JBUON 2017; 22(3): 638-643
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Modulatory effect of neoadjuvant chemotherapy on the prognosis of patients with breast cancer

Jasna Trifunovic[1,2], Numa Memisevic[2], Borislava Nikolin[1,2], Svetlana Salma[1], Tihomir Dugandzija[1,2], Vladimir Vidovic[1]

[1]Oncology Institute of Vojvodina, Department of Clinical Oncology, Sremska Kamenica, Serbia; [2]University of Novi Sad, Medical Faculty, Department of Oncology, Novi Sad, Serbia

Summary

Purpose: *To evaluate the changes in biological markers ER, PR, HER2 and Ki67 in residual tumor after surgery for locally advanced breast cancer (LABC), and also to evaluate the outcome of breast cancer patients treated with neoadjuvant chemotherapy (NAC).*

Methods: *144 breast cancer patients treated with NAC at the Oncology Institute of Vojvodina, Serbia from 2011 to 2015 were included in this study. Changes in biologic markers ER,PR, HER2/neu and Ki-67 were evaluated at diagnostic core biopsy and at the final surgery tissue specimens.*

Results: *Of 144 patients pathological complete response was achieved in 17 (12%) and these were excluded from the study. Evaluated were 127 patients with residual tumor after the final surgery. A change in hormone receptor status (ER,PR) occurred in 9.4% of the patients (ER in 5%, PR in 14.5%) and HER2 status in 4.7% of the patients. ER and PR status change from negative to positive was associated with better overall survival (OS), but without statistical significance (p=0.16). Patients with conversion of HER2 status from negative to positive lived longer (65 vs 42 months). Furthermore, it was determined that HER2 change from negative to positive was associated with better OS (p=0.03). Ki-67 changed in 17 (11.8%) patients. The decrease of Ki-67 expression after NAC was associated with better outcome. Median follow up was 37.5 months (range 16.2-76.8).*

Conclusion: Changes in hormone receptor status, HER2 status and Ki-67 occurred after NAC in patients with LABC. A change from negative to positive hormone receptor status and HER2 status offers new treatment options, like endocrine therapy, and/or trastuzumab therapy for breast cancer patients. The decrease of Ki-67 expression after NAC was associated with better outcome.

Key words: *breast cancer, ER, HER2, Ki-67, neoadjuvant therapy, PR*

Introduction

Neoadjuvant systemic therapy is the gold standard in the treatment of inoperable LABC. Neoadjuvant therapy is usually associated with persistent outcome benefit, such as disease-free survival (DFS) and OS [1].

NAC was associated not only with persistent outcome benefit, but also with breast conservation. Results from large clinical trials [2] and many retrospective reviews [3,4] have indicated that breast conservation rates are improved with the use of preoperative systemic therapy. Introduction of NAC in breast cancer has increased the percentage of complete pathological remission (pCR) of the patients [5,6] and the pCR influences DFS [7].

NAC has induced changes in expression of ER, PR, HER2 and Ki-67 in patients with invasive breast cancer [8-12]. Discordance of the hormone

Correspondence to: Numa Memisevic, MD. Oncology Institute of Vojvodina, Put dr. Goldmana 4, 21204 Sremska Kamenica, Novi Sad, Serbia. Tel: +381 643745082, Fax: +381 216613741, E-mail: numamemisevic@gmail.com
Received: 06/01/2017; Accepted: 25/01/2017

receptor status was reported in four studies in 8-33% of the patients [13]. About half of the studies reported discordances of ER (2.5-17%) and PR (5.9-51.7%) [13]. Many relevant studies have investigated the ER/PR and HER2 status after NAC with or without trastuzumab. When NAC was combined with trastuzumab, a switch to a negative HER2 expression was reported in up to 43% of the patients [13]. So far, only limited data are available about the prognostic value of changes in the biological markers of residual tumors after NAC in breast cancer patients [14,15]. It has been suggested that long-term outcomes and pathologic response are correlated stronger with triple-negative breast cancer, less for HER2-positive disease, and the least for hormone-positive receptor disease [16].

