



THE RELATIONSHIP HER2 OVEREXPRESSION AND SENTINEL LYMPH NODE AS A PREDICTOR FACTOR FOR EARLY-STAGE BREAST CANCER METASTASIS IN USU GENERAL HOSPITAL

Natanael Bonardo Sinaga¹, Dedy Hermansyah², Denny Rifsal Siregar²

¹Department of Surgery, Faculty of Medicine University of North Sumatera, Medan, Indonesia.

²Department of Surgery, Oncology Division, Faculty of Medicine University of North Sumatera, Medan, Indonesia.

ABSTRACT

Introduction: Breast cancer is a malignancy in breast tissue that can originate from the ductal epithelium or lobules. Axillary lymph node status has become one of the strongest prognostic factors in women with early stage breast cancer. Several studies have been conducted to evaluate the relationship of HER-2 with detection, metastasis, and prognosis of breast cancer. This study is aimed at evaluating overexpression of HER2 as a prognostic factor in breast cancer with sentinel lymph node metastases.

Methods: This is an analytic study with cross sectional research design.

Results: In this study, a sample of 51 people was obtained. Most types of breast cancer are invasive ductal carcinoma in 40 patients (78.4%), then invasive no other specific type in 7 patients (13.7%), then invasive lobular carcinoma and DCIS in 2 patients (3.9%). From the results of statistical tests found no relationship between overexpression of HER-2 with sentinel lymph node metastases ($p = 0.255$). Patients who had HER2 expression had a 1.477 times greater risk of having sentinel lymph node metastases compared to a group of patients with no HER2 expression.

Conclusion: There is no relationship between HER-2 overexpression with the occurrence of sentinel lymph node metastases.

Keywords: Breast cancer, HER2, Sentinel lymph node, Prognosis.

1. Introduction

Breast cancer is a malignancy in breast tissue that can originate from the ductal epithelium or lobules. Breast cancer is the most common cancer in women, with an incidence rate of 43.1 per 100,000 people. (Ghoncheh, Pournamdar, & Salehiniya, 2016). According to the Hospital Information System in 2010, the number of outpatients or inpatients in breast cancer reached 12,014 people (28.7%). The incidence of breast cancer in Indonesian women according to Globocan in 2012 was 40 per 100,000 population. (Ministry of Health, 2016)

Axillary lymph node status has become one of the strongest prognostic factors in women with early-stage breast cancer. (Schröder et al., 2018) Dissemination of lymph nodes (ALND) has long been used as a method to identify axillary lymph node metastases, and has now begun to be replaced with another more non-invasive method namely sentinel lymph node biopsy (SLNB). (Guiliano et al., 2017) Sentinel lymph node biopsy is a minimally invasive technique that can confirm the presence of regional lymph node metastases in cancer. (Nieweg, Uren, & Thompson, 2015) Sentinel lymph node biopsy can be done with a number of lymphatic mapping techniques using blue-dye, radiotracer or a combination of both. (Zahoor et al., 2017)

Human epidermal growth factor receptor type2 (HER-2) appears as a molecular biomarker in breast cancer, where 20-30% of primary breast tumors show overexpression of HER-2. (Ishikawa et al., 2014) HER-2 overexpression has shown a close correlation with poorer survival rates, both in breast cancer patients with positive or negative lymph nodes and thus being a prognostic factor and influencing therapeutic choices in breast cancer management. (English, Roque, & Santin, 2014) The researchers wanted to observe the overexpression of HER2 as a prognostic factor in breast cancer with sentinel lymph node metastases at the USU General Hospital.

2. Methods

This study took place from June 2016 until August 2019 at USU General Hospital. This is an analytic study with cross sectional research design. The population in this study were all breast cancer patients who came for treatment at the USU General Hospital. The sample was breast cancer patients who met the inclusion and exclusion criteria. Data were analyzed using chi square test.

3. Results

A total of 51 patients were included in this study. The mean age of sample was 49.39 years. In the study, many of sample have T2 tumor size with 44 patients (86.3%). Whereas based on the results of anatomic pathology examination, many of sample have grade 3, as many as 40 patients (78.4%). In the immunohistochemical examination, 15 HER-2 (+) were obtained (29.4%) and 36 HER-2 (-) (70.6%).

Table 1 and 2 showed characteristics of sample.

