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# The Relationship Of Hormonal Receptor, Her-2 And Ki-67 Changes After Administration Of Anthracycine-Based Neoadjuvant Chemotherapy With The Results Of Histopathological Grading In Stage Iii Breast Cancer Patiens At Saiful Anwar Malang Regional Public Hospital 2018

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***Abstract***
***Background:***
*Breast cancer is a cancer with the highest incidence in women worldwide. It also has a very high mortalitydue to late treatment. The most common treatment of stage III breast cancer is administration of neoadjuvant chemotherapy (NACT), which aims to reduce tumor size and control micro metastasis. Immunohistochemical examination is an important factor in determining breast cancer subtypes and subsequent therapy. However, NACT has been reported to change the expression of immunohistochemical examinations of Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor-2 (HER-2) and Ki-67 examined from biopsy and mastectomy preparations, so the breast cancer subtypes and its histopathological grading change.*
***Method:*** *We graded the changes in immunohistochemical examinations of ER, PR, HER-2, Ki-67 and histopathological grading from 59 cases of stage III breast cancer after NACT administration. We analyzed the relationship between the changes in the expression of immunohistochemical examinations on the biopsy tissue specimens before NACT administration and from the tissue mastectomy after NACT administration associated with its histopathological grading with spearman correlation analysis.*
***Findings:*** *There were changes in the results of the expression of immunohistochemical examinations of ER, PR, HER-2, KI-67 and histopathological grading by 23.7%, 22.03%, 32.2%, 32.2% and 40.68% in stage III breast cancer patients who received NACT. There was a relationship with a weak correlation between the changes in immunohistochemical examinations of ER, PR, HER-2 and KI-67 with the changes in histopathological grading. The correlation coefficients between ER, PR, HER-2, Ki-67 and the histopathological grading were r=0.265, r=0.317, r=0.352 and r=0.335.*
***Conclusions****: Patients with stage III breast cancer who were treated with NACT experienced changes in the expression of immunohistochemical examinations of ER, PR, HER-2 and KI-67 and would experience changes in histopathological grading, causing changes in the breast cancer subtypes. The changes that occur must be interpreted carefully since it will change the subsequent therapy. Therefore, it is necessary to conduct further research on the therapy response to patients who experience changes in the expression.*
***Keywords:*** *ER, PR, HER-2, KI-67 andhistopathological grading*

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## I. Introduction

According to global data, breast cancer is a cancer with the highest incidence in women worldwide which is equal to 25% of all cancers in women with a proportion of 27-92 among 100.000 residents. It is also a disease with the second largest mortality after lung cancer, which is 12.9% (WHO, 2013). In Indonesia, it is the second highest number of cancer after cervical cancer, the ratio between breast cancer and cervical cancer is 5:8 and in a short time is expected to be a cancer with the highest incidence in women (Riskesdas, 2013). Data from *Komite Penanggulangan Kanker Nasional* (KPKN) up to February 2017 showed that the number of breast cancer patients increased compared to cervical cancer patients. This is because early detection of cervical cancer is easier by using Visual Acetic Acid Inspection (IVA) and Pap smear methods, and cervical cancer can be prevented by using Human Papilloma Virus (HPV) vaccine (Soehartati G, 2017).

The mortality from breast cancer is quite high since many patients come with late conditions. Many studies have shown that with an early detection, it can save thousands of lives every year. Based on data from Dharmais National Cancer Center Hospital, the number of breast cancer patients who come in the early stages (stage I and II) is 13.42%, stage III is 17% and many more (29.98%) come with an advanced stage (stage IV). Most patients come with recurrence, which is equal to 39.66%. Diagnostic delay can be caused by patient delay, doctor delay, or hospital delay (Purwanto DJ, 2010).

Breast cancer consists of various complex and heterogeneous subtypes that have different clinical properties. These various subtypes require individualized treatment. In addition to treatment based on conventional prognosis factors such as menopause status, age and stage, currently treatment is also based on bio molecular examination (Fumagalli et al, 2012). Several modalities for the breast cancer therapy indicate possible variations in the treatment. For instance, development of surgical technique, radiation therapy, hormonal therapy, target cell therapy and chemotherapy to alternative or complementary treatment (Purwanto H et al., 2015).

