

DESCRIPTION OF CLINICOPATHOLOGY PATIENTS WITH INVASIVE BREAST CARCINOMA NO SPECIAL TYPE (NST) THAT HAVE NOT BEEN AND HAS NOT BEEN EXPERIENCED LYMPHOVASCULAR IN RS. H. ADAM MALIK MEDAN IN 2018

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ABSTRACT

Background: Breast carcinoma is the most common type of cancer affecting women. Breast cancer is cancer that can metastasize to other organs such as bones, liver, lungs, and brain, most of which cause this disease can not be treated. In breast cancer, LVI has become one of the factors for disease-free survival as well as overall survival.

Objective: to know the description of clinicopathology (age, grading, tumor size, the involvement of lymph nodes, and stage) patients with breast carcinoma *Invasive No special type (NST)* who have and have not experienced *Lymphovascular Invasion*.

Material and Methods: This research is a descriptive study with a cross-sectional approach of 54 NST patients. Data on the clinicopathological characteristics were obtained from the patient's medical records. Then, a slide review is conducted. The results of the data analysis are presented in the form of a frequency table.

Results: Based on age, LVI positive breast cancer was most vulnerable at the age of 35-49 years 4 people, LVI tumor size was highest at ≤ 5 cm in size of 3 people, LVI positive with no involvement of 5 KGB people, at LVI positive stage most at stage II that is equal to 2 people, and the most positive grade is LVI in grade 2 which is equal to 3 people.

Conclusion: LVI is one of the prognostic factors in patients with invasive breast cancer no special type (NST) and should be reported in the diagnosis of anatomic pathology

Keywords: Invasive breast cancer *no special type (NST)* and *Lymphovascular Invasion (LVI)*

1. Introduction

Breast carcinoma is the most common type of cancer affecting women. More than 1 million women worldwide suffer from this breast carcinoma, and approximately 400,000 of them died.¹ According to 2012 Global Burden Cancer (Globocan) which is the International Agency for Research on Cancer (IARC) it is known that there were 37.1% of new cancer cases, 26.4% of deaths due to cancer. Breast cancer is most commonly diagnosed in women (24.2%, which is about one in 4 new cancer cases diagnosed in women worldwide). Breast cancer is the leading cause of death in women (15.0%)² In the United States in 2017, an estimated 30% of all new cancer cases (252,710) in women were breast cancer. (1,2,3)

In Indonesia, almost 70% of cancer patients are found at an advanced stage, and most breast cancer patients who come to the hospital/doctor, (> 50%) are in an advanced stage. Every year 100 new cases occur among 100,000 residents. Increasing cigarette users, alcohol consumption, obesity or obesity and lack of physical/sports activities also play a role in increasing the incidence of cancer in Indonesia. Based on age group, the older the age the risk of getting cancer is higher, reaching its peak in the age group 35-44 years, then slowly the risk will decrease and there will be an increase again at the age of > 65 years. According to sex, the risk of cancer is higher in women than in men (4)

LVI is assessed in carcinoma tissue in parts stained by hematoxylin and eosin (H&E), this is defined as carcinoma cells that are in endothelial confined spaces (lymphatics or blood vessels). So LVI includes lymphatic and blood vessel invasion. Routine assessment of LVI becomes part of the reporting of breast cancer pathology. (9)

Based on its histological type, most breast carcinomas (80%) are invasive ductal carcinomas originating from glandular epithelial cells from the Terminal Duct Lobular Unit (TDLU). Prognosis factors for breast carcinoma are divided into epidemiological, anatomical and cellular prognosis factors as well as

molecular genetics. These prognostic factors include stage, histological degree, hormonal status, Her-2 status (Human Epidermal Growth Factor Receptor-2) and cell proliferation rate. (7)

Staging, including clinical and pathological stages, is an important clinical prognosis factor for breast carcinoma. Clinical status is determined based on TNM classification which includes the size of the primary tumor (T), lymph node status (N) and distant metastasis (M). The pathological stage is determined after examination of pathology, including the size of the primary tumor (T), lymph node status after pathology (N) and distant metastases (M). The TNM system has been accepted by UICC (The International Union Against Cancer) and AJCC (The American Joint Committee on Cancer) and is determined to be stages I, II, III and IV. (10)