Table 1. Distribution of Subjects' Characteristics

Age	N	%
Age, (Mean±S.D)	49,39±8,511	
Sex	N	%
Female	51	100
Male	0	0
Breast Cancer Type	N	%
Ductal Carcinoma in situ (DCIS)	2	3,9
Invasive Ductal Carcinoma	40	78,4
Invasive Lobular Carcinoma	2	3,9
Invasive No other Specific type	7	13,7
Tumor Size	N	%
T1	7	13,7
T2	44	86,3
Grade	N	%
1	3	5,9
2	8	15,7
3	40	78,4
LVI	N	%
Positive (+)	25	49%
Negative (-)	26	51%
TIL	N	%
Severe	34	66,7
Mild	17	33,3

Table 2. Distribution of Subjects' Characteristics

Immunohistochemistry	n		%	
	(+)	(-)	(+)	(-)
Overexpression HER-2	15	36	29.4	70.6
Hormonal (ER(+/-)/PR(+/-)/HER-2 (+)	5	46	9.8	90.2
Hormonal (ER(+/-)/PR(+/-)/HER-2 (-)	25	26	49	51

Based on sentinel lymph node examination performed, there were 21 patients (41.2%) with positive sentinel lymph node metastases and 30 patients (58.8%) without sentinel lymph node metastasis.

Table 3. Sentinel Metastasis of Lymph Nodes

Sentinel Metastasis of Lymph Nodes	n	%
Positive	21	41,2
Negative	30	58,8

Statistical test results obtained p value = 0.255, it can be concluded that there is no relationship between overexpression of HER-2 with sentinel lymph node metastasis. From the analysis results also obtained PR value = 1.477, meaning that patients who have HER2 expression have a risk of 1.477 x greater to experience sentinel lymph node metastasis compared to groups of patients without HER2 expression.

Table 4. Relationship of HER-2 Overexpression to Sentinel lymph node metastases.

	Sentinel lymph node			PR	P value	
	+	-	Total			
HER-2 expression	+	8 (53.3%)	7 (46.7%)	15 (100%)	1,477	0,255
	-	13 (36,1%)	23 (63,9%)	36 (100%)		
Total	21 (41,2%)	30 (58,8%)	51 (100%)			

4. Discussion

Breast cancer, in addition to being the cancer most often found in women, is also cancer with a high mortality rate in the world, and also in Indonesia. Based on the 2018 GLOBOCAN, the incidence rate is 24.2% of the total 8.6 million new cases, and the mortality rate is 15% of the 4.2 million reported deaths. (Bray F. et al, 2018). This death rate is greatly influenced by lymph node metastasis, histological grade, tumor size, age, blood vessel invasion, and breast cancer subtypes. (Bland et al, 2018)

Axillary lymph node status has become one of the strongest prognostic factors in women with early-stage breast cancer. (Schröder et al., 2018) Dissemination of lymph nodes (ALND) has long been used as a method to identify axillary lymph node metastases, and has now begun to be replaced by another more non-invasive method namely sentinel lymph node biopsy (SLNB). (Guiliano et al., 2017) ALND often causes controversy due to an increase in morbidity in patients who apparently do not experience lymph node metastases. (Tanis, Nieweg, Olmos, Rutgers, & Kroon, 2010) Eighty percent of women with axillary dissection experience complications such as decreased mobility, seroma formation, paresthesia or lymphedema, ipsilateral pain with axillary dissection, where these complications can be difficult to treat and affect quality of life patient significantly. (D'Angelo-Donovan, Dickson-Witmer, & Petrelli, 2012) Axillary lymph nodes are the main area of lymphatic drainage from all areas of the breast. The involvement of axillary lymph node in breast cancer has been recognized as the most powerful factor for recurrence, and life expectancy, together with axillary lymph node involvement, large tumor size also decreases life expectancy. (Malter, 2018). Correlation of lymph node metastases is even considered a more credible prognostic and predictive factor compared to breast cancer subtypes. (Bland et al, 2018)

Sentinel lymph node biopsy is a minimally invasive technique that can confirm the presence of regional lymph node metastases in cancer. (Nieweg, Uren, & Thompson, 2015) Sentinel lymph node biopsy can be done with a number of lymphatic mapping techniques using blue-dye, radiotracer or a combination of both. (Zahoor et al., 2017) In developing countries, sentinel lymph node biopsies are often performed using a single blue dye method, at a more affordable cost compared to using radiotracers or a combination of both. (Abass, Gismalla, Alsheikh, & Elhassan, 2018) Although there is no standard SLNB mapping technique, the combination method is believed to be better and is the technique most often used for mapping of lymph node sentinel in breast cancer. (Bland et al., 2018) For this reason, other predictor factors are needed to help identify sentinel lymph nodes using methylene blue