Locally advanced breast cancer (LABC) is stage III breast cancer, its presentations or incidents in Indonesia are still quite high and vary from various educational centers, ranging from 40-80%. Included in the stage III breast cancer are stage IIIA, IIIB and IIIC breast cancer. Stage III therapy is recommended in the form of neoadjuvant chemotherapy, neoadjuvant hormonal therapy and neoadjuvant radiation. The role of surgical modality in LABC is limited, especially in stage IIIA, and in several studies, the administration of neoadjuvant chemotherapy at the stage is still a benchmark. The recommended surgery after neoadjuvant chemotherapy is Modified Radical Mastectomy (MRM) or standard radical mastectomy (Halstedt mastectomy). Postmenopausal patients with positive hormone receptors can be given hormonal neoadjuvant therapy. The grading can be done in 4 months after administration. If it is not responsive or progressive, then the neoadjuvant chemotherapy is given (Peraboi, 2015; Purwanto H, 2015).

*Neoadjuvant Chemotherapy* (NACT) is the administration of chemotherapy before surgery. NACT aims to reduce tumor size (tumor shrinkage) and control micro metastasis. The administration of NACT can prevent tumor multiplication and allow significant regression of the primary tumor so that the surgery can be performed. NACT is given to locally advanced stage or stage III breast cancer (Suyatno et al., 2014). The most frequently used and most cost-effective NACT is anthracycline-based NACT since this regimen is quite sensitive and cheap.

Immunohistochemical examination (IHK) is an examination method byusing antibody as a marker for detecting antigens in the tissue sections or other cell preparation forms.

IHK is a standard in determining breast cancer subtypes. Its determination will play a role in helping to determine the type and prediction of the response to its systemic and prognostic therapies. The standard IHK done for breast cancer is hormonal receptors, namely *estrogen receptor* (ER) and *progesterone receptor* (PR),*Human Epidermal Growth Factor Receptor-2* (HER-2) and Antigen KI-67 (Ki-67). Hormonal receptors play a role in the administration of hormonal therapy in breast cancer while HER-2 plays a role in the administration of the targeting therapy (Halls, 2015).

Immunohistochemicalexaminations before and after NACT administration show significant changes from hormonal receptors (ER and PR) and HER-2 expressions (Kaya Osman et al, 2010). NACT will significantly reduce HER-2 and Ki-67 expressions. However, it does not significantly alter the hormonal receptors (ER and PR) in patients with stage III breast cancer (Avci Nilufer et al, 2015). From the background above the writers are very interested in conducting research on changes inimmunohistochemical examinations (ER, PR, HER-2 and Ki-67) after the administration of anthracycline-based neoadjuvant chemotherapy with the results of histopathological grading in patients with stage III breast cancer. Where the immunohistochemical examination is very important for hormonal therapy and targeting therapy that are known to be quite expensive, and if there is a change from this IHK examination, it is possible that the therapy still can be used.

## II. Research Method

This research was a descriptive analytic observational research with a prospective cohort approach aimed to find out the relationship of hormonal receptors (estrogen receptor and progesterone receptor), HER-2, and Ki-67 changes after the administration of anthracycline-based NACT with the results of histopathological grading changes in patients with stage III breast cancer at Saiful Anwar Regional Public HospitalMalang. This research was conducted at the Integrated Oncology Surgical Polyclinic of Saiful Anwar Regional Public Hospital Malang and Laboratory of Anatomy Pathology, Faculty of Medicine, Brawijaya University, conducted between January and December 2018.

The population of the research subjects was locally advanced stage or stage III breast cancer patients who fulfilled the inclusion criteria and had undergone examination procedures such as incisional biopsy/core biopsy, anthracycline-based NACT and had undergone definitive operative procedures for breast removal or breast cancer mastectomy that needed to have outpatient treatment in the Integrated Oncology Surgical

Polyclinic of Saiful Anwar Regional Public Hospital Malang. In this research, there was 1 research group that was in accordance with the inclusion criteria and exclusion criteria. Each patient was given informed consent and obtained an ethical clearance from the Health Research Ethics Commission of Saiful Anwar Regional Public Hospital Malang. From the preliminary data of the medical record of Saiful Anwar Regional Public Hospital Malang, it was found that the number of new breast cancer patients during 2017 was 196 patients in which 114 of them were patients with stage III breast cancer.