2. Material and Methods

In this study, examined 54 cases of Invasive No Carcinoma breast carcinoma No Special Type (NST) who underwent surgery at RSUP.H. Adam Malik Medan in 2018 who was diagnosed histopathologically with the coloration of Hematoxylin-Eosin (HE). The following are the results of the research obtained. This research is a type of descriptive study that aims to find out the description of the clinicopathology of patients with breast carcinoma type Invasive No Special Type (NST) who have and have not undergone Lymphovascular Invasion with a cross-sectional approach (cross-sectional) each sample in this study is only observed once and once

3. Results

In this study, obtained 54 people with invasive breast carcinoma No Special Type (NST) underwent surgery at RSUP.H. Adam Malik Medan in 2018 who was diagnosed histopathologically with the coloration of Hematoxylin-Eosin (HE).

The following are the results of the research obtained. In this study based on the age distribution of people with breast carcinoma Invasive No Special Type (NST) the most age was found in the age group of 35-49 years, 25 patients (46.3%), and the least encountered at age <35 years that is as many as 2 people (3.7%), aged 50-64 years that is as many as 24 people (44.4%), the rest found at age ≥ 65 years that is as many as 3 people (5.6 %) (Table 1).

Table 1. Distribution of patients with invasive breast carcinoma No Special Type (NST) based on the age group of patients

The age group of sufferers (years)	Total (n)	Percentage (%)
<35 Age	2	3.7
35-49 Age	25	46.3
50-64 Age	24	44.4
≥ 65 Age	3	5.6
Total	54	100

In this study, it is known that the most tumor size of patients is tumor size $0.1 - \leq 2$ cm, which is 33 patients (61.1%) and the least is tumor size $> 2-5$ cm, which is 7 patients (13%), while the remaining tumor size > 5 cm by 14 people (25.9%). Involvement of lymph nodes in this study were 34 patients (63%), there was no lymph node involvement and there was lymph node involvement as many as 20 sufferers

(37%). Most of the stadiums in this study were stadium I with 20 patients (42.6%) and no grade IV was found in the remaining grade II with 21 patients (38.9%), and stage III with 10 patients (18, 5%) (Table 2).

Table 2. Distribution of patients with invasive breast carcinoma No Special Type (NST) based on Clinipatology

Clinipatology	Total (n)	Percentage (%)
Tumor size (T)		
< 0,1 cm - 2 cm	33	61.1
>2 cm - 5 cm	7	13.0
> 5 cm	14	25.9
Lymph involvement (N)		
Negative	34	63.0
Positive	20	37.0
Stadium		
Stadium I	23	42.6
Stadium II	21	38.9
Stadium III	10	18.5
Stadium IV	0	0.00
Total	54	100

In this study, it was known that the highest grade of histology was grade 2 with 24 patients (44.4%) and the least was grade 3 with 11 patients (20.4%), with the remaining grade 1 with 19 patients (35.2%), (Table 3).

Tabel 3. Distribution of Invasive No Special Type (NST) breast carcinoma based on Histological Grade

<i>Grade Histology</i>	Total (n)	Percentage (%)
Grade 1	19	35.2
Grade 2	24	44.4
Grade 3	11	20.4
Total	54	100

In this study based on patient distribution, it was found that the highest number was Lymphovascular Invasion (LVI) which was negative as many as 49 people sufferers (90.7%) while there were found positive Lymphovascular Invasion (LVI) as many as 5 people sufferers (9.3%) (Table 4).

