (n=62)
Age (years)	<45	17
	45–60	40
	>60	5
Stadium	III A	12
	III B	50
	III C	0

General Hospital Bandung with the Ethics Approval number LB.02.01/X.6.5/481/2022.

Results

Subjects' characteristics are displayed in Table 1. Sixty-two subjects were admitted in this study, and the patient's age, lymph vascular invasion, surgery report, and cancer stadium were documented. In this study, it was discovered that the majority of breast cancer patients are between the age of 45-60 years old (40 subjects). Cancer stadium IIIB is the most common cancer stadium found in the population.

The relationship between histopathological aspects and breast cancer recurrence is displayed in Table 2. It was found that lymph vascular invasion, histopathological grading, and incision margin correlate with the incidence of recurrence in locally advanced breast cancer patients (p values of 0.005, 0.037, and 0.005 respectively). As for the histopathological classification and immunohistochemistry, probability values greater than 0.05 (p>0.05) were obtained, indicating no remarkable relationship.

Discussion

Breast cancer recurrence is a growing problem where 7% to 11% of the total incidence of breast cancer has recurred in the last 10 years. Breast cancer recurrences also have poor survival

Table 2 Correlation between Histopathological Aspects and Cancer Recurrency

Histopathological Aspects		Group		Total	p	RR
		Recurrent	Non-recurrent			
Types of anatomical pathologies	Invasive	27 (48.2%)	29 (51.8%)	56 (100%)	0.671	0.72
	Non-invasive	4 (66.7%)	2 (33.3%)	6 (100%)		
Lymph vascular Invasion	Yes	29 (59.2%)	20 (40.8%)	49 (100%)	0.005	3.85
	No	2 (15.4%	11 (84.6%)	13 (100%)		
Immunohistochemistry	Triple Negative	4 (66.7%)	2 (33.3%)	6 (100%)	0.567	2.00
	Luminal A	2 (33.3%)	4 (66.7%)	6 (100%)		
	Her 2 Types	3 (50.0%)	3 (50.0%)	6 (100%)	0.999	1.50
	Luminal A	2 (33.3%)	4 (66.7%)	6 (100%)		
	Luminal B Her 2 Positive	7 (58.3%)	5 (41.7%)	12 (100%)	0.620	1.75
	Luminal A	2(33.3%)	4 (66.7%)	6 (100%)		
	Luminal B Her 2 Negative	15 (46.9%)	17 (53.1%)	32 (100%)	0.672	1.41
	Luminal A	2 (33.3%)	4 (66.7%)	6 (100%)		
Histopathology Grading	High	23 (60.5%)	15 (39.5%)	38 (100%)	0.037	1.82
	Moderate	8 (33.3%)	16 (66.7%)	24 (100%)		
	Low	0 (0%)	0 (0%)	0 (0%)		
Incision margin	Non-tumor-cell free	14 (77.8%)	4 (22.2%)	18 (100%)	0.005	2.01
	Tumor-cell free	17 (38.6%)	27 (61.4%)	44 (100%)		

rates. In previous studies, it was found that local recidivist patients had a survival rate of 44% in 5 years. If local recurrence occurs more than 3 years after a complete therapy is carried out, it will have a better 5-year survival rate. Many factors influence the recurrence of breast cancer. However, the relationship of factors with the occurrence of recurrence is still widely unstudied. Risk factors obtained from previous studies include cancer subtypes, histopathological grading, lymphovascular invasion, receptor hormone status, nodal status, tumor size, and tumor stage. Higher histopathology grading has a greater chance of recurrence.[7]

In a previous study, tumor size had a positive relation with the involvement of lymph nodes, and that locoregional recurrence rates increased significantly.[12] Slightly different from the research conducted by Cheng et al.,[13] annual hazard ratio figures for recurrence for the first time in ten years follow-up showed that patients with high histopathological grading had the highest recurrence rate in the first 5 years compared to other gradings. The difference in hazard ratio will be more dynamic in patients with advanced stages. Another research found that in 138 patients, histopathological grading is associated with tumor size and lymph node status, in tumors <1cm in diameter, high histopathological grading can significantly predict recurrence. The prognosis in tumors with a size of <1cm and negative lymph node status can be assessed by looking at their histopathological grading. In this study, 62 patients were divided into 2 groups, the group with patients who experienced breast cancer recurrence and the second group of patients who did not experience recurrence. As many as 50% of the study subjects experienced recurrences with the highest average recurrence occurring the first time between 6 months to 1 year after. This is likely due to the radicality of the operation not being achieved, the determination of the preoperative stage is not correct, and the operation time is not right.[14]

