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# Clinical Usefulness of AJCC Response Criteria for Neoadjuvant Chemotherapy in Breast Cancer

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## ABSTRACT

**Purpose.** Recently, the American Joint Committee on Cancer (AJCC) 7th edition proposed new response criteria for neoadjuvant chemotherapy (NAC) in breast cancer. The purpose of this study was to evaluate the clinical usefulness of AJCC response criteria.

**Methods.** A total of 398 consecutive stage II or III breast cancer patients who received NAC were enrolled in this study. AJCC response criteria were as follows: (1) complete response (CR)—absence of invasive carcinoma in the breast and node; (2) partial response (PR)—decrease in either or both T or N stage; (3) no response (NR)—no change or increase in either or both T or N stage.

**Results.** Complete response, PR, and NR by AJCC criteria were 9.8, 59.3, and 30.7 %, respectively. Among the 398 patients, 337 patients were available for both paired pre- and post- breast MRI and chest CT. AJCC response criteria were significantly associated with RECIST criteria ($P < 0.001$). AJCC response was significantly associated with relapse-free survival (RFS) and overall survival (OS). The 5-year RFS rates were 89.6 % in CR, 74.1 % in PR, and 62.6 % in NR ($P = 0.002$). The 5-year OS rates were 97.4 % in CR, 88.6 % in PR, and 78.3 % in NR ($P = 0.012$). When adjusting potential prognostic factors, AJCC response was independently associated with RFS and OS.

**Conclusions.** AJCC response criteria for NAC in breast cancer have clinical usefulness in evaluating response of NAC, as well as predicting survival. AJCC response criteria can discriminate among patient subgroups with respect to survival.

Breast cancer is the second most common cancer in Korean women.[1] Neoadjuvant chemotherapy (NAC), also called as preoperative chemotherapy, has become widely accepted as the standard treatment for locally advanced breast cancer.[2] When breast cancer patients received NAC, prechemotherapy initial clinical stage and postchemotherapy pathologic stage coexist. It is not yet certain which has more prognostic value between clinical and pathologic staging. A major disadvantage of NAC is the loss of prognostic value provided by the tumor size and nodal status at surgery and before adjuvant chemotherapy.[3,4] To date, pathologic complete response (pCR) is repeatedly confirmed as the most important prognostic factor and surrogate marker for longer survival in a neoadjuvant setting.[5–8] However, the dichotomization of a response, as pCR or non-pCR, is too simple, because non-pCR after NAC includes a broad range of actual responses from near pCR to no response (NR). Hence, many researches proposed a novel index, which enables precise measurement of the residual disease, in addition to the development of novel models for staging that incorporate clinical and pathologic staging.[9–12]

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Furthermore, there is no consensus regarding response evaluation criteria to NAC in breast cancer. The relative importance of pretreatment clinical stage, posttreatment pathologic stage, and degree of response in predicting survival remains to be clarified. Recently, the American Joint Committee on Cancer (AJCC), 7th edition, proposed new response criteria for NAC, using clinical and pathologic staging.[13] Details of the new AJCC response criteria were as follows; (1) complete response (CR)—absence of invasive carcinoma in the breast and node; (2) partial response (PR)—decrease in either or both T or N stage; and (3) NR—no change or increase in either or both T or N stage.

However, the clinical usefulness of AJCC response criteria has not yet been evaluated nor validated. The purpose of this study was to evaluate the clinical usefulness of AJCC response criteria for NAC in breast cancer.

## MATERIALS AND METHODS

### *Study Population and Treatment*

Between January 2002 and October 2008, a total of 398 consecutive stage II or III breast cancer patients who received NAC were enrolled in this study. The detailed eligibility criteria and regimen have been described in our previous reports.[14–18] In brief, the eligibility criteria were (1) pathologically proved breast cancer by core needle biopsy, (2) initial clinical stage II or III, (3) objective measurable lesion, (4) Eastern Cooperative Oncology Group performance status 0–2, and (5) previously untreated. In total, 383 patients received three cycles of neoadjuvant docetaxel/doxorubicin chemotherapy. After three cycles of NAC, the patients were reevaluated for the response and underwent curative surgery. Thereafter, the patients received three more cycles of docetaxel/doxorubicin chemotherapy, as an adjuvant, and hormonal or radiation therapy, if indicated.[14–20] After introduction of trastuzumab in a neoadjuvant setting, the other 15 human epidermal growth factor receptor 2 (HER2) positive patients received six cycles of paclitaxel, gemcitabine, and trastuzumab as a part of the other phase II trial.[21] Estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 expressions were evaluated using tissues obtained before NAC.

