Am J Transl Res 2019;11(9):6110-6116
www.ajtr.org /ISSN:1943-8141/AJTR0094151

Original Article

Loss of HER2 and disease prognosis after neoadjuvant treatment of HER2+ breast cancer

Francisco P Branco[1], Duarte Machado[2], Filipa F Silva[3], Saudade André[4], Ana Catarino[5], Rosa Madureira[6], João M Pinto[1], João P Godinho[1], Pedro D Simões[1], Margarida Brito[2], Mafalda Casa-Nova[1], António R Moreira[2], José L Passos-Coelho[1,3]

[1]Hospital Beatriz Ângelo, Medical Oncology, Av. Carlos Teixeira, 3, 2674-514, Loures, Portugal; [2]Instituto Português de Oncologia de Lisboa Francisco Gentil, Medical Oncology, R. Prof. Lima Basto, 1099-023, Lisbon, Portugal; [3]Hospital da Luz, Medical Oncology, Av. Lusíada 100, 1500-650 Lisbon, Portugal; [4]Instituto Português de Oncologia de Lisboa Francisco Gentil, Pathology and Laboratory Medicine, R. Prof. Lima Basto, 1099-023, Lisbon, Portugal; [5]Hospital da Luz, Pathology, Av. Lusíada 100, 1500-650, Lisbon, Portugal; [6]Hospital Beatriz Ângelo, Pathology, Av. Carlos Teixeira, 3, 2674-514, Loures, Portugal

Received March 3, 2019; Accepted July 2, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Introduction: HER2 overexpression/amplification occurs in 15-20% breast cancers (BC) and is associated with worse prognosis. The addition of anti-HER2 treatment to neoadjuvant chemotherapy significantly improves the pathological complete response (pCR) rate. Changes in HER2 status after neoadjuvant treatment (NAT) have been reported and may affect prognosis. The aim of this study was to assess the efficacy of NAT in patients with HER2+ BC and its influence on HER2 status and associated prognostic impact. Methods: Retrospective chart review and pathologic evaluation of all consecutive patients with HER2+ BC (defined as IHC 3+ or IHC 2+ confirmed by SISH) submitted to NAT between 2010-2015 in three Portuguese Hospitals. Results: One hundred eight female patients were included; 40 with stage II, 68 with stage III. Hormone receptors were positive in 70. pCR (ypT0/isN0) was achieved in 48 patients (44%). With a median follow-up of 52 months, there were 5 disease free survival (DFS) events among pCR patients and 19 among non-pCR (P = 0.02). Of the 60 patients with residual disease at surgery, 52 remained HER2+ and 8 (13%) lost HER2 overexpression/amplification. 5y-DFS and 5y-OS was 70% and 84%, respectively, for patients whose residual tumors remained HER2+, and 21% and 50% for patients whose residual tumors became HER2 negative (P = 0.02 and < 0.001). Discussion: We confirmed the negative prognostic impact of NAT-induced HER2 loss on residual tumor leading to worse DFS and OS. Despite the retrospective design and small sample size, these results suggest that it is important to retest HER2 after NAT, to better refine patient outcome.

Keywords: Breast cancer, HER2, neoadjuvant therapy, chemotherapy, trastuzumab

Introduction

The human epidermal growth factor receptor 2 (HER2) is overexpressed in 15%-20% of breast cancers (BC) and is associated with worse prognosis. The introduction of anti-HER2 treatment had a major impact on the outcome of patients with HER2-positive (HER2+) breast cancer, both in early and advanced stages [1, 2]. Neoadjuvant treatment (NAT) is the standard of care for locally advanced breast cancer. In earlier stages of disease, NAT allows higher rates of breast-conserving surgery. In the neoadjuvant setting, the addition of trastuzumab and, more recently, pertuzumab, to chemotherapy significantly improves the pathological complete response (pCR) rate compared to chemotherapy alone [3, 4]. pCR after neoadjuvant treatment (NAT) is a surrogate for overall survival (OS), in particular in HER2-positive and triple negative breast cancer [5-7].