The histopathological grading used in this study is based on the histological classification system according to The Nottingham Combined Histologic Grade.[14,15] Grading histopathology is determined from the mitotic index, the formation of tubules, and nucleation. Histopathological assessment is divided into three groups, namely low, moderate, and high grades.[16] Statistical calculations carried out on 62 study subjects showed that there was a relationship between histopathological grading and the occurrence of recurrence in breast cancer at Dr. Hasan Sadikin General Hospital with the highest histopathological grading was high grade by 61.3%.

In this study, the histology type was grouped into 2 types, namely invasive and non-invasive where the most subjects were invasive types as many as 56 subjects (90.3%), while non-invasive types were 6 subjects (9.7%). This is in line with research by Makki et al.[17] in 2015 which showed that non-specific invasive types have a prevalence of 40-75%.

Patients with positive hormonal status had a longer disease-free survival and overall survival compared to the group of patients with negative hormonal status. In contrast, in this study from 62 samples, hormonal status was not associated with recurrence. Luminal B is the most common finding in this study which is a subtype of HER2-positive cancer with a worse prognosis compared to HER2-negative luminal B and luminal A.[17] Treatments for luminal B include chemotherapy, hormone therapy, and anti-HER2 if HER2 is positive. In line with previous studies, risk factors and intrinsic subtype types did not have a significant relationship. It is also known that breast cancer has different characteristics for each subtype. Regarding epidemiology, the luminal subtype of breast cancer is the most common and is related to exposure to endogenous hormones, while the non-luminal subtype of breast cancer is less common and is related to non-hormonal factors is more likely.[17] A previous study on subjects with T1a and T1b found that 10% of breast cancer patients with HER2-/Neu positive experienced recurrence with a ratio of 5.09 times ($p<0.001$) and experienced metastasis or distant recurrence of 7.81 times ($p<0.0001$) compared to breast cancer patients who had negative hormonal receptors. Patients with HER-2/Neu positive have a statistically significant rate for recurrence regardless of hormonal status and histopathological grading.[18] Whereas in the studies we conducted, immunohistochemistry was statistically not associated with recurrence (p 0.837). Immunohistochemistry test data are retrospective data that cannot be accounted for or this is an anomaly that we have not been able to explain. From the research of Cheng et al.,[13] the recurrence rate was highest in negative hormonal status at all stages of breast cancer. In negative hormonal status, the hazard ratio increases sharply and is statistically highest in the first 5 years after surgical therapy.

Positive angioinvasion suggests that the cancer is growing more aggressively. In this study, angioinvasion was significantly associated

with recurrence ($p<0.05$). Tumor angiogenesis is relevant as a prognostic factor first reported by counting the number of microvascularizations of tumors where it appears that the tumor has an area of high vascularization density.[18] Tumor angiogenesis assesses the prognosis of the presence or absence of blood vessels that stimulate tumor growth and metastasis.

In this study, the margins that are still not tumor-free were associated with the incidence of recurrence in breast cancer ($p<0.05$). In line with the meta-analysis conducted by Bundred et al.,[14] on 68 studies consisting of 112140 women, it was found that margins that are still not free of tumor cells were associated with increased recurrence in breast cancer. Involved or close pathological margins after breast-conserving surgery for early-stage, invasive breast cancer is associated with increased distant recurrence and local recurrence. Surgeons should aim to achieve a minimum clear margin of at least 1 mm.[19] Based on 33 studies (LR in 1,506 of 28,162) the odds of LR were associated with margin *status*, meta-analysis confirms that negative margins reduce the odds of LR however increasing the *distance* for defining negative margins is not significantly associated with reduced odds of LR, allowing for follow-up time.[20]

The limitation of this study is some medical records were not been recorded in the same format, it depends on who wrote on it, so there are differences in each research sample. From this study, it can be concluded that histopathological grading can be used as a predictor of the incidence of breast cancer recurrence. Histopathological classification examination cannot be used as a predictor of the incidence of breast cancer recurrence. Immunohistochemistry examination of breast cancer cannot be used as a predictor of the incidence of breast cancer recurrence. Examination of lymphovascular invasion can be used as a predictor of the incidence of breast cancer recurrence. The basic boundary of the tumor-free incision can be used as a predictor of the incidence of breast cancer recurrence.

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