Tabel 4. Distribution of Invasive No Special Type (NST) breast carcinoma based on Lymphovascular Invasion (LVI)

<i>Lymphovascular Invasion (LVI)</i>	Total (n)	Percentage (%)
Positive <i>LVI</i>	49	90.7
Negative <i>LVI</i>	5	9.3
Total	54	100

Of the 49 patients who did not experience Lymphovascular Invasion (LVI), 21 patients (42.9%) aged 35-49 years, 23 patients (46.9%) aged 50-64 years, 3 patients (6.1 %) aged ≥ 65 years and 2 patients (4.1%) aged <35 years. From 5 sufferers experiencing Lymphovascular Invasion (LVI), 4 sufferers aged 35-49 years old and 1 sufferer aged 50-64 years (Table 5).

Tabel 5. Frequency Distribution of Lymphovascular Invasion (LVI) in breast carcinoma Invasive No Special Type (NST) to tumor Age

<i>Lymphovascular Invasion (LVI)</i>	Age								Total	
	<35 Age		35-49 Age		50-64 Age		≥ 65 Age		N	%
	n	%	n	%	N	%	n	%		
Positive LVI	2	4,1	21	42,9	23	46,9	3	6,1	49	100,0
Negative LVI	0	0	4	80	1	20	0	0	5	100,0
Total	2		25		24		3		54	

Of the 49 patients who did not experience Lymphovascular Invasion (LVI), 27 patients (55.1%) had tumor size > 0.1 - 2cm, 12 patients (24.5%) tumor size > 2-5cm and 10 patients (20.4%) tumor size > 5cm. From 5 sufferers experience Lymphovascular Invasion (LVI), as many as 2 sufferers with tumor size > 0.1-2cm, and 3 sufferers tumor size > 2-5cm. (Table 6).

Tabel 6. Frequency Distribution of Lymphovascular Invasion (LVI) in breast carcinoma Invasive No Special Type (NST) to tumor size

<i>Lymphovascular Invasion (LVI)</i>	Tumor size						Total	
	> 0,1 cm - 2cm		>2 cm - 5cm		>5cm		n	%
	N	%	n	%	n	%		
Positive LVI	27	55,1	12	24,5	10	20,4	49	100,0
Negative LVI	2	40	3	60	0	0	5	100,0
Total	29		15		10		54	

Of the 49 patients who did not experience Lymphovascular Invasion (LVI), 29 patients (59.2%) with no KGB involvement and 20 patients (40.8%) with KGB involvement. Of the 5 sufferers experiencing Lymphovascular Invasion (LVI), with no involvement of the lymph nodes (Table 7).

Tabel 7 Frequency distribution of Lymphovascular Invasion (LVI) in invasive breast carcinoma No Special Type (NST) to lymph node involvement (KGB)

<i>Lymphovascular Invasion (LVI)</i>	lymph node involvement				Total	
	Negative lymph		Positive lymph			
	node involvement		node involvement		N	%
Negative LVI	n	%	n	%		
	29	59,2	20	40,8	49	100,0
Positive LVI	5	100	0	0	5	100,0
Total	34		20		54	

Of the 49 patients who did not experience Lymphovascular Invasion (LVI), as many as 21 patients (42.9%) with stage I, 19 patients (38.8%) at stage II and 9 patients (18.4%) at stage III. From 5 sufferers who experience Lymphovascular Invasion (LVI), there are 2 sufferers with stage I, 2 sufferers of stage II and 1 sufferer in stage III (Table 8).