The aim of this study was to evaluate the changes in biological markers ER, PR, HER2, and Ki-67 in residual tumor after breast surgery and to define the outcome of breast cancer patients treated with NAC.

Methods

Information was collected from the database of patients with biopsy-proven invasive ductal breast cancer treated with NAC at the Oncology Institute of Vojvodina from 2011 to 2015.

A group of 144 patients with LABC treated with NAC was evaluated. All patients had pathological evaluation, including ER,PR,HER2 and Ki-67,which were determined by tumor core biopsy in the pretreatment and surgical resection specimens after NAC. We selected 127 patients who did not achieve pCR whose residual tumors were evaluated for hormone receptor and HER2 status and Ki-67 expression. Changes of the biologic markers between diagnostic core biopsy and at the final surgical specimens were compared.

Pathology assessment

HER2/neu status was determined by immunohistochemistry (IHC). For determination of HER2 status, a tumor with a 3+ score was considered as positive. All patients with HER2 2+ results were retested with fluorescence in situ hybridization (FISH) and found as either positive or negative. Tumors with >10% stained cells were considered to have positive ER or PR hormone receptor status. Tumors with Ki-67 >14% were considered to have high proliferation index.

Statistics

Statistical analyses were performed using SPSS 20 software package. The primary endpoints were OS and DFS. DFS was calculated from the date of surgery to the first documented local or distant disease relapse. OS was calculated from the date of surgery to the date of death from any cause or the date of the last follow-up.

Kaplan-Meier method was performed to estimate OS and DFS in patient groups and log-rank test was used for comparison of the curves between the groups. Multivariate analysis using Cox proportional hazards model was performed in order to characterize the impact of histopathological prognostic factors of the tumor on DFS and OS. Factors included in multicariate analysis were biological markers ER, PR, HER2 and Ki67 index. Significance was set at $p<0.05$.

Results

From the group of 144 patients who received NAC, 17 patients (12%) achieved pCR and were

