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THE ROLE OF LYMPHATIC AND VASCULAR INVASION IN LYMPH NODE METASTASIS IN T1/T2N0 BREAST CANCER PATIENTS AT SANGLAH GENERAL HOSPITAL

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ABSTRACT

Breast cancer is still a significant public health problem worldwide. It is the most common cancer in the female population, and second cause of mortality after lung cancer. In Indonesia, breast cancer was second to cervical cancer, with high mortality, because of the late stage at presentation of health facilities. Since mass screening program for breast cancer was established in the western world, the earlier breast cancer was detected, the incidence of ductal carcinoma in situ and non palpable breast cancers were increased a great deal. The more conservative surgeries were becoming the surgical technique of choice, such as BCT or breast conserving surgery. The small percentage of axillary lymph node positivity, was now become a controversy, looking at the morbidity it caused. At Sanglah Hospital, even though mass screening project for breast cancer was not available, and most breast cancer patients came at a late stage (70-80 % came at stage III to IV), the need to determine the axillary lymph node status was quite important especially in early breast cancer (T1/T2N0M0) in our population. Lymphatic Mapping (LM) and Sentinel Lymph node Biopsy (SLNB) was not yet established in our institution. Therefore, in this study, we tried to define the correlation between histologic grading, tumor infiltrating lymphocytes (TIL), vascular invasion (IV), lymphatic invasion (LI), the presence or absence of comedo subtype component in the breast cancer histopathology, with the presence of axillary lymph node metastasis in the T1/T2N0M0 breast cancers. Since 2002 until 2004 (24 months), a cross sectional study on T1/T2N0M0 breast cancers was performed. The correlation between histologic grading, TIL, VI, LI, the presence or absence of comedo component with axillary lymph node metastasis was analyzed. The results were, that lymphatic invasion was the strongest predictor in correlation with the axillary lymph node metastasis (p< 0.00), therefore the lymphatic invasion was a strong indicator for an axillary lympnodes dissection procedure in the management of T1/T2N0M0 breast cancers, in the institutions where LM and SLNB were not readily available. Other variables did not show any strong correlation, but this might be due to too small sample units we recruited.

KEYWORDS : Lymph Node Axillary, Grading Histophatology, Vascular Invasion, Lymphatic Invasion and Subtype Comedo

Breast cancer is considered as an important health issue for women worldwide and was the second most common cause of mortality after lung cancer. Approximately one million women had breast cancer in the European Union with a mortality rate of 100.000 annualy. (Boyle, 2003) There were over 200.000 new cases estimated for invasive breast cancer and 47.100 new cases for in situ breast cancer in the United States in 2002, with a mortality rate of 44.000 women annualy. Male breast cancer contributed to approximately 1% of all breast cancer cases (approximately 1.500 cases) with a mortality rate of 400 cases annualy. (Apantaku, 2002) Indonesia has not been able to implement a population based registry for breast cancer, but it was estimated that there were over 20.000 new cases annualy and more than 50% of new cases were in the late stage of the disease. According to the American Joint Committee on Cancer (AJCC), the incidence rate for early breast cancer (Stage I-II) was around 75-80%.(Mirza et al., 2002) Early breast cancer incidence rate had a tendency to increase in the United States, non invasive breast cancer even had a 6 times higher rate than invasive breast cancer. Early breast cancer with a diameter <2 cm had twice the incidence rate than >3 cm tumors, a 27% decrease in tumor size was observed. This situation was most likely contributed by the successful screening program (mammography) in the United States. (Boyle, 2003)

There has been no consensus about the definition of early breast cancer, specifically on tumor size and lymph node involvement. Several literatures stated that T1-T3 with N0/N1ab was categorized as early breast cancer. For T1/T2N0M0 breast cancers, it was crucial to determine lymph node involvement. Lymph node involvement played a pivotal role in therapeutic planning and also as an important prognostic factor in determining the disease free survival and overall survival rate. Determining lymph node involvement clinically is still unreliable due to a high false positive rate.(Taylor, 2004) Several factors such as tumor size, primary tumor location, histopathological type (e.g. Comedo type), hormonal factor, biochemical factor, and biological factor showed a significant correlation with

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axillary lymph node involvement. Axillary lymph node involvement was found histopathologically in 17% cT1N0 cases and 27% cT2N0.