Changes in the expression of hormonal and HER2 receptors on tumor samples from surgical specimens obtained after neoadjuvant chemotherapy (NACT), compared with initial biopsy, have been reported [8, 9]. However, frequency of discordance in HER2 expression/amplification and the prognostic impact of such discordance remains unclear [10, 11].

Table 1. Characteristics of patients, tumors and neoadjuvant treatment regimens

Age	Median (range)	52 years [30-82]
Clinical Stage	Stage II	40 (37%)
	IIA	16
	IIB	24
	Stage III	68 (63%)
	IIIA	31
	IIIB	33
	IIIC	4
Grade	2	65 (60.2%)
	3	43 (39.8%)
Hormonal Receptor Status	HR positive (ER and/or PR)	70 (64.8%)
	ER+/PR+	32
	ER+/PR-	35
	ER-/PR+	3
	HR negative (ER and PR)	38 (35.2%)
	ER	67 (62%)
	1-9%	7
	10-40%	9
	> 40%	51
	PR	35 (32.4%)
	1-9%	4
	10-40%	15
	> 40%	16
Biopsy	IHC 3+	100 (92.6%)
HER2 Status	IHC 2+/SISH+	8 (7.4%)
Neoadjuvant CT regimen	Anthracyclines and Taxanes	102 (94.4%)
	Anthracyclines without Taxanes	3 (2.8%)
	Non-anthracyclines	3 (2.8%)
Neoadjuvant anti-HER2 regimen	Yes	90 (83.3%)
	Trastuzumab	87
	Trastuzumab + Pertuzumab	3
	No	18 (16.7%)

In the metastatic setting, Niikura et al. reported that patients with discordant HER2 status between primary tumor and metastases had shorter overall survival than patients with concordant HER2 status (hazard ratio [HR) = 0.43; P = 0.003) [12]. Mittendorf et al. [10] reported a 32% loss of HER2 amplification after NACT plus trastuzumab and Guarneri et al. [11] loss of HER2 expression in 40% of patients after NACT alone and in 14.7% of patients after NACT plus trastuzumab. In both studies patients with HER2+ tumors at diagnosis but no HER2 amplification/overexpression in residual disease had worse disease free survival (DFS) compared to those who maintained HER2+ residual disease [10, 11].

The aim of this study was to evaluate HER2 overexpression and/or amplification in patients with HER2+ BC undergoing NACT, with or without anti-HER2 treatment (tras-tuzumab and/or pertuzumab), both in the biopsy at diagnosis and in the surgical specimen collected after NAT and determine the prognostic impact of loss of HER2 overexpression/amplification.

Patients and methods

Patients with HER2+ non-metastatic BC treated with NACT +/- anti-HER2 antibody were eligible

Clinical and demographic characteristics including age, TNM stage, date of diagnosis, tumor

Table 2. pCR rate and tumor response by clinical factors, change in HER2 status after neoadjuvant treatment

Characteristics	pCR		Non-pCR		*p*-value
	n	%	n	%	χ^2 test
Response to NAT[a]	48	44.4	60	55.6	
Hormonal Receptor Status[b]					0.21
HR Positive	28	40	42	60	
HR Negative	20	52.6	18	47.4	
Grade					0.25
2	26	40	39	60	
3	22	51.2	21	48.8	
Clinical Stage					< 0.001
II	27	67.5	13	32.5	
III	21	30.9	47	69.1	
Neoadjuvant anti-HER2[c]					0.6
Yes	41	45.6	49	54.4	
No	7	38.9	11	61.1	
HER2 loss[d]					
Yes			8	13.3	
No			52	86.7	

a. NAT: neoadjuvant treatment; b. hormone receptor status defined as positive if > 1% tumor cell staining; c. anti-HER2 treatment with Trastuzumab (n = 87) or Trastuzumab + Pertuzumab (n = 3); d. Her2 loss refers to absent HER2 overexpression or amplification in residual tumor at surgery after neoadjuvant treatment.

biomarkers status, neoadjuvant systemic therapy, date and type of surgery, pathological response and follow-up data were recorded.