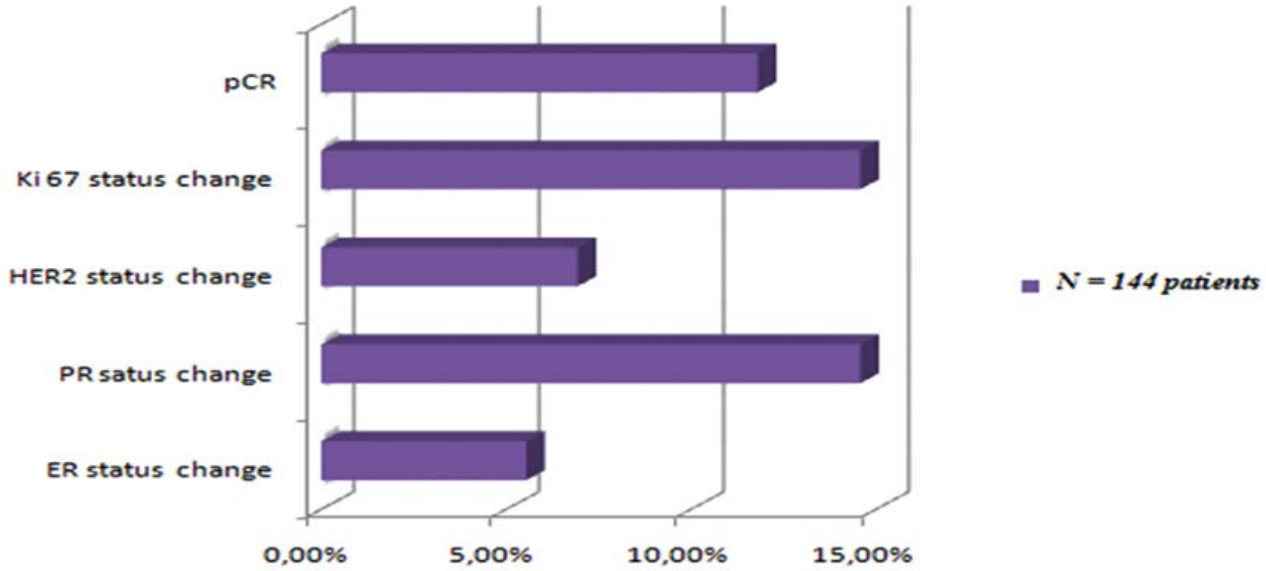

Figure 1. Frequency of changes of ER, PR, HER2 and Ki-67 expression and pathological complete response (pCR).

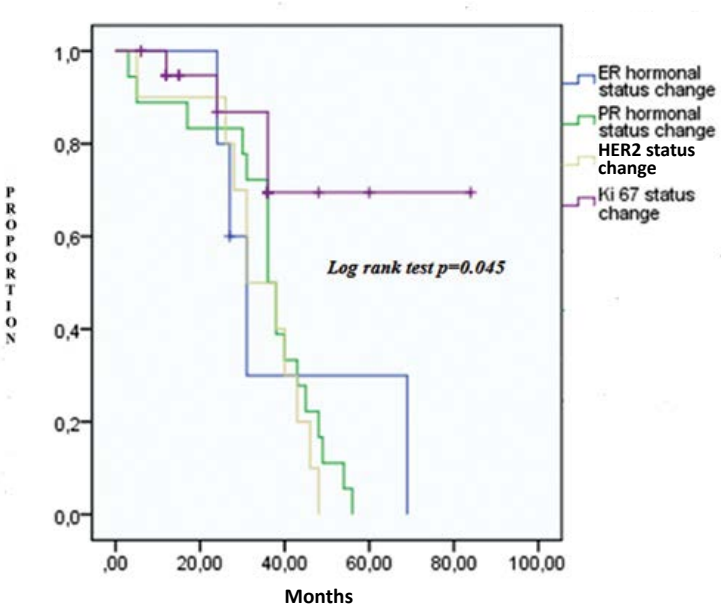

Figure 2. Kaplan-Meier overall survival curves according to ER, PR, HER2 and Ki-67 changes.

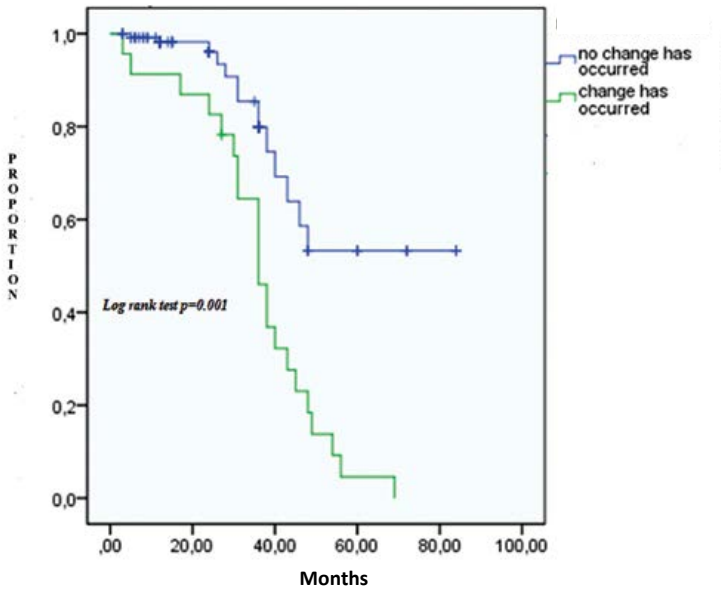

Figure 3. Kaplan-Meier overall survival curves according to ER, PR change and those with no change.

excluded from the study. The median follow up was 37.5 months (range 16.2-76.8).