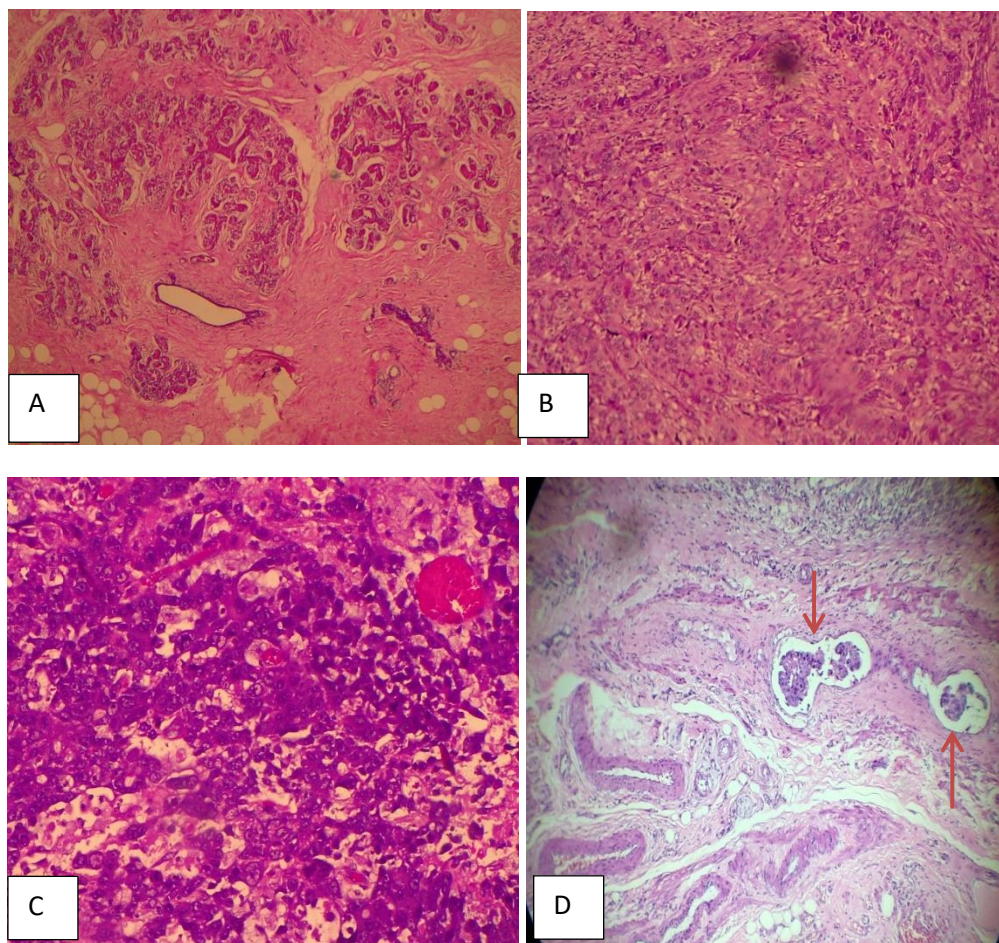
Tabel 8. Frequency Distribution of Lymphovascular Invasion (LVI) in breast carcinoma Invasive No Special Type (NST) to Stadium

<i>Lymphovascular Invasion (LVI)</i>	Stadium						Total	
	Stadium I		Stadium II		Stadium III			
	n	%	n	%	n	%	n	%
Negative LVI	21	42,9	19	38,8	9	18,4	49	100,0
Positif LVI	2	40	2	40	1	20	5	100,0
Total	23		21		10		54	

Of the 49 patients who did not experience Lymphovascular Invasion (LVI), as many as 21 patients (42.9%) with grade 2, 19 patients (38.8%) with grade 1 and 9 patients (18.3%) with grade 3. Of the 5 patients with Lymphovascular Invasion (LVI), 3 patients with grade 2 and 2 patients with grade 3. (Table 9).

Tabel 9. Frequency Distribution of Lymphovascular Invasion (LVI) in breast carcinoma Invasive No Special Type (NST) against Histopathological Grade

<i>Lymphovascular invasion (LVI)</i>	Grade Histopathology						Total	
	Grade 1		Grade 2		Grade 3			
	n	%	n	%	n	%	n	%
Negative LVI	19	38,8	21	42,9	9	18,3	49	100,0
Positif LVI	0	0	3	60	2	40	5	100,0
Total	20		24		11		54	



Picture A. *IBC NST GRADE 1* B. *IBC GRADE 2*, C. *IBC NST GRADE 3*, D. *LVI* (arrow

4. Discussion

The spread of cancer cells to local lymph vessels and blood vessels and indicates that the cancer cells have reached both vessels is Lymphovascular Invasion (LVI). Spread that has reached axillary lymph nodes and internal mammary lymph nodes are caused by the embolization of cancer cells into nodules, which are formed from a collection of cancer cells. Nodules involved will be enlarged, hard, and pale. The spread of cancer cells to blood vessels will lead to the spread of cancer cells to more distant organs or metastases. The most common metastatic breast cancer is to the bones, brain, liver, lungs, pleura, and ovaries. The presence of lymphovascular infiltration indicates a poor prognosis in patients. (12)