A dedicated breast cancer pathologist reviewed all tumor biopsies and surgical specimens. Histological type and grade, Ki67 and hormone receptors (HR) expression, HER2 status (overexpression and amplification) and response to NAT were evaluated.

HER2 status was determined in diagnostic biopsies and surgical specimens after NAT by immunohistochemically (IHC) or Silver *in situ* hybridization (SISH) and was considered positive if IHC 3+ or IHC 2+ confirmed by SISH (HER2/CEP17 ratio ≥ 2.0 or HER2 copy number ≥ 6.0 signals/cell). Complete pathological response was defined as ypT0/is N0. Hormone receptors positive (HR+) was defined as staining in more than 1% of tumor cells.

Statistical analysis was performed using SPSS version 25. Clinical characteristics between groups were compared using χ^2 test (or Fisher exact test, when appropriate). Survival was estimated using the Kaplan-Meier method and log-rank test was used to compare survival between groups of patients. Hazard ratio and confidence intervals were calculated using Cox analysis. Statistical significance was defined if $P < 0.05$.

Results

We performed a retrospective chart review and pathologic evaluation study of all consecutive patients with HER2+ BC treated with NAT between 2010 and 2015 in three Portuguese Hospitals (Hospital Beatriz Ângelo, Hospital da Luz and Instituto Português de Oncologia de Lisboa Francisco Gentil).

Patients characteristics

One hundred and eight female patients with a median age of 52 years old (range 30-82) were identified and included in this analysis. Sixty-five tumors were grade 2 and 43 were grade 3; 70 were HR+ (estrogen receptor and/or progesterone receptor). HER2 status at diagnosis was positive by IHC (3+) in 100 patients and amplified by SISH in 8 patients. Forty patients had TNM stage II disease and 68 had stage III. These results are summarized in **Table 1**.

Treatment and tumor response

All patients were treated with NAT (**Table 1**). The majority were treated with antracycline and taxane-based chemotherapy plus the anti-HER2 agent trastuzumab (T): anthracyclines/taxanes 102, anthracyclines/non-taxanes 3, non-antracyclines regimen 3; T in 90. Only 18 patients did not receive T in the neoadjuvant setting; in contrast, 3 patients received dual anti-HER2 blockage with T and pertuzumab (P) included in a clinical trial.

Pathological complete response (pCR) defined as ypT0/is N0 was achieved in 48 patients (44%): 28 of 70 (40%) with HR+ disease and 20 of 38 (53%) with HR negative (HR-) disease ($P = 0.2$, χ^2 test), and in 26 of 65 (40%) with grade 2 tumor and 22 of 43 (51%) with grade 3 ($P = 0.25$, χ^2 test). pCR was achieved in 27 of 40 (68%) with stage II and 21 of 68 (31%) with stage III ($P < 0.001$, χ^2 test) and in 41 of 90 (46%) after chemotherapy + T/P and 7 of 18 (39%) after chemotherapy alone ($P = 0.6$, χ^2 test). Relationship between tumor response to