### *Response Evaluation*

For precise evaluation of the radiologic response, we obtained chest computed tomography (CT) for lymph node evaluation and breast magnetic resonance imaging (MRI) or ultrasonography for breast evaluation twice—before and after NAC. The radiologic response was evaluated by using breast MRI for primary breast lesion and chest CT for lymph node lesions with Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[22] The initial clinical stage and post-NAC pathologic stage were evaluated, based on the AJCC 7th edition, and the details of AJCC response criteria were as follows[13]:

(1) Complete response is defined as the absence of invasive carcinoma in the breast and lymph nodes. Residual in situ cancer, in the absence of invasive disease, constitutes a CR. Patients with isolated tumor foci in LN are not classified as having a CR.

(2) Partial response is defined as a decrease in either or both yT or yN stage compared with the pretreatment T or N, and no increase in either yT or yN. After chemotherapy, one should use the method that most clearly defined tumor dimensions at the baseline for this comparison, although prechemotherapy pT cannot be measured.

(3) No response is defined as no apparent change in either the yT or yN categories compared to the clinical staging or increase in the T or N categories at the time of y pathological evaluation

(i.e., cT2N2 → ypT1N1 = PR; cT2N2 → ypT2N1 = PR; cT2N2 → ypT2N2 = NR; cT2N2 → ypT2N3 = NR; cT2N2 → ypT3N3 = NR; cT2N2 → ypT1N3 = NR).

The pCR was defined as complete disappearance of invasive carcinoma, in both the breast and the axillary lymph nodes, after NAC. Residual ductal carcinoma in situ (DCIS) was included in the pCR category.[23] Nodes with isolated tumor cells (ypN0(i+)) was not categorized as pCR. This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (H-1003-058-313). Recommendations of the Declaration of Helsinki for biomedical research involving human subjects also were followed.

### *Statistical Analysis*

Relapse-free survival (RFS) was determined as the interval between the NAC and the date when the disease relapse is first documented, or the date of death from any cause. Local, regional, and distant relapse were included in disease relapse, and contralateral breast cancer was not regarded as relapse. Overall survival (OS) was measured from the date in which NAC was initiated to the date of death. The Cox proportional hazards model was used to evaluate the prognostic significance of variables for RFS and OS. Multivariate analyses were performed by using the Cox proportional hazard regression models. The model performance was evaluated with respect to the discrimination ability, which means the predictor's ability to separate the patients with different responses or events.

Discrimination for the survival data was evaluated, using the C statistic with concordance index (C-index), which is similar in concept to that of the area under ROC curve, in the logistic model, but appropriate for the censored data.[24–26] Survival comparisons between the different groups were made, using the log-rank tests. All reported *P* values are two-sided. All statistical analyses were performed using STATA statistical software version 11.0 (STATA, College Station, TX).

## RESULTS

### *Patients and Results of Treatment*

The median follow-up duration was 61.6 months. At the end of the follow-up, 113 patients had developed recurrent disease, and 59 patients had died. At 5 years, RFS rate was 71.9 % and OS rate was 85.9 %. The median RFS and OS were not reached. The baseline characteristics of 398 patients are shown in Table 1. Eighty-nine patients (22.3 %) were initially staged as clinical stage II, and the others (87.7 %) were initially staged as clinical stage III. The median primary tumor size was 4.5 cm, in the greatest dimension. We adopted new AJCC response evaluation criteria in our patients, and Table 2 shows the results for AJCC response. CR, PR, and NR were 9.8, 59.3, and 30.7 %, respectively.