Change in ER and PR status occurred in 12 (9.4%) out of 127 evaluated patients. Change in HER2 status was found in 6 (4.7%) patients and 17 (11.8%) patients had a change in Ki-67 status from pretreatment to residual disease (Figure 1). The comparison of changes in ER, PR, HER2 and Ki-67 showed that a group of patients with changes in ER and Ki-67 status had a better OS but not DFS than other groups of patients (Figure 2).

When we compared the group of patients with changes in ER and PR status with the group of patients without such changes, a statistically

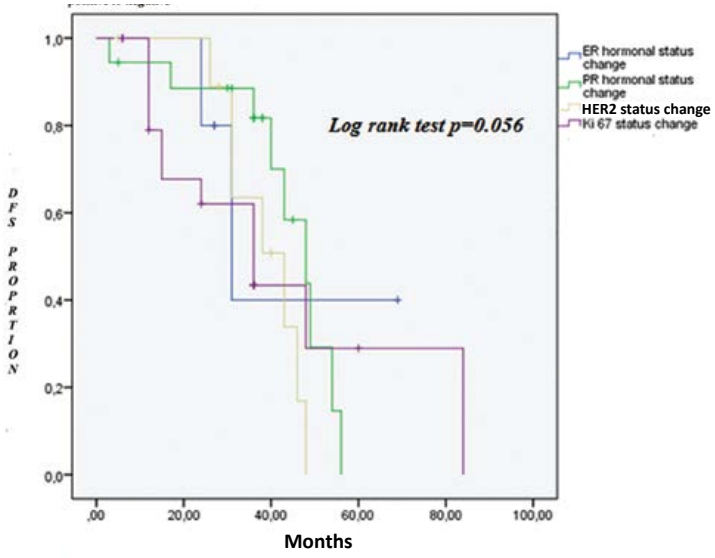

Figure 4. Kaplan-Meier disease-free survival curves of ER and PR change from negative to positive and *vice versa.*

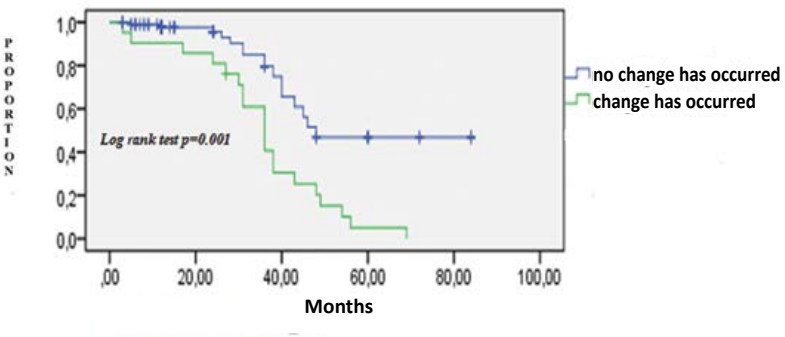

Figure 5. Kaplan-Meier overall survival curves difference in patients with HER 2 status change and no change.

significant difference in OS was found (p=0.001) (Figure 3). No significant difference (p=0.167) was found when we compared OS of hormone receptor status change from negative to positive and positive to negative (Figure 4). The change of hormone receptor status from negative to positive was associated with longer OS (47 vs 38 months; Figure 4; p=0.056).

Statistically significant difference (p=0.001) in OS was found between HER2 without change vs with change (85 vs 70 months; Figure 5).

OS was statistically significant higher (p=0.035) for HER2 status change from positive to negative when compared with the change from negative to positive (Figure 6).

Change of HER2 status from positive to negative correlated with better outcome of patients who survived at the time of follow up (65 vs 40% patients). However, the patients with conversion of HER2 status from negative to positive lived longer (65 vs 42 months) (p=0.038; Figure 6). Cox