An important step in the complex process of tumor metastasis and important criteria for further therapy is knowing LVI. So LVI is a significant prognostic factor in invasive breast cancer due to local recurrence and poorer distance and survival. It is also associated with other strong prognostic factors including tumor size, degree and lymph node involvement. (8)

One important parameter in the diagnostic and prognostic in all cancers is Lymphovascular Infiltration. Many studies have shown that there is a strong relationship between Lymphovascular infiltration and poor clinical outcomes including metastasis, recurrence, and life expectancy. Because of that in pathology,

lymphovascular infiltration has been included as one of the important things to determine the prognosis in various cancers. (13)

LVI is an independent bad prognostic factor in patients with invasive breast cancer. However, although LVI is an important prognostic factor in people with lymph node invasive breast cancer, its prognostic value in people with positive breast cancer is unclear and controversial. (9)

In this study, out of 49 patients without Lymphovascular Invasion (LVI), most aged between 50-64 years were 23 patients (46.9%). Of the 5 sufferers experiencing Lymphovascular Invasion (LVI), as many as 4 sufferers aged 35-49 years.

Besides sex, age is one of the most important breast cancer risk factors, because the incidence of breast cancer is closely related to increasing age. In 2016, around 99.3% and 71.2% of all breast cancer-related deaths in the United States were reported in women over the ages of 40 and 60. Therefore, mammography screening is needed for women aged 40 or older. (3)

Shen's 2015 study on a meta-analysis study revealed that the LVI positive rate was significantly higher in the ≤ 50 years age group than in the > 50 years age group statistically ($P = 0.003$). (8)

This study is in line with the study of Daglar, et al in 2010 of 214 cases found that most breast cancer patients aged ≥ 40 years were 170 people (79.4), and aged < 40 years as many as 44 people (20.6). (6)

If breast cancer is diagnosed as a primary tumor or in the early stages of metastasis, breast tumors can be removed surgically and chemotherapy can work effectively. Early detection is the foundation of breast cancer prevention. Mammography is an effective screening method for using low-energy X-rays to get images of breasts. Since the first recommendation for breast cancer screening by Professor Forrest, more than 70% of women (aged 50-74 years) in America have undergone breast cancer screening through mammography every 2 years. A meta-analysis of 11 randomized trials showed that women aged 50-70 years had a significant reduction in breast cancer mortality after screening by mammography ($RR = 0.81$). However, the decrease in mortality was not significant in women aged 40-49 years. These results show the importance of the mammography screening program. (3)

In this study, 49 patients did not experience Lymphovascular Invasion (LVI), 27 patients (55.1%) with tumor size $> 0.1 - 2$ cm, 12 patients (24.5%) with tumor size $> 2 - 5$ cm and 10 patients (20.4%) tumor size > 5 cm. From 5 sufferers experiencing Lymphovascular Invasion (LVI), as many as 2 sufferers of tumor size > 0.1 cm - 2cm, 3 sufferers of tumor size > 2 cm-5cm.

This study is in line with the study of Daglar, et al in 2010 found that breast cancer patients had the most tumor size ≤ 4 cm by 134 people (62.6%), and > 4 cm by 80 people (37.4%). 8 (8)

In Song's research, et al in 2012 found that breast cancer patients had the most tumor size > 20 mm with negative LVI as many as 75 people (34.2%), and positive LVI as many as 144 people (65.8%). (9)

In breast cancer, tumor size is a strong predictor for local recurrence, regional and systemic spread. Shen's study in 2015 found that individual OR values from 4 studies ranged from 0.02 to 2.05, which showed that the study was not significant about the relationship between LVI and tumor size. But the meta-analysis stated that the LVI positive level was significantly lower in the $T \leq 2$ cm group than in the $T > 2$ cm group statistically ($P < 0.001$). (8)

In this study, for lymph node involvement the most were N0 34 cases without KGB involvement (63%), and N1 as many as 20 cases had KGB involvement (37%).