The management for T1/T2N0M0 breast cancer showed high succesful rate of local and regional therapy, but a number of this group found to have distant metastasis. Modified radical mastectomy as the mainstay surgical therapy for T1/T2N0M0 cases is not recommended and there was a growing trend towards breast conserving surgery followed by radiotherapy. This is due to several randomized controlled trials that showed that there was no significant difference between disease free survival or overall survival rate between breast conserving surgery with mastectomy, while the earlier provided patients with better cosmetic result.(Robson, 2002) While other studies showed that early breast cancers treated with breast conserving surgery without axillary dissection had a 20% recurrence rate and 34% progression to metastasis rate.(Veronesi, 2002)

There is still a controversy regarding axillary dissection in T1/T2N0M0 breast cancer and almost 80% morbidity attributed to the procedure could be avoided, but axillary dissection itself has proven to be a valuable tool for staging in breast cancer.(Gusterson, 2003) The role of axillary dissection as a loco-regional control was minimal and probably it was more useful in determining the disease stage and prognosis, specifically for cN0 breast cancer patients.(Morrow, 2002) Therefore, determining axillary lymph node involvement accurately was desirable, to avoid over/under treatment of breast cancer. Several methods were used to achieved this, such as axillary sentinel lymph node biopsy using blue dye or radioisotopes. Alternative prognostic and predictor factors have been studied to determine axillary lymph node involvement, e.g.: cell differentiation, nuclear grade, necrosis, mitotic index, lymphatic invasion, vascular invasion, perineural invasion, estrogen/progesteron receptor status, biochemical factors, and biological factors (BRCA-1, BRCA-2, Her-2/neu, Bcl-2, Ki-67) were found correlated with breast cancer. (Fisher et al., 2002)

In addition to the use of sentinel lymph node and axillary lymphatic mapping to determine the status of the axillary lymph nodes, there are several alternative approaches to determine how far the behavior or properties of the cell biology of breast cancer as a predictor factor for regional metastatic axillary lymph nodes, such as histopathological grading divided into well-differentiated (grade I) , moderately differentiated (grade II) , and poorly differentiated (grade III) have a degree of differentiation of different cell, the higher the level of differentiation the worse the prognosis and increasingly have the potential for metastasis. (Mansour, 1994) Tumor infiltrating lymphocytes / TIL immune response against the tumor, such as T lymphocytes (CTL) are immune cells that are cytolytic and able to eliminate tumor cells. Vascular and lymphatic invasion served as a mechanism for carcinoma the process of metastasis. And comedo subtype, one of the histopathological subtype most common had a high potential for metastasis compared with other histopathological types.

MATERIALS AND METHODS

This research was conducted in the Department of Surgery, during two years. This was a cross-sectional study, which included the study population was all breast cancer patients who were hospitalized in Sanglah General Hospital with T1 / T2 with N0 , M0 determined clinically by the senior surgical oncologist or surgical oncologist trainee. Sampling was done by consecutive sampling where all breast cancer patients with T1/T2N0 M0 who underwent surgery. Diagnosis is established either by incision or with frozen section biopsy followed by MRM and the results of axillary lymph nodes dissection of each level are sorted by the operator then the primary tumor, as well as the lymph nodes were sent to the Department of Pathology Anatomy. Data were collected and analyzed using the chi - square test to determine the association between variables and will also be analyzed using multiple regression analysis. Chi - square test and the statistical test is said to be meaningful if the value of $p < 0.05$. The analysis was done using SPSS 11.5 .

RESULTS

The results of the data analysis will be presented in the form of tables (1-10) and figure 1. In a 2 -year period of

Table 1 : T1/T2N0M0 Breast Cancer Patients Characteristics

Characteristic	n	(%)
Age	Mean 44, 1 tahun	
Sex		
Female	42	100
Male	0	0
Tumor Location		
QLA	27	64.3
QLB	2	4.8
QMA	6	14.3
Central	7	16.7
Tumor Size		
T1 (< 2 cm)	3	7.14
T2 (2-5 cm)	39	92.85
Grade		
Grd. I	8	19.0
Grd. II & III	34	81.0
Tumor infiltrating Lymphocyte		
Positive	29	69,0
Negative	13	31,0
Vascular Invasion		
Positive	9	21.4
Negative	33	78.6
Lymphatic Invasion		
Positive	17	40.5
Negative	25	59.5
Histopathological Subtype		
Comedo	6	14.3
Non - comedo	36	85.7
Lymph Node Involvement		
Positive	20	47.6
Negative	22	52.4