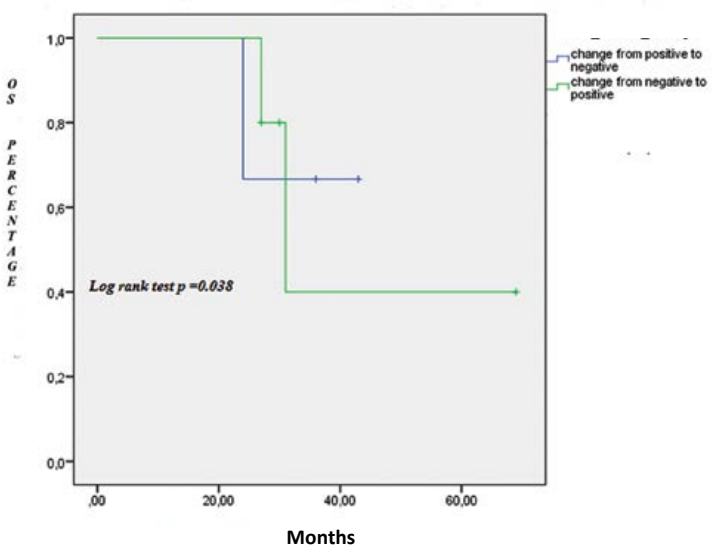

Figure 6. Kaplan-Meier overall survival curves of HER2 status change from positive to negative and *vice versa.*

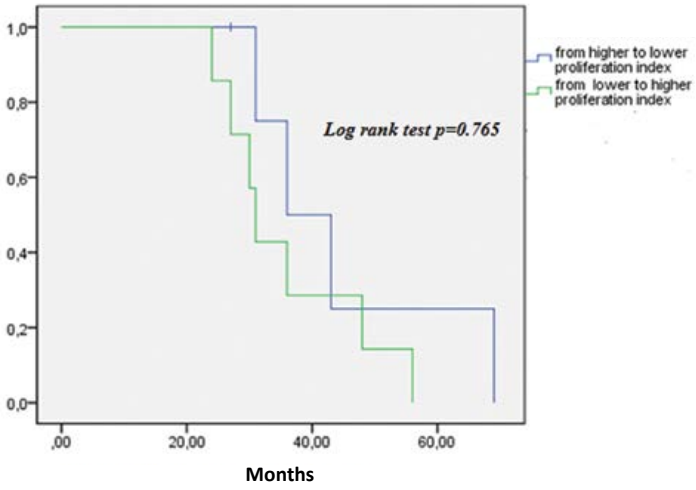

Figure 7. Kaplan-Meier overall survival curves of Ki-67 expression change from higher to lower and *vice versa.*

hazard regression analysis showed that HER2 and hormone receptor status were independently associated with OS (p=0.01).

Change in Ki-67 expression was found in 17 (11.8%) of the evaluated patients. The decrease of Ki-67 expression after NAC was associated with better outcome (Figure 7).

Results for DFS were best in the group with biological markers changes in ER status and Ki-67 expression (p=0.056) (Figure 8).

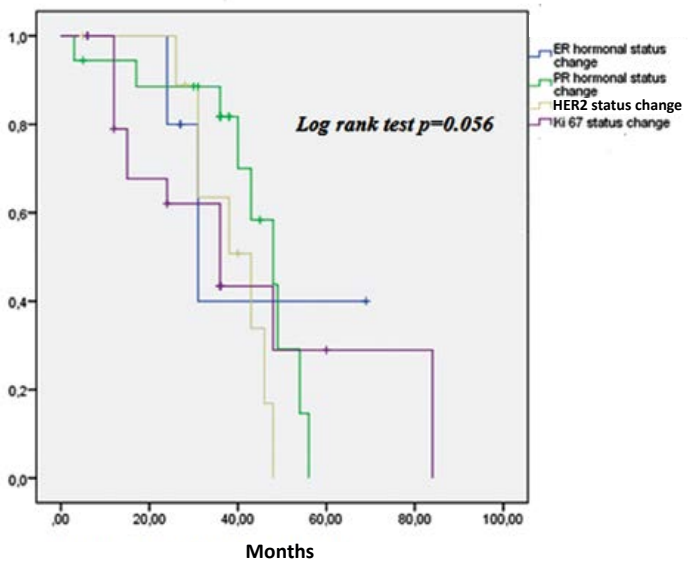

Figure 8. Kaplan-Meier disease-free survival curves according to ER, PR, HER2 and Ki-67 change.