Inclusion Criteria:

- Women aged 30 – 70 years.
- Patients with locally advanced stage (stage III) breast cancer.
- Patients have undergone tissue biopsy or core biopsy procedures, NACT and definitive surgical procedures or mastectomy in Saiful Anwar Regional Public Hospital Malang.
- Patients are willing to take part in the research proven by signing an informed consent and approval sheet as research samples.
- Patients are not in a state of trauma, infection, obesity, and do not have metabolic diseases that can cause bias.
- Undergo*anthracycline*regiment *neoadjuvant chemotherapy* and give response to the administration of WHO-based *neoadjuvant chemotherapy* in the form of *partial response*and*complete respon*se.

Exclusion Criteria:

- History of*neoadjuvant* radiation in the chest area or*neoadjuvant* hormonal therapy.
- Patients withdraw themselves from the research.
- The doubtful results of histopathological or immunohistochemical grading.

**Research Variable**

Independent variables in this research were hormonal receptors(*estrogen receptor*and*progesterone receptor*), HER-2 and Ki-67 changes after the administration of anthracycline-based chemotherapy. Dependent variables in this research were the changes in the results of histopathological grading based on*Nottingham Grading System Score* in stage IIIbreast cancer patients.

**Research Findings**

There were 94 stage III breast cancer patients who underwent therapy at the Oncology Surgical Polyclinic of Saiful Anwar Regional Public Hospital Malang. From the total 94 patients, 28 patients were excluded from the research because the writers had to replace the anthracycline-based chemotherapy regiment due to its non-optimal response (stable disease and progressive disease) and 7 patients refused to join the research.

**Table 1. Characteristics of Research Samples**

| CharacteristicInterval | | Frequency | Percentage % |
|---|---|---|---|
| Age | ≤ 40 | 5 | 8.47 |
| | 41-50 | 23 | 38.98 |
| | 51-60 | 24 | 40.69 |
| | ≥ 61 | 7 | 11.86 |
| Stage | III A | 7 | 11.86 |
| | III B | 50 | 84.75 |
| | III C | 2 | 3.39 |
| Subtype | Luminal A | 11 | 18.64 |
| | Luminal B | 33 | 55.94 |
| | HER-2 | 7 | 11.86 |
| | Triple Negative | 8 | 13.56 |
| ChemotherapyResponse | *Partial Response* | 57 | 96.61 |
| | *Complete Response* | 2 | 3.39 |
| Histopathological Response | I | 10 | 16.95 |
| | II | 16 | 27.12 |
| | III | 33 | 55.93 |
| ER | Positive | 41 | 69.49 |
| | Negative | 18 | 50.51 |
| PR | Positive | 38 | 64.41 |
| | Negative | 21 | 35.59 |
| HER-2 | Negative/+ | 32 | 54.24 |
| | ++ | 7 | 11.87 |
| | +++ | 20 | 33.89 |
| Ki-67 | High | 43 | 72.88 |
| | Low | 16 | 27.12 |

Based on the characteristics of the research samples above, it can be seen that most of the breast cancer patients is aged between 51-60 years of 24 patients (40.69%), stage III B is 50 patients (84.75%), luminal B type is 33 patients (55.94%), *partial response* is 57 patients (96.61%), positive ER is 42 patients (69.49%), positive PR is 38 patients (64.61%), negative HER-2 is 32 (54.24%) patients, *high*proliferationKi-67 is 43 patients (72.88%) andthe highest hispathological grading is stage III with33 patients (55.93%).