From the immunohistochemical examination, it was found that HER-2 was positive in 15 patients (29.4%), Hormonal-HER2 (+) by 5 people (9.8%) and Hormonal Receptor by 25 people (49%). In this study, the p value was 0.255. This shows that there is no relationship between overexpression of HER-2 with sentinel clear gland metastases. This is in line with other studies, where HER-2, has no correlation with lymph node metastasis, only lymphovascular invasion has a positive correlation with lymph node metastasis. (Yenidunya, Bayrak, & Haltas, 2011). In another study in Turkey, it was also found that HER-2 had no relationship with sentinel lymph node metastases (p 0.309). In this study 151 cases were reported, and researchers wanted to look for predictors for the occurrence of lymph node metastases in the axilla. It was found that tumor size and the presence of LVI (lymphovascular invasion) had the strongest association with the occurrence of sentinel lymph node metastases.

The results of this study are not consistent with studies conducted by Zheng-Jun and Yue-Yu reported that overexpression of HER-2 is not only strongly related to the number of lymph nodes undergoing metastasis, but also to a worse histological grade. The results of this study are also not in accordance with studies conducted by Zhen-Jun Tong and Ning-Yao Shi. Their study even mentioned that overexpression of HER-2 can be used as a biological sign to predict lymph node metastases because HER-2 is suspected to increase with the proliferation, migration and metastasis of breast cancer. HER-2 has also been shown to correlate with increased expression of Vascular Endothelial Growth Factor (VEGF-C) in breast cancer, indicating that HER-2 is a mediator of lymph node metastases. Nathanson et al. Also concluded that data with tumors with positive HER-2 had a 0.5 times greater risk of sentinel lymph node metastasis compared to tumors without these markers. (Nathanson et al., 2005)

There are several other factors that can predict the occurrence of lymph node metastases, including tumor size, histological grading, tumor location laterally and retroareolar, lymphovascular invasion. (Malter, 2018) In addition, multifocal lesions, and old age are also predictors of sentinel lymph node metastasis. (Viale et al., 2005).

In this study, there were 5 patients with Hormonal receptor (+) / HER2 (+). If associated with sentinel lymph node metastasis, a p value of 0.955 (greater than the p-value in the HER-2 expression group) was obtained. This shows that the presence of hormonal receptors can reduce the incidence of lymph node metastases. This is supported by other studies, such as in Ugras et al., Groups with hormonal receptors (+) have a lower risk than hormonal receptor (-) groups for lymph node involvement (OR 1.6 vs. OR 2.0). (Ugras et al. , 2014).

In this study, there was 1 patient who had metastases in the axilla lymph node, but not from a group of patients with sentinel lymph nodes. In other words, there was a false negative in this patient. There are several factors that cause a sentinel to become false negative. This was stated by Kataria et al., 4 possible causes of a false negative in a sentinel. (1) actual lymphatic pathways are retained (by tumor emboli, fibrosis from previous surgery or radiotherapy, or inflammation), and alternative routes are open to drain blue dye to uninhibited lymph node. (2) there are 2 lymphatic pathways for certain tumors, of which 1 path to the superficial lymph node in the lateral pectoral region, and the other pathway to the retropectoral or interpectoral region, which is not taken as a sentinel sample. (3) in some cases, the focus of metastasis in lymph node is very small (micrometastasis; 0.2-2mm) or isolated tumor cells (<0.2mm)

which are categorized by a pathologist as a sentinel negative. (4) Sentinel biopsy technique is carried out by less experienced surgeons. (Kataria K, 2016)

5. Conclusion

Based on this research, the most common type of cancer is invasive ductal carcinoma. Histologically, most breast cancer was found in grade 3 and T2 tumor size. From the immunohistochemical examination and sentinel biopsy examination, it was found that there was no correlation between HER-2 overexpression and sentinel lymph node metastasis.

6. Sugestion

- Further research is needed with a larger sample regarding the relationship of HER-2 with sentinel lymph node metastases.
- Further research is needed on other factors that can show as other predictors of sentinel lymph node metastasis.
- Prospective research is needed on this case to get more accurate results.

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