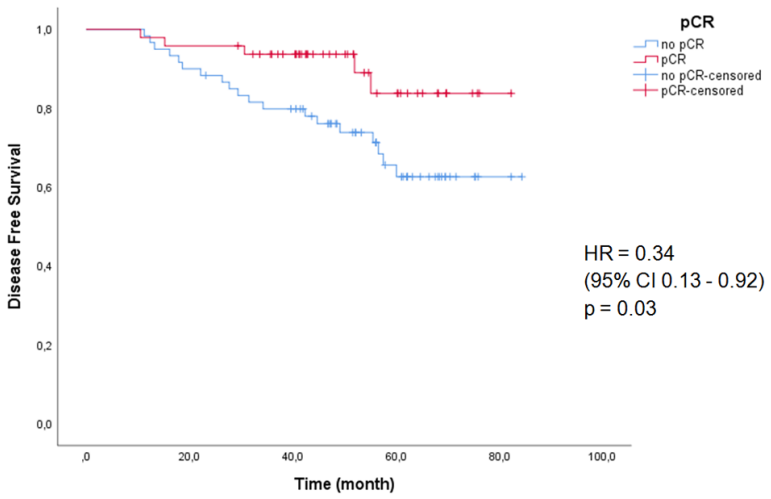

Figure 1. Kaplan-Meier disease-free survival curves according pCR status after neoadjuvant treatment. DFS curves according to pCR (ypT0/isN0) status, comparison by log-rank test with 95% CI for the hazard rate (HR) and *p*-value.

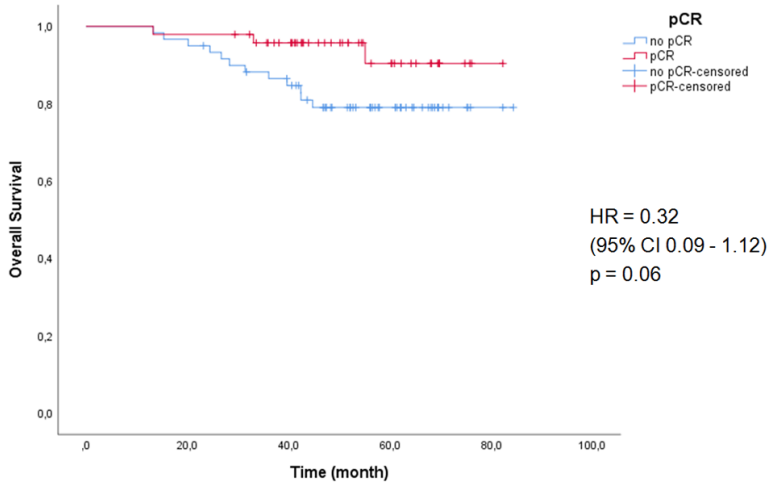

Figure 2. Kaplan-Meier overall survival curves according pCR status after neoadjuvant treatment. OS curves according to pCR (ypT0/isN0) status, comparison by log-rank test with 95% CI for the hazard rate (HR) and *p*-value.

NAT and tumor grade, TNM stage and anti-HER2 treatment are shown in **Table 2**.

Sixty patients had residual disease at surgery. In 8 (13%) of them the residual tumor did not have HER2 overexpression/amplification (**Table 2**). Loss of HER2 was more frequent among HR- tumor (5 of 18, 28%) than HR+ tumor (3 of 42, 7%) (P = 0.045, Fisher exact test).

Survival analysis

With a median follow-up of 52 months there were 20 relapses and 24 disease-free events: 4 relapses and 1 non-BC related death (73 yo patient who died of an acute ischemic stroke) among 48 (10%) patients who obtained a pCR and 16 relapses and 3 non-BC related deaths (67 yo patient who died of a traumatic brain injury with subdural hemorrhage; 56 yo woman who died with a Klatskin tumor and 73 yo woman with a death of unknown cause) among 60 (32%) patients with residual disease (no pCR) (HR = 0.34 95% CI (0.13-0.92), P = 0.03, log-rank test). The median disease-free survival (DFS) has not been reached in either group (**Figure 1**).

Fifteen deaths were observed; 3 deaths (2 from breast cancer) among 48 (6%) patients who obtained a pCR and 12 (9 from breast cancer) among 60 (20%) patients with residual disease (HR = 0.32 95% CI (0.09-1.12), P = 0.06, log-rank test). The median overall survival (OS) has not been reached in either group (**Figure 2**).