This study is in line with the study of Niemic, et al in 2017 obtained from 139 breast cancer patients who did not have N0 lymph node involvement, most with 131 negative LVIs and 8 positive LVI. Of the 219 having lymph node involvement (N0), the most with negative LVI were 169 people and positive LVI were 50 people 5 (5)

In the study of Daglar, et al in 2010 also found breast cancer patients with no involvement of KGB (N0) as many as 85 people (39.7%), and there was the involvement of N1, N2, and N3 as many as 12 people (60.3%). (6)

Status of lymph node involvement is the most powerful prognostic factor for people with breast cancer. Prognosis of breast cancer patients with positive lymph node involvement has a poor prognosis. Because LVI increases the likelihood of KGB (ALN) involvement. A meta-analysis study stated that the LVI positive level was significantly lower in the negative KGB group than the statistically positive KGB group ($P < 0.01$). (8)

In this study, invasive NST breast carcinoma was found mostly in Stage I (23 cases, 42.6%), stage II (21 cases, 38.9%), and stage III (10 cases, 18.5%) and sufferers who experience Lymphovascular Invasion (LVI) at stage 2.

This study is not much different. In the Daglar Research, et al in 2010 it was found that patients with invasive breast cancer obtained with stadium 1 as many as 21 people (9.8%), with stage 2 as many as 84 people (39.3%), and stage 3 as many as 109 people (50.9%). (6)

Grading is determined based on the shape of tumor cells and the behavior of tumor cells compared to norm 1 cells, thus it can be seen how fast the cancer cells develop. Grading is associated with life expectancy in patients for 10 years, where grade I (85%), grade II (60%), and grade III (45%). Grade I shows the best prognosis, grade II shows a moderate prognosis, while grade III shows the worst prognosis. (12)

Based on the results of the study found 49 patients who did not experience Lymphovascular Invasion (LVI), most with grade 2 totaling 21 patients (42.9%), grade 1 with 19 patients (38.8%) and) with grade 3 as many as 9 people patients (18.4%. Of the 5 patients suffering from Lymphovascular Invasion (LVI), 3 patients with grade 2 and 2 patients with grade 3.

This study is in line with Daglar Research, et al in 2010 found that breast cancer patients obtained grade 1 as many as 72 people (33.6), grade 2 as many as 103 people (48.1) and grade 3 as many as 39 people (18.2). (6)

In Niemic's study, et al in 2017 was obtained from 46 breast cancer patients who were Grade 1, with 45 negative LVIs and 1 positive LVI. Of the 139 Grade 2 levels, the most with negative LVI are 131 people and LVI is positive as many as 8 people, and out of 170 Grade 3 levels, the most are 121 negative LVIs and 49 are positive LVIs (5)

The Shen study obtained an individual OR score from 3 studies ranging from 0.02 to 1.32, which showed that the study was inconsistent about the relationship between LVI and histological level. But the meta-analysis found that the positive LVI was significantly lower in the grade 1 group than in the grade 2/3 group statistically ($P = 0.008$).

LVI has unfavorable pathological symptoms and is significant. 11 Cavities/cavities that are not blood vessels (non-vascular space) can be formed by tumor cell nests in the area of invasive carcinoma due to tissue retraction during processing, which is known as shrinkage artifacts or retraction artifacts. This non-vascular cavity retraction artifact is difficult to distinguish from lymphatic cavity retraction artifacts (true lymphatic

space) and these artifacts are more commonly found in invasive breast cancer so they need for IHC podoplanin d2-40 and CD31 / CD34. (11)

