EXPRESSION OF P53 ONCOPROTEIN IN HUMAN BREAST DUCTAL CARCINOMA (IN SITU, INVASIVE AND METASTATIC)

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ABSTRACT

Breast cancer is a malignant tumor mostly disclosed in women. It has heterogeneous biological behavior - so that the knowledge of tumor markers is very important to determine its prognosis and therapy. Up to now, the determination of prognosis and treatment of choice is still based on clinical and morphologic finding although recent studies pointed out that there was tight relationship between carcinoma growth and molecular abnormalities including normal cell gene consisting of proto-oncogene, tumor suppressor gene, programmed cell death and DNA repair gene. Therefore, the description of molecular changes is required - in determining the prognosis and therapy of breast cancer. Molecular pathologic approach may offer a prospective promise even though the genetic mechanism of molecular carcinogenesis of breast cancer is still unclear. In this study, immunopathologic investigation was carried out by using immunohistochemical method, with antibody monoclonal against protein p53. Based on multivariate test of Wilks' Lambda method, protein expression of p53 was concomitantly different in various tumor diameters of breast cancer ($p = 0,000 < \alpha = 0,05$). With methode of Wilks' Lambda method, protein expression p53 was simultaneously different in various carcinoma cell differentiation of breast cancer ($p = 0,000 < \alpha = 0,05$) and with Wilks' Lambda method, protein expression p53 was concomitantly different in various progressiveness of ductal carcinoma growth ($p= 0,000 < \alpha= 0,05$). Also with Wilks' Lambda method, protein expression p53 was concomitantly different in various grade of ductal carcinoma ($p = 0,000 < \alpha = 0,05$). The result designated that there was a significant difference among four breast cancer groups ($p= 0,000 < \alpha= 0,05$) and oncoprotein expression contributed on cellular activity in carcinogenesis of breast cancer. It showed that malignancy occurred in genetic lesion.

Keywords**:** *breast cancer, prognosis, molecular pathological role (p53 - protein expression)*

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INTRODUCTION

Breast carcinoma is a malignant tumor that mostly happens in woman and has heterogeneous biologic behavior, so that the determination of tumor marker is crucial to determine prognosis and to manage them (Indrawati et al 2004). The prognosis is determined by the progression of tumor cell growth in addition to other factors. Assessment to predict the progression of cell proliferation is important in the prognosis of disease treatment of malignancies, including breast ductal carcinoma. Are morphological assessment of cells and tissues, and morphofunctional showing biological activity of tumor cells. Today ductal breast carcinoma, divided into three groups, namely low histopathologic grading, medium and high. (Tavassoli 2003, Kumar et al 2005, Rosai et al 2004) Histopathologic grading of breast ductal carcinoma low cancer cells which are composed of relatively mature and still recognizable as the cell origin of cancer, carcinoma grading high histopathologically composed of cancer cells are immature, and can not be recognized as the normal breast ductal epithelial cells. Group histopathologic grading of breast ductal carcinoma is composed of transitional cell cancer between groups of cancer cells to low and high histopathologic grading. Low histopathologic grading of malignancy have a lower degree compared with histopathologic grading of breast ductal carcinoma high.

Tumor progression indicated by the growth of breast ductal carcinoma in situ, invasive and metastasis. Breast ductal carcinoma metastases have higher cell proliferation activity of invasive or in situ. (Tavassoli 2003), grouping based on morphological breast ductal carcinoma, the less have significant clinical value, because it cannot explain the actual degree of cell proliferation activity (Kumar V., et al., 2005). Way of grouping the breast ductal carcinoma has not been able to explain the molecular level to explain the

pathological changes in proliferative activity of cancer cells, as a basis for determining the degree of malignancy, which reflects the biological activity of cancer cells.

Hundreds of thousands of new patients, thirty thousand women died of breast ductal carcinoma each year, and is the most malignant disease of women in America and Europe. (J. Rosai 2004) Until now, the incidence and mortality of breast cancer is quite high, both in the United States and Europe that represents terbanya cancer and the second woman ever in women in Indonesia after cervical cancer. Each year, cases have been found increased in number. (National BRK 1995) Report of Director General of Medical Services Ministry of Health of the Republic of Indonesia and the National Cancer Registrar Association of Physician Specialists and Pathology Indonesia and also Indonesia Cancer Foundation in 1998, from 13 pathology centers of Indonesia, reported that breast cancer is the second (2598 cases) after cervical cancer (3682 cases), followed by lymph node tumors, skin and nasopharynx. Breast cancer is still the second largest number after cervical cancer in female malignancy in Surabaya and its surrounding areas, also in Indonesia. Interesting things happen in a few centers where the pathology of breast cancer ranks the top, like in Medan (170 cases), Kildare (120 cases), Palembang (113 cases), Yogyakarta (535 cases), and Makassar (147 cases). In Surabaya and surrounding areas reported that there are 400 to 750 people with breast cancer each year (Kusumowardojo et al 2004). Typically found on advanced conditions and a high degree of malignancy.

Data from the Department of Anatomic Pathology Airlangga University School of Medicine Dr. Soetomo General Hospital Surabaya showed 43% of breast carcinoma patients is a high degree of malignancy or poor cell differentiation. (Susraini 2001) To determine the degree of malignancy and prognosis, needed a solid scientific foundation, to reveal the molecular pathological mechanisms of the biological activity of cell proliferation. Determination of prognosis with the classification based on morphology, cell and tissue level, which is now used, it cannot yet explain the molecular pathological mechanism of biological activity of breast ductal carcinoma cell proliferation. The grouping has not been able to explain the same cells with morphological, but have different biological behavior of the activity. Such conditions led to the understanding that the diagnosis and classification of breast ductal carcinoma needs to be based pathological mechanisms of cancer cell proliferation molecular level, so that it can reveal problems controlling cell proliferation and differentiation of breast ductal carcinoma. If the problem is not immediately get attention, it is feared the diagnosis and classification of the explanations are not based on the biological activity of the molecular pathology of these mechanisms are not applicable, because of limited clinical value is significant, particularly the prognosis and treatment options, which can be detrimental to patients with ductal breast carcinoma.