this study, we found 42 cases of breast cancer with clinical stage T1 / T2N0M0 , with an average age of 44 year. The youngest age was 24 years old and the oldest 75 years . The whole case was a woman of 42 (100 %) with the majority of tumor location on upper lateral quadrant 27 (64.3 %) cases , the central region 7 (16.7 %) cases , the medial upper quadrant 6 (14.3 %) cases and at least at the lower lateral quadrant 2 (4.8 %) cases . The size of the tumor with a diameter < 2 cm / T1 3 (7.15%) cases and the size of the tumor with a diameter of 2-5 cm / T2 as many as 39 (82.85 %) cases .

Based on histopathological results , the majority of tumor grade was grade II and III 34 (81.0 %) and only 8 (19.0 %) cases of grade I tumors. In observation of the

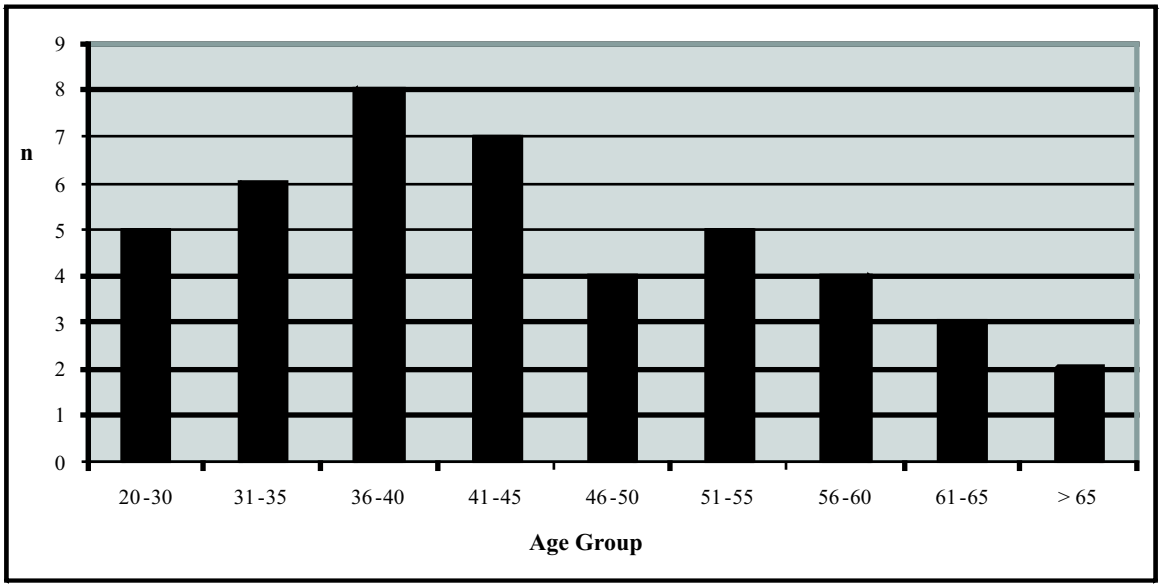

Figure 1. Case Distribution Based on Age Group

Table 2 : The Association of Tumor Grade With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
Grade	**Negative**	**Positive**	**Total**
High	16	18	34
Low	6	2	8
	22	20	42

X^2= 2.02 P=0.15 df=1 =0.05 95% CI=0.05-1.68 OR=0.29

Table 3. The Association of Tumor Infiltration Lymphocyte with Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
TIL	**Negative**	**Positive**	**Total**
High	8	5	13
Low	14	15	29
	22	20	42

X^2= 0.63 P=0.46 df=1 =0.05 95% CI=0.45-6.50 OR=1.71

presence or absence of lymphocytes surrounding the tumor, lymphocytes obtained positive in 29 (69 %) cases and negative lymphocyte cells in 13 (31 %) cases . The existence of both the tumor cell invasion of blood vessels or lymph vessels found as many as nine (21.4 %) cases with vascular invasion and cases without vascular invasion 33 (78.6 %) , whereas cases with lymphatic invasion were 17 (40.5 %) case and without lymphatic invasion 25 (59.5 %). Only 6 (14.3 %) cases with comedo subtype and 36 (85.7 %) cases with non-comedo subtype. Of the 42 samples studied only 13 cases observed with the HER-2/ neu over expression, and 6 of 13 cases (46.15 %) cases with HER-2 / neu positive with 83.33 % positive axillary lymph nodes. Of the 42 cases studied 20 (47.6 %) cases showed lymph node metastasis / axillary lymph nodes , and 22 (52.4 %) cases no lymph node metastasis / axillary lymph nodes with varying number of nodes .