Among patients with residual disease after NAT, the 5y-DFS was 70% in patients whose residual tumors remained HER2+ (14 DFS events) and 21% in patients whose residual tumors became HER2 negative (5 DFS events) (HR = 0.33 95% CI (0.12-0.91), P = 0.02, log-rank test) (**Figure 3**). Similarly, 5y-OS was 84% for patients whose tumors remained HER2+ (8 deaths) and 50% for patients whose residual tumors became HER2 negative (4 deaths) (HR = 0.17 95% CI (0.05-0.57), P < 0.001, log-rank test) (**Figure 4**, Supplementary Data).

Discussion

NAT is commonly used as initial treatment of early BC and may change the tumor characteristics and biomarkers expression. Indeed, several studies reported discordances between

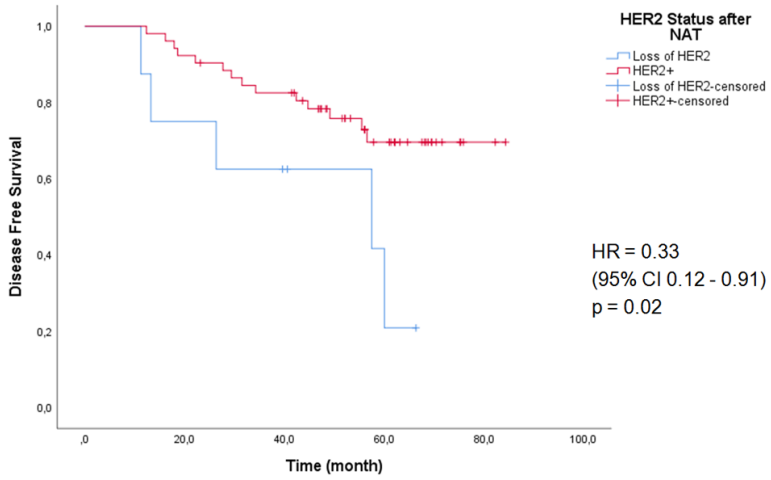

Figure 3. Kaplan-Meier disease-free survival curves according to residual tumor HER2 status after neoadjuvant treatment (no pCR patients). DFS curves according to loss of HER2 overexpression/amplification after neoadjuvant treatment in patients with residual disease, comparison by log-rank test with 95% CI for the hazard rate (HR) and *p*-value.

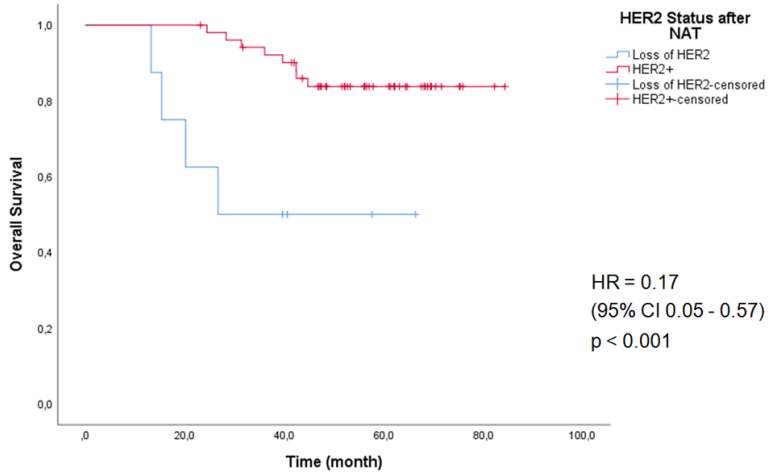

Figure 4. Kaplan-Meier overall survival curves according to residual tumor HER2 status after neoadjuvant treatment (no pCR patients). OS curves according to loss of HER2 overexpression/amplification after neoadjuvant treatment in patients with residual disease, comparison by log-rank test with 95% CI for the hazard rate (HR) and *p*-value.

ER, PR and also HER2 status before and after NAT [8], however the prognostic impact of these changes is not completely clear.