Until now breast ductal carcinoma is considered to have high histopathologic grading course of the disease worse (progressive), compared with low histopathologic grading. Under such circumstances because of high-grade breast ductal carcinoma is estimated to have higher cell proliferation activity, compared with histopathologic grading of cancer is low (Kumar et al 2005) Group poorly differentiated ductal carcinoma of breast, medium or well which is expected to have different cell proliferation activity, cannot explain the molecular level pathological mechanism controlling cell proliferation activity going on, to show the progression of the tumor, which ultimately is used to determine prognosis and management of disease. Therefore, efforts are needed to reveal the basic mechanisms of cell proliferative activity of breast ductal carcinoma. So that certain parameters can be generated from ductal breast carcinoma with clinical values as expected, through the approach of molecular pathology. Diagnosis and determination of these parameters can be used as the basis to determine management measures and evaluation, particularly the prognosis of disease.

Several decades of research shows that there are close relations between the progressions of neoplasm with abnormalities at the molecular level. Levels of molecular abnormalities that occur are not singular, but it is a complex accumulation of genetic lesions. Basically the accumulation of genetic lesions can be grouped in the form, triggering tumor gene activation (oncogenes), inactivation of tumor inhibitor gene (GST) and gene "Programmed Cell Death" (PCD), which causes a dominant oncogene. The role of dominant oncogenes will trigger the activity of excessive cell proliferation and differentiation disorder, because activity and growth inhibition of cell death program is not working. (Yarnold 1996) With the sequential use of the above can be concluded that the assessment of the degree of progressivity of the growth of tumors based on histopathologic grading and clinical staging still require the completeness of the underlying explanations at the level of molecular pathology. Reported that the prognostic implications of p53 protein expression in relation to cell differentiation and proliferation activity in breast cancer remains controversial. (Tsutsui et al 2004) To reveal the mechanism of cell biological behavior changes in molecular pathology, in an attempt to predict the prognosis of breast ductal carcinoma, it

can be shown by measuring the expression of p53 protein in various tumor diameter, differentiation, growth and progression of histopathologic grading of breast ductal carcinoma.

This study point on whether there are differences in p53 protein expression in various size, differentiation, progression and grading breast ductal carcinoma histopathologically. This study aims to uncover the mechanism of protein expression differences in the molecular pathology of p53 and to prove the existence of differences in p53 protein expression in various size, differentiation, progression and grading breast ductal carcinoma histopathologically. From the aspect of the application of science, knowing the difference in p53 protein expression in various sizes of differentiation, progression and histopathologic grading of breast ductal carcinoma, so this concept can be developed as a system to assess the degree of progression and proliferation of ductal breast carcinoma cells, which then can be used as basis for determine prognosis and appropriate therapy.

MATERIALS AND METHODS

This is an observational analytic research, using tumor tissue samples of breast ductal carcinoma patients in the Department of Anatomic Pathology Airlangga University School of Medicine Dr. Soetomo General Hospital Surabaya. In this research protein expression is identified, which reflects the biological behavior of breast ductal carcinoma, p53 protein and morphological tumor, namely: tumor diameter, differentiation, and progression (in situ, invasive and metastatic) and histopathologic grading (low, moderate and height) of breast ductal carcinoma.

Using cross sectional study, the objects of this study are cell and tumor tissue of ductal breast carcinoma that has been carried out operations in the Department of Surgery Airlangga University School of Medicine Dr. Soetomo General Hospital. Sampling porpose by sampling with matched for age, sex and test of homogeneity. Diagnosis using the procedures histopathological Hematoxylin-Eosin outward appearance, by examining cell morphology, tissue histopathologically structure and mitotic cells, conducted by two experts (specialists) pathology, by not knowing the identity of the subject to make a diagnosis by determining the diameter, differentiation, progression and histopathologic grading tumors, in the Department of Surgery Airlangga University School of Medicine Dr. Soetomo General Hospital. Assessment of p53 protein expression (apoptosis protein - DNA repair) Immunohistochemistry performed in the Department of Surgery Airlangga University School of Medicine Dr. Soetomo General Hospital, by specialists (specialist - consultant) pathology with immunohistochemical examination using monoclonal antibodies against this protein. Change the label color marker happens to be assessed by semi quantitative outward appearance.

RESULTS

Research Data

On the basis of inclusion criteria that have been determined and calculation of sample size, obtained 30 samples to be studied. Of the 30 samples studied, the ductal breast carcinoma patients age varied from 32 to 64 years, with average (mean) 45.3 years, the largest age group between 40 to 49 years. Of the 30 samples studied, showed the location of tumors in patients with right KDPD as many as 18 people or 60%, while patients with left KDPD of 14 persons or 40%. From the 10 samples studied, the age of patients ranged from 35 KDPD situ until 64 years, with the average (mean) is 49.7 year, most occurred in the age group between 40 to 49 years. Of the 10 samples studied, the size of the diameter of the tumors varied from patients with in situ KDPD 1 cm to 18 cm, with average (mean) is 5.6 cm, largest at the tumor diameter ≤ 2 cm and> 5 cm. Of the 10 samples studied, patients with tumor differentiation in situ KDPD nine cases or 90% is bad and one case or 10%, well differentiated. Of the 10 samples analyzed, the expression of p53 protein, tumor cells in situ KDPD patients varied from negative to positive, there were 3 cases or 30%.