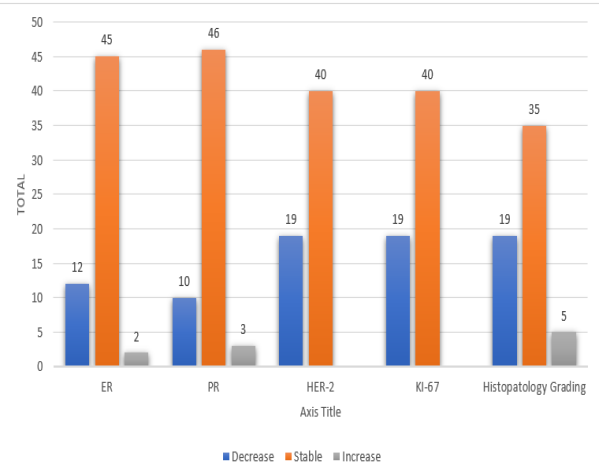


**Figure 1. Diagram of Changes in the Results of Immunohistochemical Examinations of ER, PR, Her-2 and Ki-67**

Based on the diagram above, there were changes in the immunohistochemical examinations of ER, PR, HER-2 and Ki-67 and histopathological grading after NACT administration in patients with stage III breast cancer. The changes in the immunohistochemical examinations were ER of 23.7%, PR of 22.03%, HER-2 of 32.2%, Ki-67 of 32.2%, and the change in istopathological grading was 40.68% after the administration of anthracycline-based neoadjuvant chemotherapy in stage III breast cancer patients.

In the immunohistochemical examination of ER, there were changes after NACT administration from positive to negative by 12 patients (20.34%), stable 45 patients (76.27%) andnegative to positive by 2 patients (3.39%). In the immunohistochemical examination of PR, there were changes after NACT administration frompositive to negative by 10 patients (16.95%), stable 46 patients (77.97%) andnegative to positive by 3 patients (5.08%). In the immunohistochemical examination of HER-2, there were changes after NACT administration from positive to negative by 18 patients (30.5%), stable40 patients (67.80%) and negative to positive by 1 patient (1.7%). Inthe immunohistochemical examination of Ki-67, there were changes after NACT administration from positive to negative by 19 patients (32.2%), and stable 40 patients (67.80. In the histopathological grading examination, there were changes after NACT administration namely increased by 5 patients (8.47%), decreased by 19 patients (32.20%), andstable by 35 patients (59.32%).

**Bivariate Analysis**

**The relationship of changes in immunohistochemical examination of ER with histopathological changes**

**Table 2. Cross tabulation of changes in immunohistochemical examination of ER with changes in histopathological grading**

| ER | Histopatology Grading | | | | | | Total | p | r |
|---|---|---|---|---|---|---|---|---|---|
| | Decrease | % | Stable | % | Increase | % | | | |
| Decrease | 6 | 50.00 | 5 | 41.67 | 1 | 8.33 | 12 | | |
| Stable | 13 | 28.89 | 30 | 66.67 | 2 | 4.44 | 45 | 0.000 | 0.265 |
| Increase | 0 | 0.00 | 0 | 0.00 | 2 | 100.00 | 2 | | |

The grading of the relationship between the changes in immunohistochemical examination of ER and changes in histopathologicalgrading after NACT administrationwas obtained from the *chi square*analysis with a *p* value = 0,000, because the *p* value = 0,000 < 0,05 (α=5%), it can be concluded that that there was a significant link between the changes in ER and the changes in histopathological grading. The correlational relationship by

using Spearman correlation analysis obtained a correlation coefficient value of r=0.265, so it can be concluded that that there was a weak correlation between the changes in ER and the changes in histopathological grading.

**The relationship of changes in immunohistochemical examination of PR with histopathological changes**

**Table 3. Cross tabulation of changes in immunohistochemical examination of PR with changes in histopathological grading**

| PR | Histopatology Grading | | | | | | Total | p | r |
|---|---|---|---|---|---|---|---|---|---|
| | Decrease | % | Stable | % | | % | | | |
| Decrease | 6 | 60.00 | 4 | 40.00 | 0 | 0.00 | 10 | 0.001 | 0.317 |
| Stable | 12 | 26.09 | 31 | 67.39 | 3 | 6.52 | 46 | | |
| Increase | 1 | 33.33 | 0 | 0.00 | 2 | 66.67 | 3 | | |
| Total | 19 | 32.20 | 35 | 59.32 | 5 | 8.47 | 59 | | |

The grading of the relationship between the changes in immunohistochemical examination of PR and the changes in histopathological grading after the administration of anthracycline-based NACT was obtained from the *chi square* analysis with a *p* value = 0,001, because the *p* value = 0,001 < 0,05 (α=5%), it can be concluded that there was a significant link between the changes in PR and changes in histopathological grading. The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.317, so it can be concluded that that there was a weak correlation between the changes in PR and the changes in histopathological grading.