5. Conclusion

After conducting research on patients with invasive breast carcinoma No special type (NST) in 54 cases in the Anatomic Pathology Laboratory of the USU Medical Faculty / Haji Adam Malik Hospital Medan, it can be concluded: Patients have negative Lymphovascular Invasion (LVI) of 49 people (90.7 %) and Lymphovascular Invasion (LVI) positive as many as 5 people (9.3%). Based on age, in breast cancer patients who were negative LVI was found to be higher at vulnerable ages 50-64 years by 23 people and at LVI positive at vulnerable ages 35-49 years by 4 people. Based on tumor size, breast cancer patients who were negative LVI were found to be higher in tumor size cm 2cm which was 27 people and the most positive LVI in susceptible tumor size was 2-≤5cm which was 3 people. Based on lymph node involvement, LVI negative breast cancer patients were found to be higher with no KGB involvement of 29 people and positive LVI of 5 people. Based on stage, LVI negative breast cancer patients were found to be higher in stage I with 21 people and positive LVI in stage II with 2 people. Based on grade, LVI negative breast cancer patients were found higher in grade 2 which was 21 people and positive LVI in grade 2 was 3 people.

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References

1. Gluz O, Liodtke C, Gottschal N, Pusztai L, Nitz U, Harbeck N. Triple-negative breast cancer-current status and future direc-tions. *Annals of Oncology*. 2009;20:1913-27.
2. WHO. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. International Agency For Research on Cancer, 2018
3. Sun Y., Zhao, Z. Risk factors and preventions of breast cancer. *International Journal of Biological Sciences*. 2017; 13(11): 1387-1397. doi: 10.7150/ijbs.21635
4. Oemiaty R., Rahajeng E., Kristanto A.Y. 2011. Prevalensi Tumor danbeberapafaktor yang Mempengaruhinya di Indonesia. *Bul. Penelit. Kesehat* 39(4); 190 – 204.
5. Niemiec J, Adamczyk A, Ambicka A, Mucha-Malecka A, Wysocki WM, Biesaga B et al. Prognostic role of lymphatic vessel density and lymphovascular invasion in chemotherapy-naïve and chemotherapy-treated patients with invasive breast cancer, *Am J Transl Res* 2017;9(3):1435-1447 (6)
6. Dağlar G., Yuksek Y.N., Gozalan A.U., Tutuncu T., Gungor Y., and Kama N.A. 2010. The Prognostic Value of Histopatological Grade in the Outcome of Patients with Invasive Breast Cancer. *Turk J Med Sci* 40(1); 7-15. (8)
7. Hoda SA. Invasive lobular carcinoma. In: Hoda SA, Brogi E, Koerner FC, Rosen P eds. *Rosen's Breast Pathology*. Chapter 33. 4th ed. Philadelphia. Lippincott Williams & wilkins. 2015. p855-93 (9)
8. Shen S., Zhong S. Correlation OfLymphovascular Invasion With Clinicopathological Factors In Invasive Breast Cancer: A Meta-Analysis. *Int J ClinExp Med* 2015;8(10):17789-17795 (11)
9. Song Y., Shin S., The Role of Lymphovascular Invasion as a Prognostic Factor in Patients withLymph Node-Positive Operable Invasive Breast Cancer. *J Breast Cancer* 2011 September; 14(3): 198-203 <http://dx.doi.org/10.4048/jbc.2011.14.3.198> (12)
10. Kumar, P., and Clark M., 2006, Faktor Risiko Kanker Payudara karena Riwayat Keluarga, Clinical Medicine Sixth Edition, terdapat di: <http://www.studentconsult.com/content/default.cfm?ISBN=0702027634 &ID=HC009018>

11. Shen S, Wu G, Xiao G, et al. Prediction model of lymphovascular invasion based on clinicopathological factors in Chinese patients with invasive breast cancer. *Medicine (Baltimore)*. 2018;97(43):e12973. doi:10.1097/MD.00000000000012973 (43)
12. Stevens A, Lowe J, Scott I, editor (penyunting). Core Pathology. Edisi ke-3. United Kingdom: Elsevier; 2009. (47)
13. Kim S, Park HK, Lim SD. ERG Immuno histochemistry as an endothelial marker for assessing lymphovascular invasion. *The Korean Journal of Pathology*. 2013;47:503.