Of the 10 samples studied, Invasive KDPD patients varied from 33 to 56 years, the average (mean) 45.5 years, mostly in the age group between 40 to 49 years. Of the 10 samples studied, tumor diameter Invasive KDPD patients varied from 1.5 cm to 10 cm, with average (mean) is 4:05 cm, largest at the size of> 2 cm to ≤ 5 cm. Of the 10 samples studied, the differentiation KDPD Invasive tumor patients varied from moderate to poor, mostly in group differentiation medium, ie six people or as many as 60%. From the 10 samples studied, the expression of p53 protein Invasive tumor cells KDPD patients varied from negative to positive, there were four patients or 40%. Of the 10 samples studied, the age of patients was found KDPD metastases varies from 32 to 50 years, with average (mean) is 40.7 years, mostly in the age group between 30 to 39 years. Of the 10 samples studied, tumor diameter KDPD metastases varies from 1 to 8 cm, with average (mean) is 3.35 cm, the largest in the group of ≤ 2 cm in size. Of the 10 samples studied, the differentiation of tumor metastases KDPD vary from moderate to poor, mostly poorly differentiated group, ie nine patients or as many

as 90%. Of the 10 samples analyzed, the expression of p53 protein KDPD Metastasis tumor cells varies from negative to positive. ie 7 patients or 70%.

Protein Expression Data Research on Various Variables

P53 Expression in Various Diameter Sizes KDPD Insitu

Of the 10 samples analyzed, the expression of p53 protein, tumor cells in situ KDPD vary from 1 + to 2 + at various diameter tumor tissue. KDPD situ cases with positive expression of p53 protein found in tumor tissue diameter size group of less than or equal to 2 cm (the value of 1 + and 2 +, each with two cases of patients), 2 <x ≤ 5 cm (the value of 1 + and 2 +, each 1 case patient). While KDPD group with tumor diameter> 5 cm in p53 protein expression with the value 1 + occurred in four patients or 40%. It was found that the excessive expression of p53 was not found on certain tumor size groups.

P53 Expression in Various Diameter Sizes KDPD Invasive

Of the 10 samples studied, it was found that p53 protein expression KDPD Invasive tumor cells varied from 1 + to 2 + at various tumor diameter. Invasive KDPD cases with p53 protein expression with a value of 2 + there is only the size of tumors in group 2 <X ≤ 5 cm, there were four people (40%). While KDPD with p53 protein expression with a value of 1 + occurred in all groups of tumor diameter, ie each two patients or 20%. Got the impression that there is an excessive expression of p53 found in tumor size group, large diameter, which falls in group size 2 <x ≤ 5 cm.

P53 Expression in Various Diameter Sizes KDPD Metastases

Of 10 samples analyzed, the expression of p53 protein KDPD cell metastases varies from values 1 + to 3 + on a variety of tumor size. P53 protein expression on Metastasis KDPD group size ≤ 2 cm in diameter with as many as one case value1 + (10%), the value 2 + as many as three cases (30%) and the value of 3 + 1 cases (10%). Diameter size group 2 <x ≤ 5 cm in the value of 1 +, 2 + and 3 + of each one cases (10%), while the group of> 5 cm at a value of 1 + and 2 + of each one cases (10%) . Metastasis KDPD positive expression of p53 protein found in all groups of tumor size ≤ 2 cm (4 patients or 40%), 2 <x ≤ 5 cm (2 patients or 20%), and> 5 cm that is as much a patient (10%) . While KDPD negative p53 protein expression occurred in all tumor size groups, each with a patient, or by 10%. It was found that the excessive expression of p53 tumor size of certain groups, ie ≤ 2 cm in size.

Table 1. p53 expression in various diameter sizes KDPD in situ

Tumor Diameter (cm)	p53 Expression				Total (%)
	0	1	2	3	
≤ 2	-	2	2	-	4 (40 %)
2 < x ≤ 5	-	1	1	-	2 (20 %)
> 5	-	4	-	-	4 (40 %)
Total	-	7	3	-	10 (100 %)

Table 2. p53 expression in various diameter sizes KDPD invasive

Tumor Diameter (cm)	p53 Expression				Total (%)
	0	1	2	3	
≤ 2	-	2	-	-	2 (20 %)
2 < x ≤ 5	-	2	4	-	6 (60 %)
> 5	-	2	-	-	2 (20 %)
Total	-	6	4	-	10 (100 %)

P53 Expression in Various Differentiation KDPD Insitu

Of 10 samples studied, the p53 protein expression of tumor cells varied from the value of in situ KDPD 1 + to 2 + at different differentiation of tumor cells. P53 protein expression in situ KDPD found on the differentiation of both groups with a value of 1 + as a sufferer atau10% of cases. KDPD with poorly differentiated group there were six cases (60%) with a value of 1 + and 2 + values were three cases (30%).

KDPD situ cases with positive p53 protein expression contained in the group of tumors with poor cell differentiation, there were three patients (30%). Negative p53 protein expression in the group of tumor cell differentiation of good and bad, that is each one and six patients or 10% and 60%. It was found that the expression of p53 protein is excessively on certain groups, namely poor cell differentiation.

Table 3. p53 expression in various diameter sizes KDPD metastases

Tumor Diameter (cm)	p53 Expression				Total (%)
	0	1	2	3	
≤ 2	-	1	3	1	5 (50 %)
2 < x ≤ 5	-	1	1	1	3 (30 %)
> 5	-	1	1	-	2 (20 %)
Total	-	3	5	2	10 (100 %)

Table 4. p53 expression in various differentiation KDPD in situ

Differentiation	p53 Expression				Total (%)
	0	1	2	3	
Fine	-	1	-	-	1 (10 %)
Medium	-	-	-	-	-
Bad	-	6	3	-	9 (90 %)
Total	-	7	3	-	10 (100 %)

P53 Expression in Various Differentiation KDPD Invasive

Of the 10 samples showed that the expression of p53 protein KDPD patients Invasive tumor cells varied from a value of 1 + to 2 + at various differentiation. C-erbB2 Expression in Invasive KDPD in differentiation medium with the value of group 1 + in 4 patients or 40% of cases and the value of 2 + were 2 cases (20%). KDPD poorly differentiated group there were two cases with a value of 1 + (20%) and the value of 2 + were 2 cases (20%). Invasive KDPD case of positive p53 protein expression in the group of moderate and poorly differentiated tumors, each with two patients (20%). While KDPD negative p53 protein expression in the same group of tumors, respectively four and two patients or 40% and 20%. It was found that there is not excessive expression of p53 protein found on certain groups.