Discussion

In the past, many studies have shown conflicting results concerning to the impact of NAC on the status of ER, PR and HER2 in breast cancer [11].

In general, earlier studies have reported non-significant changes in hormone receptor and HER2 status under the influence of NAC, but recent studies report significant changes in hormone receptor status. However, there is a paucity of data in the literature on the duration of OS and DFS after the modulatory effect of NAC [14,16].

In this study we evaluated patients with LABC treated with NAC. Changes in biologic markers ER,PR, HER2 and Ki-67 were assessed at diagnostic core biopsy and at the final surgical specimens. Patients who achieved pCR were excluded from the analysis. Evaluated were the impact of hormone receptor status conversion on OS and DFS as well as on achieving pCR.

Our results were similar to the results of recently published studies for the hormone receptor switch: PR status (14.5 vs 13%) and HER2 status (7.1 vs 4.72%) but not in ER status (12 vs 5 %) [14]. Our results in ER status switch were concordant with another study that reported statistically significant changes (p<0.001) [10].

There might be a possibility for a modulatory effect of NAC on hormone receptor status. As one possible explanation of this phenomenon is that chemosensitive cancer cells are destroyed by chemotherapy and the resistant ones survive, hence the hormone receptor status switch. Furthermore, ER, PR, and HER2 are highly interdependent and modulating one receptor can change the others [7].

Several authors have reported that switch from negative to positive ER,PR, and HER2 status correlated with better patient OS [17-19]. The better outcome in patients with ER switch from neg-

ative to positive has to do with the possibility of administering endocrine therapy whereas in hormone receptor negative status this is not possible as shown in the study by Hirata et al. [15].

In addition, it has been shown in the past that patients with stable profile of hormone receptor status have better outcome as compared to patients with hormone receptor switch [20].

Several studies have shown that patients with tumors that switched from HER2 positive to negative status after NAC had significantly shorter recurrence-free survival and a higher risk of relapse than patients with tumors of stable profile, which is concordant with the results of our study [21-23].

Our results showed that patients with no change of HER2 status had better outcome (OS). The change of HER2 status from positive to negative correlated with better outcome (OS=65%, p=0.035), but patients with HER2 status conversion from negative to positive lived longer (65 vs 42 months).

In the present study 11.8% of the patients had Ki-67 expression change. The decrease of Ki-67 expression after NAC was associated with better outcome, which is concordant with another study [8].

Because the administration of NAC might cause changes in biological markers in patients with breast cancer, retesting of hormone receptors and HER2 and Ki-67 after NAC should be done. This is particularly important for ER/PR and/or HER2-negative pre-treatment tumors as these may switch to a positive status, which implies application of endocrine therapy and/or trastuzumab. The results of these changes might influence the therapy decision in further treatment and might be useful to identify patients with better outcome after NAC. The results of this study show a change in the trend of accepting negative predictors of OS, thus showing a sinister nature of cancer - its new mutation. Therefore, future clinical trials would help to better understand the effect of therapy to tumor biology.

Conflict of interests

The authors declare no confict of interests.