**The relationship of changes in immunohistochemical examination of HER-2 with histopathological changes**

**Table 4. Cross tabulation of changes in immunohistochemical examination of HER-2 with changes in histopathological grading**

| HER-2 | Histopathology Grading | | | | | | Total | p | r |
|---|---|---|---|---|---|---|---|---|---|
| | Decrease | % | Stable | % | Increase | % | | | |
| Decrease | 11 | 57.89 | 7 | 36.84 | 1 | 5.26 | 19 | 0.014 | 0.352 |
| Stable | 8 | 20.00 | 28 | 70.00 | 4 | 10.00 | 40 | | |
| Total | 19 | 32.20 | 35 | 59.32 | 5 | 8.47 | 59 | | |

The grading of the relationship between the changes in immunohistochemical examination of HER-2 and the changes in histopathological grading based on the results of the *chi square* analysis with a *p* value = 0,014, because the *p* value = 0,014< 0,05 (α=5%), it can be concluded that that there was a significant link between the changes in HER-2 and changes in histopathological grading. The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.352, so it can be concluded that that there was a weak correlation between the changes in HER-2 and the changes in histopathological grading.

**The relationship of changes in immunohistochemical examination of Ki-67 with histopathological changes**

**Table 5. Cross tabulation of changes in immunohistochemical examination of Ki-67 with changes in histopathological grading**

| Ki67 | Grading PA | | | | | | Total | p | r |
|---|---|---|---|---|---|---|---|---|---|
| | Menurun | % | Tetap | % | Meningkat | % | | | |
| Menurun | 10 | 52.63 | 9 | 47.37 | 0 | 0.00 | 19 | 0.035 | 0.335 |
| Tetap | 9 | 22.50 | 26 | 65.00 | 5 | 12.50 | 40 | | |
| Jumlah | 19 | 32.20 | 35 | 59.32 | 5 | 8.47 | 59 | | |

The grading of the relationship between the changes in immunohistochemical examination of Ki-67 and the changes in histopathological grading based on the results of the *chi square* analysis with a *p* value = 0,035, because the *p* value = 0,035 < 0,05 (α=5%), it can be concluded that that there was a significant link between the changes in Ki-67 and changes in the histopathological grading. The correlational relationship by

using Spearman correlation analysis obtained a correlation coefficient value of r=0.335, so it can be concluded that that there was a weak correlation between the changes in Ki-67 and the changes in histopathological grading.

## III. Discussion

Breast cancer is the most common cancer in women worldwide. Based on the estimation from International Agency for Breast Cancer (IARC) in 2012, the incidence of breast cancer was 43.1 per 100,000 women with a mortality of 12.9 per 100,000 women. In Indonesia, the estimation reaches 134 per 100,000 women. Locally advanced breast cancer is stage III A, III B, and III C breast cancer. The recommended treatment modality is NACT or hormonal Neoadjuvant therapy (chosen based on the immunohistochemical examinations taken during biopsy of breast tumor tissue before), followed by surgery therapy or radiation therapy (Harry D. Bear et al, 2011).

NACT ischemotherapy done before surgery in cases of stage III breast cancer that aims to reduce tumor size and control micro metastasis. In NACT, the most commonly used regimen is anthracycline-based. The NACT grading is given at least after 2-3 cycles at 21 days intervals. The chemotherapy response is graded in a loco regional and systemic manner. The effects of chemotherapy can cause spontaneous death of the cancer cells, inhibit the formation of blood vessels, inhibit the division or replication of cancer cells and prevent the cell division by changing the structure of cancer cells (Lee et al, 2007). NACT will affect changes in the immunohistochemical examinations of ER, PR, HER-2 and Ki-67, and will also affect changes in its histopathological grading. With the changes in ER, PR, HER-2, Ki-67 and the changes in histopathological grading the response from subsequent treatment can be graded. In this case, the researchers would like to find out whether or there is a relationship or not between changes in immunohistochemical examination ER, PR, HER-2 and Ki-67 with changes in histopathological grading.

Immunohistochemical examinations of ER, PR, HER2 and Ki-67 are useful for molecular classification so that it is useful in determining the therapy to be given to breast cancer patients. This classification is based on the similarity of protein expression profiles. This gene expression-based classification is associated with effective treatment of breast malignancy (Rosai J. And Ackerman's, 2012).