P53 Expression in Various Differentiation KDPD Metastases

Of the 10 samples found that p53 protein expression KDPD Metastasis tumor cells varied from the value of 1 + to 3 + at various differentiation. C-erbB2 expression in KDPD metastases in group differentiation is with the value 2 + as much as 1 or 10%. KDPD poorly differentiated group there were three cases with a value of 1 + (30%) and the value 2 + as many as four cases (40%) and the value of 3 + 2 cases (20%). Positive p53 expression in the group of moderate and poorly differentiated tumors each one patients (10%) and six patients (% 60). Negative p53 expression in poorly differentiated group, the three patients or 30%. It was found that there is an excessive expression of p53 in the group of certain tumors, namely poor differentiation.

Table 5. p53 expression in various differentiation KDPD invasive

Differentiation	p53 Expression				Total (%)
	0	1	2	3	
Fine	-	-	-	-	-
Medium	-	4	2	-	6 (60 %)
Bad	-	2	2	-	4 (40 %)
Total	-	6	4	-	10 (100 %)

Table 6. p53 expression in various differentiation KDPD metastases

Differentiation	p53 Expression				Total (%)
	0	1	2	3	
Fine	-	-	-	-	-
Medium	-	-	1	-	1 (10 %)
Bad	-	3	4	2	9 (90 %)
Total	-	3	5	2	10 (100 %)

P53 Protein Expression in Different Grading of Invasive KDPD

Of the 10 samples showed that the expression of p53 tumor cells varied from values KDPD 1 + to 2 + at different grade tumors. P53 protein expression contained in the grade I group with a value of 1 + 1 case (10%), grade II with a value of 1 + and 2 + as much value each 2 cases (20%). KDPD grade III group there were three cases with a value of + (to 30%), and the value 2 + were 2 cases (20%). P53 expression was positively present in the group of grade II tumors, namely two patients (20%) and grade III by two patients (20%). It was found that there is no excessive expression of p53 protein found on certain tumor groups.

Table 7. p53 expression in various histopathologic grading KDPD invasive

Histopathologic Grading	p53 Expression				Total (%)
	0	1	2	3	
Grade I	-	1	-	-	1(10 %)
Grade II	-	2	2	-	4 (40 %)
Grade III	-	3	2	-	5 (50 %)
Total	-	6	4	4	10 (100 %)

P53 Protein Expression in Various Grading KDPD Metastases

Of the 10 samples showed that the expression of p53 protein, tumor cells vary from patient KDPD value of 1 + to 3 + on a variety of histopathologic grading. Expression of p53 protein in the group of Grade II value of 2 + as a sufferer or a 10%. Group III KDPD grade 3 cases with a value 1 + (30%), the value 2 + in 4 cases (40%) and the value of 3 + 2 cases (20%). Positive p53 expression in the group of grade II tumors, ie one (10%) and grade III by six patients (60%). It was found that excessive p53 expression in tumors grade III.

Table 8. p53 expression in various grading KDPD metastases

Histopathologic Grading	p53 Expression				Total (%)
	0	1	2	3	
Grade I	-	-	-	-	-
Grade II	-	-	1	-	1 (10 %)
Grade III	-	3	4	2	9 (90 %)
Total	-	3	5	2	10 (100 %)

Research Data Analysis

With One-Sample Kolmogorov-Smirnov Test, p53 protein expression ($p = 797 > \alpha = 0.05$), indicating that research data are in the normal distribution range.

Analysis of p53 Protein Expression in Various Diameter Sizes KDPD

In terms of statistical analysis, homogeneity test data for each study variable to be tested. With the Box's Test of Equality of covariance Matrices of expression data in various sizes KDPD p53, got Box's M = 40.297 with sigma = .055> $\alpha = 0.05$, indicating that the variance-covariance matrix of all variables p53 same expression for each tumor size group, which means that all research

data homogeneous. Table 9 shows the average (mean) expression of p53 in tumor KDPD groups of various sizes, ie <2 cm,> 2 - <5 cm, and> 5 cm.

From the table shows the expression of p53 in different groups collectively KDPD size is different, proven methods of multivariate statistical test of Wilks' Lambda ($p = 0.000 < \alpha = 0.05$). From the table shows that the expression of p53 in different groups KDPD size (<2 cm,> 2 - <5 cm, and> 5 cm) is different, evidenced by multivariate statistical tests Hotelling's Trace, $p = 0.000 < \alpha = 0.05$. Tables and figures show the average difference (mean) expression of p53 in group KDPD in various sizes, ie <2 cm (35.91),> 2 - <5 cm (36.64), and> 5 cm (16.50).

Table 9. p53 expression on different size diameter KDPD

Protein Expression	Tumor Diameter		
	≤ 2 cm	>2 - ≤ 5 cm	> 5 cm
	Mean	Mean	Mean
p53	35.91	36.64	16.50