According of these data that the association between high grade histopathology with the incidence of metastatic axillary lymph nodes in clinical stage T1 /

Table 4 : The Association of Vascular Invasion With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
VI	**Negative**	**Positive**	**Total**
Negative	21	12	33
Positive	1	8	9
	22	20	42

X^2= 7.82 P=0.00 df=1 =0.05 95% CI=1.55-125.91 OR=14.00

Table 5. Lymphatic Invasion Correlation With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
LI	**Negative**	**Positive**	**Total**
Negative	19	6	25
Positive	3	14	17
	22	20	42

X^2= 13.81 P=0.00 df=1 =0.05 95% CI=3.14-69.50 OR=14.77

Table 6. Comedo Subtype Correlation With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
VI	**Negative**	**Positive**	**Total**
Negative	19	17	36
Positive	3	3	6
	22	20	42

X^2= 0,01 P=0.90 df=1 =0.05 95% CI=0.19-6.29 OR=1.11

Table 7 : Age Correlation With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
Age	**Negative**	**Positive**	**Total**
< 35 years	4	5	9
> 35 years	18	15	33
	22	20	42

X^2=0.28 p=0.59 df=1 α=0.05 95%CI=0.15-2.93 OR=0.66

T2N0M0 breast cancer was not show a significant association (p = 0.15).

According of these data that the association between tumor infiltrating lymphocytes negative with the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 showed no significant association (p = 0.46).

Based on the above data analysis showed a significant association between positive vascular invasion with metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (p = 0.00).

From the calculation above, data showed that the relationship between positive lymphatic invasion on the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 was significant (p = 0.00).

Comedo subtype relationship with the incidence of metastasis to axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 by analysis showed no statistically significant association (p = 0.90).

Statistical test showed no significant relationship between age group <35 years to the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (p = 0.59).

Based on the calculations above, tumor size

Table 8 : The association of Tumor Size With Axillary Lymph Node Involvement in T1/T2N0M0 Breast Cancer

	Lymph Node		
Tumor Size	**Negative**	**Positive**	**Total**
< 2 cm	3	0	3
> 2 cm	19	20	39
	22	20	42

X^2=2.93 p=0.08 df=1 α=0.05 95%CI=1.48-2.83 OR=2.05

Table 9 : Association of Her-2 Overexpression With Axillary Lymph Node Metastasis in T1/T2N0M0 Breast Cancer

	Lymph Node		
Tumor Size	**Negative**	**Positive**	**Total**
Negative	3	4	7
Positive	1	5	6
	4	9	13

X^2=1.04 p=0.30 df=1 α=0.05 95%CI=0.27-51.37 0R=3.75

Table 10 : Multivariate Analysis of Axillary Lymph Node Involvement Risk Factors in T1/T2N0M0 Breast Cancer

	B	Wald	P - Value	OR	95.0% C.I	
					Lower	Upper
High Grade	0,39	0,14	0,70	0,67	0,09	5,08
TIL Negative	0,66	0,56	0,45	1,93	0,34	10,79
VI Positive	1,34	1,08	0,29	3,83	0,30	48,20
LI Positive	2,26	6,56	0,0 1	9,58	1,70	53,99
Comedo	0,16	0,02	0,87	1,18	0,1 3	10,30
Constanta	1, 62	3,52	0,06	0,19		

B : regression coefficient, S.E : standard error, Wald : Chi Square, OR : odds ratio

greater than 2 cm did not have a significant relationship to the incidence of axillary lymph nodes metastasis (p = 0.08).

Statistical analysis showed no significant relationship between positive Her-2 overexpression with axillary lymph node metastasis in T1/T2N0M0 breast cancer (p = 0,30).