In a retrospective series of HER2+ metastatic BC reported by Niikura et al., 24% of tumors became HER2 negative after treatment with chemotherapy +/- anti-HER2 target therapy [12]. Other series of metastatic HER2+ BC reported loss of HER2 amplification in 5 to 13, 6% of tumors [6, 13, 14]. Furthermore, two studies reported worse survival rates in patients whose tumors had lost HER2 amplification in the course of metastatic disease [12, 15].

In early stage HER2+ BC, there are conflicting data on the loss of HER2 overexpression/amplification associated with NAT. Several retrospective and prospective studies did not report a significant change in HER2 amplification between initial biopsy and the surgical specimen obtained after NAT [8]. In contrast others reported that NAT is associated with loss of HER2 amplifications in 2.3 to 43% of patients [16, 17].

The largest study comparing HER2 receptor status before and after NAT by Niikura et al. [18], reported a 21.4% (601/2811 patients) discordance of HER2 overexpression between biopsy and surgical specimen after NAT. As assessed by IHC the rate was 20.4% (499/2447), and by FISH 8.4% (17/203). This conversion rate was higher in patients treated with trastuzumab and chemotherapy compared to chemotherapy alone (24.7% vs 18.2%, P < 0.0001). In contrast, Guarneri et al. [11] reported HER2 loss in 28% of 69 patients treated with NAT (14.7% after treatment with chemotherapy + T vs 40% with chemotherapy alone).

Several reasons have been suggested to explain HER2 changes after NAT. These include technical reasons, such as sampling error, intratumoral heterogeneity, preanalytical and analytical pitfalls, and HER2 amplification methods. IHC, used in most studies, can be influenced by variation in tissue processing and fix-

ation, as well as by intra- and inter-observer variability. In contrast, HER2 evaluation by FISH is less likely to document discordance than IHC. Indeed, Harris et al. reported 12% change in HER2 overexpression by IHC but no change by FISH analysis [19].

Although technical reasons may explain the differences in HER2 amplification in biopsy and surgical specimens, one study in which no NAT was administered before surgery, no discrepancies were reported between biopsy and surgical samples (concordance rate of 98.8%) [20]. These data suggest that NAT is the main reason for difference of HER2 overexpression/amplification over time with clonal selection and development of resistance mechanisms induced by chemotherapy and/or anti-HER2 therapies. Additionally, as the expression of ER, PR and HER2 are highly dependent on each other, modulating one receptor with NAT may change the expression of other receptors as well [21].

Whether HER2 alterations induced by NAT in patients with primary breast cancer affect prognosis is unclear. Some studies describe no impact on prognosis (Guarnery et al. 2013, P = 0.063) [11], but others report worse recurrent-free survival (RFS) in patients with tumors with loss of HER2 amplification after NAT (Mittendorf et al., P = 0.042) [10], as observed by us.

The present study has several limitations. It is a retrospective series, with a small sample and without a control cohort. Nevertheless, we observed a small but important difference in expression of HER2 after treatment with NAT: 13% of HER2+ tumors had no HER2 overexpression/amplification in the surgical specimen removed after NAT. Furthermore, HER2 loss was associated with worse prognosis. These patients had a higher rate of relapse and higher risk of death compared to patients whose tumors remained HER2+.

Thus, we confirmed the negative prognostic impact of NAT-induced HER2 loss on residual tumor, leading to worse DFS and OS. Despite the retrospective design and small sample size, these results suggest that it is important to retest HER2 after NAT. The subpopulation of tumors with loss of HER2 overexpression must be studied further in order to better define their prognosis and tailor subsequent adjuvant therapy. If these results are confirmed in larger data sets, they may influence the design of clinical trials in patients with residual tumors after NAT for HER2+ BC.

Disclosure of conflict of interest

None.

Address correspondence to: Francisco P Branco and Jose L Passos-Coelho, Hospital Beatriz Ângelo, Medical Oncology, Av. Carlos Teixeira, 3, 2674-514, Loures, Portugal. E-mail: fpbbranco@gmail.com (FPB); passoscoelho@sapo.pt (JLPC)

References

[1] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J and Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-792.