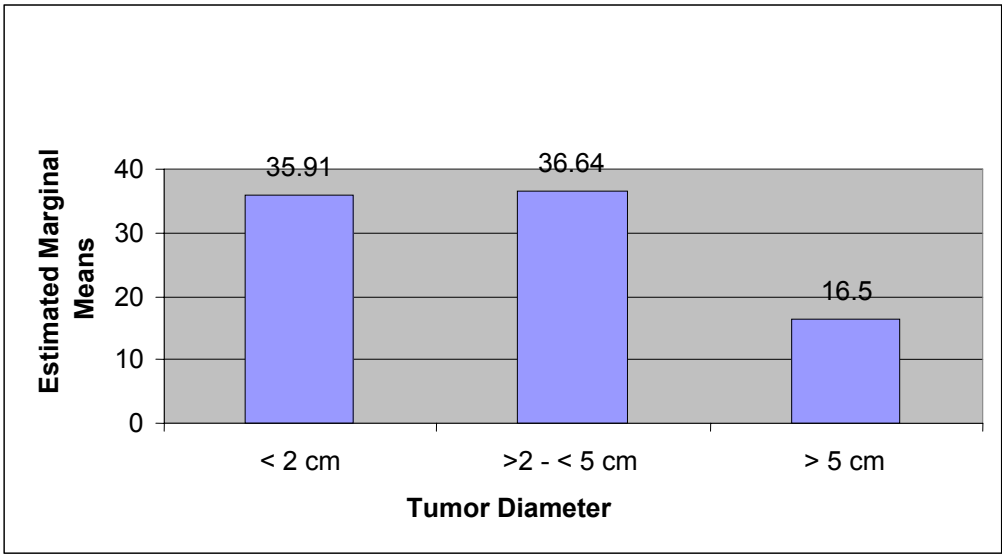

Figure 1. p53 protein expression on different size of tumor diameter

Analysis of p53 Protein Expression in Various Differentiation KDPD

With the Box's Test of Equality of covariance Matrices of p53 protein expression data at various KDPD cell differentiation, showed that Box's M = 13.998 with sigma = 0.426> α = 0.05. Variance-covariance matrix of all variable expression of p53 is the same for each group of tumor cell differentiation, it means that all research data is homogeneous. Table 10 shows the difference in average (mean) expression of p53 protein in tumor KDPD groups with different cell differentiation. The table shows that the expression of p53 in different groups collectively KDPD cell differentiation was different, with proven statistical multivariate Wilks' Lambda ($p = 0.000 < \alpha = 0.05$).

From the table shows that p53 protein expression in various cell differentiation KDPD different groups, evidenced by the multivariate statistical tests Hotelling's Trace $p = 0.000 < \alpha = 0.05$. Tables and figures show the average difference (mean) expression of p53 in group KDPD with various cell differentiation, ie differentiation of both (10.00), medium (18.71) and bad (35.86). From the table shows that the expression of p53 in various tumor cell differentiation KDPD group is different, with a multivariate test statistic Wilks' Lambda ($p = 0.000 < \alpha = 0.05$).

Table 10. p53 protein expression on various cell differentiation KDPD

Protein Expression	Tumor Differentiation		
	Fine	Medium	Bad
	Mean	mean	mean
p53	10.00	18.71	35.86

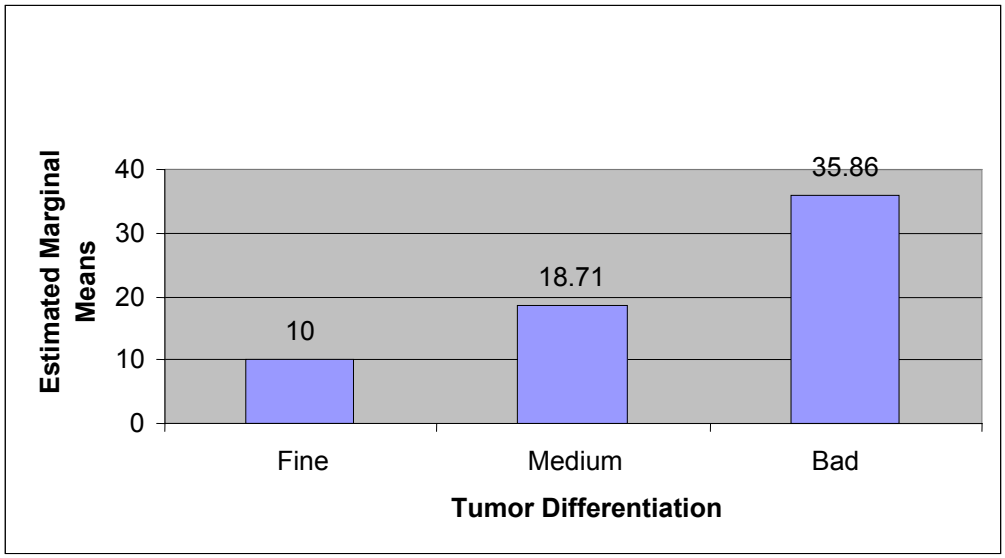

Figure 2. Expression of P53 protein in various tumor cell differentiation KDPD

Analysis of p53 Protein Expression in Various Progressivity KDPD

By using the Box's Test of Equality of covariance Matrices of p53 expression data of progressivity KDPD, showed that Box's M = 17.604 with sigma = 0.843> α = 0.05, variance-covariance matrix of all variable expression of p53 is the same for any group of progression of tumor growth , which means that all research data is homogeneous. Table 11 shows the difference in average (mean) expression of p53 tumor KDPD with tumor progression, namely in situ, invasive and metastatic. From the table shows that the expression of p53 in various tumor progression KDPD together is different, with proven statistical multivariate Wilks' Lambda (p = 0.000 <α = 0.05). From the table shows that the expression of p53 in various tumor progression KDPD is different. This is evidenced by multivariate statistical tests Hotelling's Trace p = 0.000 <α = 0.05. The table and figure above shows the difference in average (mean) expression of p53 protein in tumors KDPD on various progressivity, namely breast ductal carcinoma in situ (16.80), KDPD invasive (24.70), and KDPD metastases (51,50).