*Neoadjuvant chemotherapy*is used for therapy in stage III breast cancer and the tendency to treat breast cancer based on the presence of ER, PR and HER-2 receptors. The changes in the status of the immunohistochemical examinations of ER, PR and HER-2 between the biopsy result tissue and mastectomy result tissue have been reported after NACT administration, but these results have not been consistent. The changes in the status of immunohistochemical examinations of ER, PR or HER-2 will have consequences for therapeutic, prognostic, and financial financing of important treatment for patients and health care providers. With the increased use of NACT, it is important to know whether there are changes in the examinations of ER, PR and HER-2 and the possible consequences for subsequent additional systemic therapy. NACT is able to change the expression and status of ER, PR, and HER-2 receptors (Van de Ven S et al, 2011: Zhang N et al, 2011).

**Changes in the results of the immunohistochemical examinations ofER and PR with changes in hispathological gradingafter NACT administration**

From the findings of this research, it was found that there was a link with weak correlation between the changes in the expressions of the immunohistochemical examinations of ER and PR with the changes in histopathological grading after NACT administration in stage III breast cancer. This research was in accordance with Guangchao et al.'s, 2015 research,which stated that there were significant changes in ER and PR receptors after NACT administration, namely the changes in immunohistochemical examination of ER by 28.6% and PR by 22.9%.Another research conducted by Bala Basak et al., 2014 also stated that there was a significant change in immunohistochemical ER and PR examinations after NACT administration by 12.5% and 21.2%

The changes in hormonal receptors from positive to negative were more common in the breast cancer with positive HER-2 than negative HER-2. In addition, the conversion of hormonal receptor status observed occured more frequently in tumors with poor differentiation than good differentiation. The relatively high proportion of Ki-67 index was found in breast tumors with positive to negative hormonal receptor changes compared to breast cancer which had a negative hormonal receptor status (Burcombe R. et al, 2005).

Chen *et al*, 2012 reported that patients with positive to negative hormonal receptor changes after NACT administration did not benefit from hormonal therapy compared to patients whose hormonal receptor status remained stable. In contrast, Hirata et al., 2009 reported that there were no significant differences in the level of Progressive Free Survival (PFS) and Overall Survival (OS) between patients given the hormonal therapy with hormonal receptors that turned negative, and patients given the hormonal therapy with hormonal receptor that turned negative, and patients given the hormonal therapy with hormonal receptor which remained positive after NACT administration.

**Changes in the results of the immunohistochemical examination of HER-2 with changes in the hispathological grading after NACT administration**

From the findings of this research it was found that there was a link with weak correlation between the changes in the expressions of immunohistochemical examination of HER-2 with the changes in histopathological grading after NACT administration in stage III breast cancer. The change in HER-2 expression was 32.2% of the total sample examined, and 57.89% experienced decrease in its histopathological grading. This was also in line with Neubauer et al.'s, 2008 research, which stated that there was a change in HER-2 expression after NACT administrationby 15%, where 85% was a change from the expression of positive HER-2 to negative HER-2. In contrast, Avci N. et al., 2015 stated that the presence of NACT would give a quite major change in the expression of immunohistochemical examination of HER-2 in breast cancer patients by 61.9%.

The changes in HER-2 expression were also related to the prognosis of breast cancer.The comparison of the results of HER-2 expression after NACT administration from the research was 32.25%, in which 57.8% of change in HER-2 expression was accompanied by a decrease in the tissue histopathology grading. Thus, it can be concluded that changes in HER-2 expression and the changes in the tissue histopathology grading had a better response to NACT administration. In other words, the changes in HER-2 expression and the changes in histopathological grading affected the success of neoadjuvant chemotherapy response of stage III breast cancer.

**Changes in the results of the immunohistochemical examination of Ki-67 with changes in hispathological grading after NACT administration**

From the findings of this research, it was found that there was a weak correlational relationship between the changes in Ki-67 expression and the changes in histopathological grading. The change in Ki-67 expression in this research was 32% after NACT administration. This research was in accordance with Ramteke P, et al.'s, 2017 research.which stated that there was a change in Ki-67 expression after NACT administration by 17%. Meanwhile, according to Guangchao Jin et al, 2015, the change in Ki-67 expression after NACT administration was 54.3%.