References

1. Aigner J, Schneeweiss A, Sohn C, Marme F. The role of neoadjuvant chemotherapy in the management of primary breast cancer, Minerva Gynecol 2011;63:261-274.
2. Von Minckwitz G, Untch M, Nuesch E et al. Impact of treatment characteristics on response of different breast cancer phenotypes:pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cnacer Res Treat 2011;125:145-156.
3. Makhoul I, Kiwan E. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011;103:348-357.
4. Kaufmann M, von Minckwitz G, Mamounas EP et al. Recommendation from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012;19:1508-1516.
5. Di Cosimo S, Arpino G, Generali D. Neoadjuvant treatment of HER2 and hormone-receptor positive breast cancer – Moving beyond pathological complete response . Breast 2014;23:2:188-192.
6. Von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-1804.
7. Tan MC, Al Mushawah F, Gao F et al. Predictors of complete pathologic response after neoadjuvant systemic therapy for breast cancer. Am J Surg 2009;198:520-525.
8. Montanga E, Bagnardi V, Viale G et al. Changes in PgR and Ki67 in residual tumour and outcome of breast cancer patients treated with neoadjuvant chemotherapy. Ann Oncol 2015;26:307-313.
9. Yu-Feng Yang, Ying-Yang Liao, Le-QunLi, Shu-RuiXie,Yan-Fang Xie, Ning-Fu Peng. Changes in ER, PR and HER2 receptors status after neoadjuvant chemotherapy in breast cancer. Pathol Res Pract 2013;209:797-802.
10. Dede DS, Gumuskaya B, Guler G, Onat D, Altundag K, Ozisik Y. Evaluation of changes in biologic markers ER,PR,HER 2 and Ki67 index in breast cancer with administration of neoadjuvant dose dense doxorubicin, cyclophosphamide followed by paclitaxel chemotherapy. JBUON 2013;18:366-371.
11. Shet T, Agrawal A, Chinoy R, Havalder R, Parmar V, Badwe V. Changes in the tumor grade and biological markers in locally advanced breast cancer after chemotherapy-Implications for a pathologist. The Breast J 2007;13:457-464.
12. Ge WK,Yang B, Zuo WS et al. Evaluation of hormone receptor, human epidermal growth factor receptor-2 and Ki-67 with core needle biopsy and neoadjuvant chemotherapy effects in breast cancer patients. Thorac Cancer 2015;6:64-69.
13. Van de Ven S, Smit VT, Dekker TJ, Nortier JW, Kroep JR. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev 2011;37:422-430.

14. Untch M, Konecny GE, Paepke S, von Mnickwitz G. Current and future role of neoadjuvant therapy for breast cancer. Breast 2014;23:526-537.
15. Hirata T, Shimizu C, Yonemori K et al. Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer. Br J Cancer 2009;101:1529-1536.
16. Cubucku E, Kanat O, Fatih Olmez O et al. Prognostic significance of estrogen receptor, progesterone receptor,HER2/neu, Ki67 and nm23 expression in patients with invasive breast cancer. JBUON 2013;18:359-365.
17. Gahlaut R, Bennett A, Fatayer H et al. Effect of neoadjuvant chemotherapy on breast cancer phenotype, ER/PR and HER2 expression. Implications for the practicing oncologist. Eur J Cancer 2016;60:40-48.
18. Kinsella MD, Nassar A, Siddiqui MT, Cohen C. Estrogen receptor (ER),progesterone receptor (PR) and HER2 expression pre- and post-neoadjuvant chemotherapy in primary breast carcinoma:a single institutional experience. Int J Clin Exp Pathol 2012;5:530-536.
19. Lorgis V, Algros MP, Villanueva C et al. Discordance in early breast cancer for tumor grade, estrogen receptors, progesterone receptors and human epidermal growth factor receptor-2 status between core needle biopsy and surgical excisional primary tumor. Breast 2011;20:284-287.
20. Pedrini JL, Francalacci Savaris R, Casales Schorr M, Cambruzi E, Grudzinski M, Zettler CG. The effect of neoadjuvant chemotherapy on hormone receptor status, HER2/neu and prolactin in breast cancer. Tumori 2011;97:704-710.
21. Simon SP. Neoadjuvant therapy of early stage human epidermal growth factor receptor 2 positive breast cancer: latest evidence and clinical implications. Ther Adv Med Oncol 2014;6:210-221.
22. Jin G, Han Y, Lin C et al. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol 2015;8:914-921.
23. Hacioglu B, Akin S, Sever AR, Altundag K. Clinical implication of intratumoral heterogeneity of HER2 gene amplification in locally advanced HER2-positive breast cancer patients. Future Oncol 2015;11:2495-2497.