Table 11. p53 protein expression in various progressivity KDPD

Protein Expression	Tumor Progressivity		
	In situ	Invasive	Metastasic
	Mean	Mean	Mean
p53	16.80	24.70	51.50

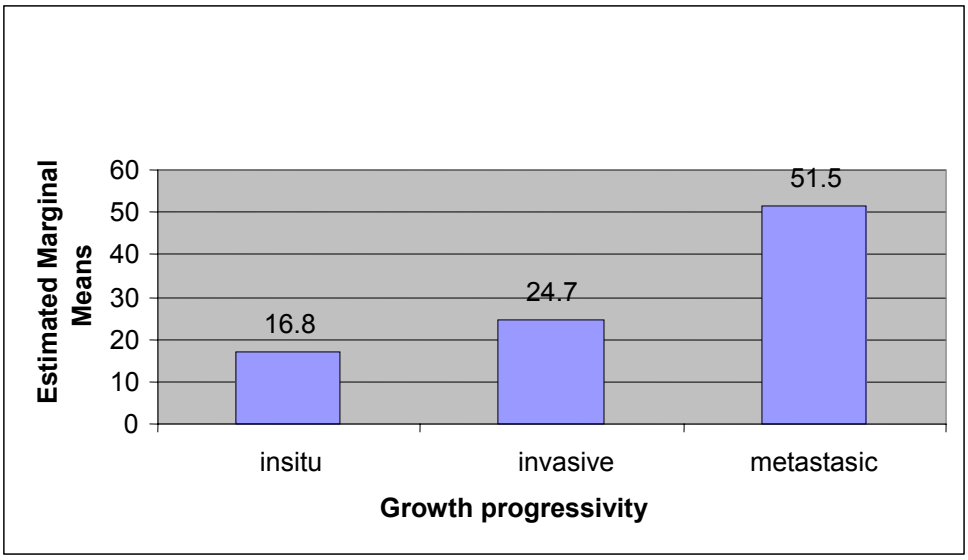

Figure 3. p53 protein expression in various progressivity KDPD

DISCUSSION

In this research note that the age of ductal breast carcinoma patients (KDPD) ranged from 32 to 64 years (mean 45.3 years), with the largest at the age group between 40 to 49 years of breast ductal carcinoma in situ found in most age groups between 40 to 49 years, with average age of 49.7 years. Most invasive ductal breast carcinoma located in the age group between 40 to 49 years, with a mean age of 45.5 years. Most breast ductal carcinoma metastases found in the age group of 30 to 39 years, with a mean age of 40.7 years. This is consistent with previous reports stating that breast ductal carcinoma is rarely found in women before age 25 years, except in families with a history of the disease. Neoplasms that occurred at an earlier age has been known that more progressive history of the disease and have a poorer prognosis. These diseases are reported to increase from one among the 323 women in four decades to become one among the 29 women in the seventh decade. (Cotran et al., 1999; Kumar V., et al., 2005) The modernization process led to many physical and psychological stressors, unhealthy food because of contamination with harmful substances, the wrong treatment, viral infections, exposure to pollutants and waste industrial products that are not friendly to health and environment, plus the existence of the vulnerability of the body that is triggered by genetic lesions, causing the incident KDPD found earlier and more progressive growth. Environmental conditions, social systems, and psychiatric someone can cause behavioral changes in unhealthy life habits. Environmental stimulation and information can also cause early menstrual changes in women today. Early menstruation is one of the factors increasing incidence of breast carcinoma. (Kumar V., et al., 2005)

Another interesting feature can also be found on the tumor location data of breast ductal carcinoma (KDPD), where all sample groups (KDPD situ, invasive and metastatic), shows the same information, namely that 60% occurred in the right breast and the rest occur in the left breast. The occurrence of breast cancer is associated with many women who do not have kids or absence of activity of lactation. This is very probably due to physiological activity does not occur in breast ductal epithelial cells. In general, children performed breastfeeding women in Indonesia, much more frequently in left than right breast. This causes the physiological activity of the right breast more or less than the left. So it is understandable that the KDPD more often found on the right breast. Therefore, lactation activity should be performed in a balanced between right and left breast. In this regard, the publication issued by the WHO, said that lactation has a protective effect against the occurrence of breast carcinoma, so that now the duration of breast milk (lactation) was extended to up to two years (Tavassoli FA., et al., 2003)

From the survey data obtained information that the tumor diameter varied from less than 2 cm to more than 10 cm. Breast ductal carcinoma in situ are found in most large in diameter, tumor size <2 cm and> 5 cm, with average size 5.6 cm. Most invasive KDPD found on the large size of the tumor diameter of more than 2 cm to less than or equal to 5 cm, with average size 4.05 cm diameter tumor. KDPD metastases found at most large tumor diameter less than or equal to 2 cm, with a mean diameter of 3.35 cm. It is inferred that KDPD carcinoma in situ has a lower degree of malignancy compared with invasive or metastatic KDPD. Patient endurance ductal carcinoma in situ is also said to be more powerful compared with invasive ductal carcinoma or metastases. It is evident that the research sample, breast ductal carcinoma in situ are found the process of fibrosis and inflammatory cell infiltration around tumor growth. Such conditions resulted in an average diameter at breast ductal carcinoma in situ can be relatively larger. That information caused the tumor diameter is less reflects the biological activity of breast ductal carcinoma. Data from research shows the impression that the more progressive growth of breast ductal carcinoma smaller the diameter of the tumor. Such situation can occur also because of possible biological activity KDPD cells not only one kind of cascade to the process of increasing proliferation (cell cycle) alone. Also occurs in tumor cells of other processes, such as biological activity to penetrate and pass through the basal membrane, infiltration and invasion through the connective tissue stroma of invasive KDPD Buffer. Biological activity can also occur in KDPD cell metastasis, such as the ability to escape from the bond of tumor cells to be able to live in other organs or lymph nodes by passing vessels and participate in the blood or lymph flow toward a new metastases. Therefore, tumor diameter did not show significant as a determinant of prognosis of breast carcinoma. (Tsutsui S., 2004)

Differentiation of tumor cells that reflects the biological activity, mainly represented by the shape and size of tumor cells, particularly tumor cell nucleus and cell nucleus chromatin conditions. From the research data obtained information that the differentiation of tumor cells in situ KDPD 10% is good, while 90% poorly differentiated tumor cells. Breast ductal carcinoma (KDPD) consists of 60% of invasive tumor cells are differentiated and 40% were bad. While breast ductal carcinoma (KDPD) metastases, comprising 10% of tumor cells are differentiated and 90% were poorly differentiated. When viewed closely it appears that there are interesting things KDPD in two groups, namely in situ carcinoma and metastases. Both showed a high cell activity, which appeared with 90% tumor cells KDPD are poorly differentiated. This may occur because of biological activity, particularly in the nucleus of cells associated with increased tumor cell activity in preparation for KDPD infiltration and invasion in situ, and is associated with the activity of tumor cells to migrate to other places through the blood or lymph vessels pada KDPD metastases.