By using multivariate analysis, the data in the table above illustrates that lymphatic invasion variables as independent variables on the dependent variable (axillary nodes) demonstrate the value that was highly statistically significant (p = 0.01) as a predictor factor of the likelihood of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 . While other independent variables such as histopathologic grading , tumor infiltrating lymphocytes , vascular invasion and comedo subtype showed a p-value above the average value of 0.05 . By looking at the value of the odds ratio of 9.58 at the 95 % confidence intervals (95 % CI = 1.70 to 53.99) illustrates that lymphatic invasion had the strongest relationship between these variables on the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 . Vascular invasion variable is a variable number two strongest (p = 0.29) on the value of the odds ratio of 3.83 with 95 % confidence intervals (95 % CI = 0.30 to 48.20)

DISCUSSION

Histopathological grading of a tumor describes the level of differentiation of the tumor cells, which was associated with therapy and prognosis of the breast cancer

patient. In this study, we found that high histopathological grading has a greater association with the incidence of metastatic axillary lymph nodes compared with low histopathological grade tumors. But on the above test data analysis did not show a significant relationship (p = 0.15 . 95 % CI = 0.05 to 1.68 . OR = 0.29) between high histopathological grading on the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (table . 2). This is probably due to the very small sample size . Brenin , et al . 2001 reported that high histopathological grading has a greater relationship to the incidence of metastatic axillary lymph nodes compared with histopathological grading low and so are Silverstein , et al . 2001 reported that the core grading an independent predictor factors on the incidence of metastatic axillary lymph nodes. Other researchers have also reported that higher histopathologic grading increasingly related to the occurrence of metastatic axillary lymph nodes.

Tumor infiltrating lymphocyte acts as surveillance for cellular immunity against tumor cells, which are able to suppress or even kill tumor cells in the amount of 105, this case illustrates that when the tumor infiltrating lymphocytes is negative, it means it does not show an immune response against tumor cells. From the results of this study showed that negative TIL associated with the incidence of metastatic axillary lymph nodes with a lower figure than the positive TIL (Table . 3). The statistical test shows that the negative TIL does not have a significant relationship to the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (P = 0.46 . 95 % ci = 0.45 to 6.50 . Or = 1.71) .

In Table 4 about the influence of vascular invasion of tumor cells to metastatic axillary lymph nodes showed that vascular invasion positively associated with the incidence of metastatic axillary lymph nodes is much higher than the negative vascular invasion. From the statistical analysis showed that the positive vascular invasion has a significant relationship to the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (p = 0.00. 95 % CI = 1.55 to 125.91 . OR = 14.00). Silverstein , et al , 2001 said that the lymphovascular invasion was an independent prognostic factor and a predictor factor on the incidence of metastatic axillary lymph nodes. Rosen , 1997 said that vascular invasion of breast cancer cells was very significant and so did Hoque , Loscalzo , Day , et al . 2004 reported that the relationship between breast cancer cell lymphovascular invasion on the incidence of metastatic axillary lymph nodes is very significant , they even recommended axillary dissection if there is the lymphovascular invasion on breast cancer clinical stage T1 / T2N0M0.

Infiltration of tumor cells into the lymph vessels or blood vessels is a mechanism of metastasis. Brenin, et al . 2001, said that the size of the tumor with a diameter of 1-2 cm / T1 to invade lymph vessels have a relationship with the incidence of metastatic axillary lymph nodes and so did in table 5 of this study found positive lymphatic invasion that has a relationship with the incidence of metastatic axillary lymph nodes with test analysis shows that lymphatic invasion has a very significant relationship to the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (p = 0.00. 95 % CI = 3.14 to 69.50 . OR = 14.77). Likewise Hoque, et al. 2004 reported that the lymphovascular invasion on the incidence of metastatic axillary lymph nodes has a significant relationship and Silverstein , et al . 2001 reported studies with similar results.

Comedo subtype is ductal breast cancer subtype that has a higher metastatic ability compared with other subtypes. (Mansour;1994) But in this study, we found that comedo subtype positive and negative showed the same figures on the incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (tabel.6). There was no significant association between positive comedo subtype to the incidence of axillary lymph nodes metastasis (p = 0.90 . 95 % CI = 0.19 to 6.29 . OR = 1.11).

According to the consensus St. Gallen Conference 1998 said that the age of approximately 35 years included a group at high risk for breast cancer. The younger the age of the patient describes the aggressiveness of tumor cells associated with the presence of genetic mutations or familial cancer. From the results of this research data analysis table 7 on the relationship of age to the incidence of metastatic axillary lymph nodes illustrates that under the age of 35 years showed no significant relationship to the

incidence of metastatic axillary lymph nodes in breast cancer clinical stage T1 / T2N0M0 (p = 0.59 . 95 % CI = 0.15 to 2.93 . OR = 0.66). This may be caused by a very small number of samples.