Ki-67 as a proliferative marker is a nuclear antigen in humans, and forms an integrated part with both normal cell division and malignant cell division. Because the characteristic of cancer is uncontrolled and continuous cell proliferation, the Ki-67 proliferation index is used to grade and manage breast cancer. The Ki-67 value is a prognostic indicator, a guide to select the therapies, and a method of measuring responses on the ongoing treatment. Grading of Changesin Ki-67 expression is related to Histopathological changes, where cancer cells that have high Ki-67 expression will have good response to chemotherapy (partial response and complete response), so that it will change the grading of tumor tissue histopathology (A. Mannell et al. 2016). The same thing was conveyed by Yin H F. et al, 2013, who stated that changes in cell proliferation and changes in tissue histopathology degrees were the most important factors that were effective in grading the effectiveness of neoadjuvant chemotherapy.

Qi-Xing Tan et al., 2014 reported that there were significant changes in the expression of immunohistochemical examinations of ER, PR in breast cancer with neoadjuvant chemotherapy. The changes in hormonal receptor status were found more frequently in tumors with positive HER-2 status, poor differentiation and a relatively high proportion of Ki-67 index. Progressive Free Survival and Overall Survival grading in patients with positive to negative hormonal receptor changes with chemotherapy will be worse than patients with constantly positive hormonal receptors after chemotherapy, while tumors with negative to positive hormonal receptor changes will have better prognosis.

Recently, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines that recommend re-biopsy of breast cancer metastasis to reevaluate expression of immunohistochemical examinations of ER, PR and HER-2. Nonetheless, the evidence is still lacking about whether there is a change for chemotherapy regimens to be carried out on the basis of changing biomarkers in the setting of adjuvant therapy. The panel consensus is usedas biomarker testing of the metastatic tumors to the appropriate direct therapy (Van Poznak C et al, 2015).

Lindstrom L.S.*et al*, 2012 stated that there wasno ASCO guideline about whether the exclusion of thebiopsy specimens must be retestedafter*neoadjuvant chemotherapy* therapy, and whether the adjuvant chemotherapy should be changedif there are changes. As a result, the practice is different throughout the world. The neoadjuvant chemotherapy is increasingly used before surgical resection of breast cancer, with a treatment regimen guided by hormonal receptor status and HER-2 expression from biopsy samples of breast tumors. Previous research has shown that biomarker expression can change after neoadjuvant chemotherapy in breast cancer. Several possibilities can explain the differences between hormonal receptors and HER-2 expression and amplification of ERBB-2 and Ki-67 genes after neoadjuvant chemotherapy.

## References


[1]. A Mannell. 2016. The role of Ki-67 in breast cancer. South Africa Journal Surgery vol. 54 no. 2

[2]. Avci Nilufer, Adem Deligonul, Sahsine Tulonay, Erdem Cubukcu, Omer Fatih Olmez, Ariefe Ulas, Mustafa Hartavi, Ender Kurt, Turkkkan Evrensei. 2015. Neoadjuvant Chemotherapy-Induce Change In Immunohistochemical Expresion Of Estrogen Reseptor, Progression Receptor, Her-2, And Ki-67 In Patiens With Breast Cancer. JBUON; 20(1): 45-49.

[3]. Bala Basak Oven Ustaalioglu, Fugen Aker Vardar, Ahmet Bilici, Gunay Gurleyik, Burcak Erkol, Umut Kefeli, Mehmet Aliustaoglu. 2014. Clinical importance of discordance of hormone receptors and Her2/neu status after neoadjuvant chemotherapy in breast cancer. JBUON; 19(4): 879-886.

[4]. Burcombe R, Makris A, Richman P, Daley F, Noble S, Pittam M, Wright D, Allen S, Dove J and Wilson G. 2005. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. Br J Cancer; 92: 147- 155.

[5]. Chen S, Chen CM, Yu KD, Zhou RJ and Shao ZM. 2012. Prognostic Value of a Positive-to-negative Change in Hormone Receptor Status after Neoadjuvant Chemotherapy in Patients with Hormone Receptor-positive Breast Cancer. Ann Surg Oncol; 19: 3002-3011.

[6]. Guangchao Jin, Yu Han, Cun Liu, Liansheng Chen, Butong Ding, Shijin Xuan, Xianqiang Liu, Guohui Ma, Jun Gao1, Xingsong Tian. 2015. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol; 8(1): 914-921.