[2] Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V and D'Amico R. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 2012; Cd006243.

[3] Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P and Baselga J. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377-384.

[4] Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G and Valagussa P. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 25-32.

[5] Guarneri V, Broglio K, Kau SW, Cristofanilli M, Buzdar AU, Valero V, Buchholz T, Meric F, Middleton L, Hortobagyi GN and Gonzalez-Angulo AM. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and

other factors. J Clin Oncol 2006; 24: 1037-1044.
[6] Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN and Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275-1281.
[7] von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K and Loibl S. 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.
[8] van de Ven S, Smit VT, Dekker TJ, Nortier JW and Kroep JR. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev 2011; 37: 422-430.
[9] Li P, Liu T, Wang Y, Shao S, Zhang W, Lv Y, Yi J and Wang Z. Influence of neoadjuvant chemotherapy on HER2/neu status in invasive breast cancer. Clin Breast Cancer 2013; 13: 53-60.
[10] Mittendorf EA, Wu Y, Scaltriti M, Meric-Bernstam F, Hunt KK, Dawood S, Esteva FJ, Buzdar AU, Chen H, Eksambi S, Hortobagyi GN, Baselga J and Gonzalez-Angulo AM. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res 2009; 15: 7381-7388.
[11] Guarneri V, Dieci MV, Barbieri E, Piacentini F, Omarini C, Ficarra G, Bettelli S and Conte PF. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol 2013; 24: 2990-2994.
[12] Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, Tokuda Y, Gonzalez-Angulo AM, Hortobagyi GN and Ueno NT. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012; 30: 593-599.
[13] Amir E, Miller N, Geddie W, Freedman O, Kassam F, Simmons C, Oldfield M, Dranitsaris G, Tomlinson G, Laupacis A, Tannock IF and Clemons M. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 2012; 30: 587-592.
[14] Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G and Clemons MJ. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009; 20: 1499-1504.
[15] Dieci MV, Barbieri E, Piacentini F, Ficarra G, Bettelli S, Dominici M, Conte PF and Guarneri V. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Ann Oncol 2013; 24: 101-108.
[16] Taucher S, Rudas M, Gnant M, Thomanek K, Dubsky P, Roka S, Bachleitner T, Kandioler D, Wenzel C, Steger G, Mittlbock M and Jakesz R. Sequential steroid hormone receptor measurements in primary breast cancer with and without intervening primary chemotherapy. Endocr Relat Cancer 2003; 10: 91-98.
[17] Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, Pauletti G, Powell JE, Pegram MD and Slamon DJ. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 2006; 24: 1831-1838.
[18] Niikura N, Tomotaki A, Miyata H, Iwamoto T, Kawai M, Anan K, Hayashi N, Aogi K, Ishida T, Masuoka H, Iijima K, Masuda S, Tsugawa K, Kinoshita T, Nakamura S and Tokuda Y. Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21,755 patients from the Japanese breast cancer registry. Ann Oncol 2016; 27: 480-487.
[19] Harris LN, You F, Schnitt SJ, Witkiewicz A, Lu X, Sgroi D, Ryan PD, Come SE, Burstein HJ, Lesnikoski BA, Kamma M, Friedman PN, Gelman R, Iglehart JD and Winer EP. Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. Clin Cancer Res 2007; 13: 1198-1207.
[20] Arnedos M, Nerurkar A, Osin P, A'Hern R, Smith IE and Dowsett M. Discordance between core needle biopsy (CNB) and excisional biopsy (EB) for estrogen receptor (ER), progesterone receptor (PgR) and HER2 status in early breast cancer (EBC). Ann Oncol 2009; 20: 1948-1952.
[21] Rakha EA, El-Sayed ME, Green AR, Paish EC, Powe DG, Gee J, Nicholson RI, Lee AH, Robertson JF and Ellis IO. Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype. J Clin Oncol 2007; 25: 4772-4778.