Tumor size as a predictor factor for the incidence of metastatic axillary lymph nodes in this study are in accordance with table 8, cannot be concluded as one of the cells in the table does not qualify. The aforementioned problems can be solved by getting a greater number of samples. But based on the value of the confidence intervals of the odds ratios mentioned above illustrates that the larger the tumor the more likely the occurrence of metastatic axillary lymph nodes. Some workers reported that a large tumor growing increasingly have a relationship with the incidence of metastatic axillary lymph nodes. In another study found that the larger the size of the tumor increasingly has a relationship with the incidence of metastatic axillary lymph nodes. (Mansour;1994)

In Table 9 of the influence of the HER - 2 / neu for metastatic axillary lymph nodes analyzed in 13 of 42 samples there and from 13 cases in the statistical test shows that the HER - 2 / neu positive showed no significant relationship to the incidence of metastases in the axillary lymph nodes breast cancer clinical stage T1 / T2N0M0. But by looking at the value of the odds ratio in the above confidence interval shows strong enough that HER - 2 / neu positively associated with the incidence of metastatic axillary lymph nodes . As prognostic factors and predictors of HER - 2 / neu is a gene product (c - erbB - 2 / neu) which was associated with tumor cell progression and metastasis ability to hold a regional or distant metastases. (Apantaku;2002)

Based on multivariate analysis using logistic regression, of the five independent variables mentioned above such as: histopathologic grading, tumor infiltrating lymphocytes, vascular invasion, lymphatic invasion and comedo subtype associated with the incidence of metastatic axillary lymph nodes in breast cancer stage T1 / T2N0M0 showed that lymphatic invasion as an independent variable that has the strongest relationship between other independent variables on the incidence of metastatic axillary lymph nodes in breast cancer T1 / T2N0M0 and vascular invasion is an independent variable number two strongest associated with axillary lymph nodes metastasis. Other researchers such as Hoque , Loscalzo , Day , et al . 2004 found similar results which lymphovascular invasion factor is a very significant factor related to the incidence of metastatic axillary lymph nodes and so did Silverstein, et al . 2001 reported that lymphovascular invasion was an independent predictor for metastatic axillary lymph nodes.

CONCLUSION

Lymphatic or vascular invasion can be used as a guideline to determine the indication of axillary lymph nodes dissection in cases of breast cancer clinical stage T1 / T2N0M0 so that morbidity from dissection of axillary lymph nodes can be prevented, especially in hospitals that have not been able to do a sentinel node biopsy.

REFERENCES

Apantaku LM. Breast-conserving surgery for breast cancer. American family physician. 2002 Dec 15;**66**(12):2271-8. PubMed PMID: 12507165.

Boyle P. Mammographic breast cancer screening: after the dust has settled. Breast. 2003 Dec;**12**(6):351-6. PubMed PMID: 14659104.

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. The New England journal of medicine. 2002 Oct 17;**347**(16):1233-41. PubMed PMID: 12393820.

Gusterson BA. The new TNM classification and micrometastases. Breast. 2003 Dec;**12**(6):387-90. PubMed PMID: 14659110.

Mansour EG, Ravdin PM, Dressler L. Prognostic factors in early breast carcinoma. Cancer. 1994 Jul 1;74(1 Suppl):381-400. PubMed PMID: 8004612.

Mirza NQ, Vlastos G, Meric F, Buchholz TA, Esnaola N, Singletary SE, et al. Predictors of locoregional recurrence among patients with early-stage breast cancer treated with breast-conserving therapy. Annals of surgical oncology. 2002 Apr; **9**(3):256-65. PubMed PMID: 11923132.

Morrow M. Rational local therapy for breast cancer. The New England journal of medicine. 2002 Oct 17; **347**(16):1270-1. PubMed PMID: 12393826.

Robson ME. Clinical considerations in the management of individuals at risk for hereditary breast and ovarian cancer. Cancer control : journal of the Moffitt Cancer Center. 2002 Nov-Dec; **9**(6):457-65. PubMed PMID: 12514563.

Taylor KO. Morbidity associated with axillary surgery for breast cancer. ANZ journal of surgery. 2004 May;**74**(5):314-7. PubMed PMID: 15144248.

Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. The New England journal of medicine. 2002 Oct **17**;347(16):1227-32. PubMed PMID: 12393819.