[7]. Halls, S. 2015. *Breast Cancer Immunohistochemistry*. from Moose & Doc BreastCancer: http://breastcancer.ca/immunocanc.

[8]. Harry D. Bear et al, 2011. The Effect of Tumor Response of Adding Sequential Adjuvant Chemotherapy: The Primary Result From National Surgical Adjuvant Breast and Bowel project Protokol B-27. J Clin Oncol 21; 4165-4174.

[9]. International Agency for Breast Cancer (IARC). Globalcon 2012. Estimate cancer incident, mortality and prevalence Worlwide. Lyon.

[10]. Kaya Osman A., Suleyman Buyukberber, Denis Yamac, Ugur Coskun, Ramazan Yildiz, Emel Yaman, Banu Ozturk, Mustafa Benekli. 2010. Change in Hormon Receptor and Her-2 Status After Neoadjuvant Chemotherapy In Breast Cancer. 2010. Turkiye Klinikleri J Med Sci; 30(2)

[11]. Lindström LS, Karlsson E, Wilking UM, *et al*. 2012. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. JClin Oncol : 30-2601-8.

[12]. Purwanto, D. J., 2010, Deteksi Dini Kanker Payudara,http://www.omni-hospitals.com/omni alamsutera/blog_detail.php?id_post=5

[13]. Purwanto H, Handojo Djoko, Haryono Samuel J, Harahap Wirsma A. 2015. Panduan Penatalaksanaan Kanker Payudara. Peraboi: Jakarta p1-123.

[14]. Qi-Xing Tan et al. 2014. Prognostic value of hormone receptor status conversion following neoadjuvant chemotherapy in a series of operable breast cancer patients. Int J Clin Exp Pathol; 7(7):4086-4094 www.ijcep.com

[15]. Ramteke P et al. 2017. Alteration in steroid hormone and Her-2/neu receptor status following neoadjuvant chemotherapy in locally advanced breast cancer: Experience at a tertiary care centre in India. Indian Journal of Cancer.

[16]. Riset Kesehatan Dasar (Riskesdas) Kementrian Kesehatan. 2013. Badan Penelitian dan Pengembangan Kesehatan, Kementrian Kesehatan RI: Jakarta Selatan.

[17]. Rosai J. And Ackerman's. 2012. Surgical pathology. 10th ed. Toronto: Elsevier. Tovassol FA, Piter D. Word Health Organization: Clasification of Tumours pathology and genetic of tumours of Breast. Lyon : IARC Press

[18]. Sistem Informasi Rumah Sakit (SIRS), 2010. Kementrian Kesehatan Republik Indonesia. Kementrian Kesehatan RI 2010.

[19]. Suyatno, Pasaribu ET. 2014. Bedah Onkologi Diagnosis Dan Terapi. Edisi-2. Sagung seto : Jakarta p60-65

[20]. Soehartati G. 2017.Jumlah penderita Kanker Payudara Lebih Besar Daripada Kanker Servix dalamhari-kanker-sedunia-2017.http://lifestyle .okezone.com

[21]. Yin HF, Wang YH, Qin XQ, Zhang H, Li T, Ye JM, Liu YH. Zhonghua Zhong Liu Za Zhi. 2009. Effect of neoadjuvant chemotherapy on histologic grade and expression of biological markers in breast cancer. Breast Journal Chinese. Nov;31(11):858-62.

[22]. Van de Ven S, Smit V, Dekker T, Nortier J and Kroep J. 2011. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev; 37: 422-430.

[23]. Van Poznak et al. 2015. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.J Clin Oncol. Aug 20; 33(24): 2695–2704.

[24]. World Health Organization Globalcan. 2013. Estimated Incidence, Mortality and Prevalence Worldwide In Breast Cancer. IARC. Available at http://globocan.iarc.fr/old/FactSheets/cancers/breast-new.asp

[25]. Zhang N, Moran MS, Huo Q, Haffty BG and Yang Q. 2011. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. Cancer Invest; 29: 594-598.


Risal Wintoko. "The Relationship Of Hormonal Receptor, Her-2 And Ki-67 Changes After Administration Of Anthracycine-Based Neoadjuvant Chemotherapy With The Results Of Histopathological Grading In Stage Iii Breast Cancer Patiens At Saiful Anwar Malang Regional Public Hospital 2018." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 4, 2019, pp 47-54.