In breast ductal carcinoma in situ 90% have type poorly differentiated blackheads and 10% other types (kribriformis) that have a good differentiation. KDPD situ blackheads type has a higher biological activity than other types, so having a high ability to proliferate. Therefore there is a significant increase in the number of cells, but not with the formation neovaskularisasi dimbangi adequate, resulting in necrosis of tumor cells in the central part. Information from earlier research shows that biological activity in situ type of blackheads KDPD higher than other types. (Tsuda H., 2005) The differentiation KDPD metastases have worse than invasive. This suggests that the differentiation of tumors that reflect the biological activity of tumor cell growth is reflected in the progressivity of KDPD. It is known that the more poorly differentiated tumors, the more progressive KDPD growth. Therefore, tumor differentiation has a significant correlation with the biological activity of cells, with demonstrated with increased oncoprotein expression by tumor cell compiler. (Tsusui S., 2004, Tsuda H., 2005)

Histopathologic grading (grade) which reflects the morphological description of the tumor tissue, pleomorfisitas cells and mitotic activity of cells, in this study indicate that in the number of grade I invasive KDPD as many as 10%, 40% grade II and grade III 50%. In KDPD metastases number as many as 10% grade II and grade III by 90%. These data indicate that the more progressive KDPD growth, the higher the grading histopatologisnya. In this study indicate that histopathologic grading KDPD metastatic tumors was higher than KDPD invasive. This is consistent with previous research reports, which stated that the biological activity of tumor cells as indicated by excessive expression of several oncoprotein, occur in KDPD with histopathologic grading of high picture and both have positive correlation values. (Tsuda H., 2005)

In this study, although all three groups of sample data (ductal carcinoma in situ, invasive and metastatic) are the same, but the actual overall populasai number of breast ductal carcinoma in situ which is the early phase of cancer growth, not until it reached 10% of patients. Even microscopically obtained data that the differentiation of breast ductal carcinoma cells that are still good only between thirty-one patients overall sample (3.33%). Such conditions will cause cancer management has become increasingly difficult and requires greater costs, treatment outcomes can be worse

than if the disease is found and treated appropriately at an early stage. As has been known that cancer will provide clinical complaints when it's happening at the level of tissue disorders, organ or system in the human body. The same condition also found in previous research reports, the data showed that most patients with ductal breast carsinoma found after the information phase and the degree of malignancy (grading histopathologically) high and poor differentiation. In Part / SMF / Anatomy Pathology Airlangga FK - RSU. Dr. Soetomo, of all malignant breast ductal epithelium, it was reported that 43% were breast carcinoma with a high degree of malignancy and poor differentiation of cancer cells (Susraini, 2001)

As has been known that cancer progression starting from the occurrence of changes at the sub cells, and cells certain cell groups, tissues, before continuing on the organs and body systems are more extensive. (Kumar, et al., 2005) Occur thought that should the diagnosis and prognosis determination could be done on time before the occurrence of symptoms and clinical signs and morphological abnormalities. Furthermore, treatment options could be done based on the diagnosis and determining the prognosis of the abnormalities that occur in sub-cell level, before the clinical signs and symptoms that lead to dysfunction of organs and systems in the human body. Researchers had thought that it was time for the medical world is now sub-cell approach as the basis and foundation of thought and decision-making steps in the diagnosis, determining prognosis and choice of cancer therapy, even long before that step is prevention.

This study is expected to reveal the molecular mechanism of pathology cascade path that starts from stimuli stimulus type ligand growth factors (GF) extra cells that subsequently bind to cell surface receptors and form a complex bond that will stimulate and trigger a complex reaction and complicated but orderly and trace until in the cell nucleus, with the target affects the function of specific genes in the nucleus, especially in relation to growth or tumor cell proliferation. In general, human cells are in resting state until receiving a signal from outside that change the behavior of specific biological signals in accordance with information received. Growth, differentiation and survival of normal cells rely heavily on information received by an external signal. This process begins when a cell signaling molecule produced information.

The signal is then binds to receptors on the cell surface of specific targets, and provide no biological impact on cells that do not display receptors that are not relevant. Binding of an extra signal molecules on the cell receptor stimulates the intrinsic biochemical functions of the corresponding cell receptors. Furthermore, these receptors are activated, will modify the line that controls intracellular gene expression, cycle control, metabolism, cytoskeleton architecture, cell adhesion and migration. Therefore it is understood that various signaling molecules may organize various aspects of the biological behavior of the cell, including its growth. The process occurs sequentially in a cell in response to stimuli and lasted in a very orderly biochemical cascade that starts from the receptors on the cell membrane to the nucleus and activate various transcription factors. Cell growth cycle is controlled by various oncogenes (genes trigger) and suppressor gene (gene inhibitors), which produces a variety of proteins and serves as a component in the signal transduction that allows cells to respond to stimuli from the outside. Abnormalities in oncogenes (genes triggers) and / or suppressor genes (genes inhibiting) tumors can produce an abnormal protein with abnormal function of signal transduction, which causes malignant transformation. (Krisno B., 2003)

Many growth factors (GF) and its receptor is known. Most of them are groups tirosine protein kinase (PTK). PTK receptors normally activated by ligand binding to the extracellular domain. Tirosine protein kinase activation induces dimerization of the receptor protein kinase tirosine, then cross-phosphorylation occurs between residues tirosine each (autofosforilasi). Binding of ligand to its receptor alter the structure and function of receptors from dormant to active state and stimulate various biochemical receptor intrinsic functions concerned. Various ligands, such as epidermal growth factor (EGF), can act as a mitogen to stimulate proliferation. Family ligand growth factor (GF), which acts as an external signal binds to its receptor (EGFR or c-erbB), then these receptors activates a variety of "signal transduction pathways" includes the Ras path that will synthesize and maintain the stability of cyclin D, which binds CDK4 form a complex with cyclin D-CDK4. CyclinD-CDK4 complex would memfosforikasi Rb binding to E2F proteins (E2F-Rb complex forms) in the cell nucleus. Rb contained in the E2F-Rb complex is active, but otherwise with E2F proteins, which is one of transcription factors in the cell is in an inactive state. Phosphorylated Rb becomes inactive, causing E2F proteins released from E2F-Rb complex bond and make the transcription activity of E2F becomes active. Active E2F is encouraged trakskripsi cyclin E, cyclin A and other proteins needed by cells to pass through "restriction point" in late G1 phase, thus running the cell cycle. The cell cycle can be stopped in response to DNA damage and stress in other cells mediated by p53. Expression of p53 itself under the influence of negative regulation by MDM2, a negative regulatory function can be inhibited by p14ARF. Tues carcinomas

frequently show disturbances role of p53, resulting in a decrease or loss of function of this protein.

In molecular pathology of p53 protein expression and relationship KDPD growth can be shown by the increasing significantly between the expression of these proteins at different tumor sizes, large diameter (ie <2 cm,> 2 - <5 cm, and> 5 cm), differentiation (well, medium and bad), the progressivity KDPD (in situ, invasive and metastatic), and histopathologic tumor grading (low, medium and high). This means that the protein expression of the above work on the determination of various sizes, large diameter of tumor differentiation, tumor progression and histopathologic grading KDPD. P53 protein in normal cells is as controlling the DNA repair process and trigger the occurrence of events of programmed cell death (programmed cell death). KDPD function in tumor cells p53 protein expression was reduced even be lost. So that in tumor cells with damaged genetic had no opportunity to get repairs and continued to follow the process of proliferation and can not be programmed death (apoptosis), so that cell cycle control. Thus it is understandable that the accumulation of genetic damage in tumor cells has increasingly become more widespread. P53 protein expression like this is detected and reacted positively in the study. In nearly all human cancer cells most commonly found mutations in the p53 gene. (Duffi M., 2005) P53 gene protein expression assessed by semi quantitative immunohistochemical examination. To show the difference between all the protein expression of various groups of tumor diameter, differentiation, progression and histopathologic grading of breast ductal carcinoma (KDPD) jointly conducted a multivariate test.

Protein expression suggests a relationship is not linear with increasing tumor diameter. Even looks the impression there is an inverse relationship, which decreased protein expression (mean expression) in a large increase in the size of the tumor diameter KDPD. That this was partly because the large size of the tumor diameter is not all reflect the biological activity of the constituent cells. Even in tumor metastasis KDPD indicated by the diameter of the small size. In KDPD biological activity of tumor cell metastasis is the most high. But the biological activity as reflected in protein expression and gene not only controls the cell cycle control, but also cell metabolism, cytoskeleton architecture, cell adhesion and migration. Thus, it is understood that although the relative size of the metastases KDPD diameter smaller than the KDPD situ and invasive, but grew more progressive. In the present study had previously been reported that age, tumor size, type of surgery, therapy adjuvant chemotherapy, adjuvant hormonal therapy, and post operative radio therapy, have a non-significant p value in the prognosis. (Tsutsui S., et al., 2004)

Multivariate analysis of p53 protein expression on various tumor differentiation of breast ductal carcinoma (KDPD) showed a positive linear correlation, which increases protein expression (mean expression) to increase the biological activity of cells, namely tumor differentiation KDPD worse. This occurs because the tumor differentiation reflects the biological activity of tumor cells KDPD. Nevertheless the statistical tests that can be seen from the table show that cp53 protein expression in various differentiation KDPD is different, with the proven methods of multivariate statistical tests, Wilks' Lambda $p = 0.000 < \alpha = 0.05$. It is reported that previous research has obtained information which indicates that there is a correlation between p53 protein expression with tumor cell differentiation, with $p < 0.0001$.

That p53 protein expression increases with tumor progression in this study, may be explained that the p53 protein expressed by tumor cells KDPD still not normal p53 protein (wild type), but the protein had changed with the decline or loss of function of the truth. So the ability to inhibit tumor cell growth was reduced or lost. Almost all malignancies that occur in humans, found a mutation in the gene p53. There is a positive linear relationship, where increased protein expression (mean expression) to increase the biological activity of cells, namely with the increasing tumor grade KDPD. This occurs because the increase in tumor grade was KDPD reflects the biological activity of the tumor. Based on the data and discussion of the results obtained in this study, that tumor cell differentiation (morphological), p53 protein expression (morphofunctional) had significant prognostic value of breast ductal carcinoma, which subsequently can be used as a tumor marker in determining the prognosis and choice of appropriate therapy in carcinoma ductal breast (KDPD).

CONCLUSIONS

P53 protein expression was significantly different in various tumor diameter (<2 cm,> 2 cm to <5 cm and> 5 cm), differentiation (well, moderate and bad), the progressivity of the growth (in situ, invasive and metastatic) and the histopathologic grading (low, medium and high) in breast ductal carcinoma, which is the morphological appearance and clinical manifestations. Growth process of breast ductal carcinoma (KDPD), as indicated by the size, differentiation, progression and histopathologic grading, is one of the functions of accumulation of p53 protein expression in tumor cells. P53 protein (of apoptosis and

DNA repair genes) expressed increased significantly and linearly on a variety of differentiation, progression of growth and histopathologic grading in ductal carcinoma of breast (KDPD). P53 protein is produced and expressed by tumor cells differ from normal cells, which causes decreased p53 protein function (hipofungsional) or lost (afungsional) altogether. This can occur due to mutation of the p53 gene.

P53 protein expression can be used as a marker for morphofunctional in an attempt to determine prognosis and appropriate treatment options in breast ductal carcinoma tumors (KDPD). Differentiation parameters can be used as a morphological marker in an attempt to determine prognosis and appropriate treatment options in breast ductal carcinoma tumors (KDPD).

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