### *Correlation between AJCC Response and RECIST Criteria*

Among the 398 patients, 337 patients were available for both pairs of pre- and post- breast MRI and chest CT. Table 3 shows a correlation between AJCC response criteria and RECIST criteria. Among the 18 patients who showed CR by RECIST, 8 patients (44.4 %) were CR by the AJCC criteria. Among the 252 patients who showed PR by RECIST, 168 patients (66.7 %) were PR by the AJCC criteria. AJCC response criteria and RECIST criteria have a statistically significant correlation ($P < 0.001$).

### *Correlation between AJCC Response and Survival*

AJCC response was significantly associated with RFS and OS. Patients with PR or NR by AJCC criteria showed shorter RFS and OS than patients with CR (Fig. 1). The 5-year RFS rates were 89.6 % in the CR patients, 74.1 % in the PR patients, and 62.6 % in the NR patients (log-rank, $P = 0.002$). The 5-year OS rates were 97.4 % in the CR patients, 88.6 % in PR the patients, and 78.3 % in the NR patients (log-rank, $P = 0.012$). When excluding the 15 patients who received different regimen, the results were observed to be similar (Supplementary Fig. 1). RECIST criteria was not significantly associated with RFS ($P = 0.331$; Supplementary Fig. 2).

**TABLE 1** Baseline characteristics of 398 patients

| Characteristics | No. of patients (%) |
|---|---|
| Median age (range, years) | 45 (range, 24–75) |
| Age < 35 | 46 (11.6) |
| Age ≥ 35 | 352 (88.4) |
| Performance status | |
| ECOG 0 | 86 (21.6) |
| ECOG 1 | 306 (76.9) |
| ECOG 2 | 6 (1.5) |
| Pathologic characteristics | |
| Invasive ductal carcinoma | 378 (95) |
| Others | 20 (5) |
| Initial tumor size (cm) | |
| Median (range) | 4.5 (0.5–13.5) |
| Initial clinical stage | |
| IIA | 14 (3.5) |
| IIB | 75 (18.8) |
| IIIA | 197 (49.5) |
| IIIB | 60 (15.1) |
| IIIC | 52 (13.1) |
| Inflammatory breast cancer | |
| No | 368 (92.5) |
| Yes | 30 (7.5) |
| Type of surgery | |
| Breast conserving | 193 (48.5) |
| Mastectomy | 205 (51.5) |
| Adjuvant hormonal therapy | |
| No | 222 (55.8) |
| Yes | 176 (44.2) |
| Radiation therapy | |
| No | 56 (15.1) |
| Yes | 342 (85.9) |
| Estrogen receptor | |
| Negative | 208 (52.3) |
| Positive | 190 (47.7) |
| Progesterone receptor | |
| Negative | 262 (65.8) |
| Positive | 136 (34.2) |
| HER2[a] | |
| Negative | 268 (67.3) |
| Positive | 130 (32.7) |
| Chemotherapeutic regimen | |
| Docetaxel+ Doxorubicin | 383 (96.2) |
| Paclitaxel+ Gemcitabine+ Trastuzumab | 15 (3.8) |

*ECOG* Eastern Cooperative Oncology Group, *HER2* human epidermal growth factor receptor 2

[a] HER2 positivity was defined as either FISH+ or IHC 3+

**TABLE 2** Results of AJCC response for neoadjuvant chemotherapy

| AJCC response | No. of patients (%) |
|---|---|
| CR | 39 (9.8) |
| PR | 236 (59.3) |
| NR | 122 (30.7) |
| Not evaluable[a] | 1 (0.3) |

[a] One patient was not able to evaluate yT stage and measure exact tumor size because of severely scattered pattern of invasive carcinoma and DCIS component

We also performed a univariate and multivariate Cox proportional hazard regression analysis between clinicopathologic variables and survival. HER2 positivity was not significantly associated with RFS ($P = 0.718$; Supplementary Fig. 3). When adjusting for the potential prognostic factors, AJCC response was independently associated with RFS (Table 4) and OS (Table 5). There were no significant interactions among the five factors, which were retained in the model. The discriminatory ability of the model was measured, using C statistics. The C-index was 0.734 for the RFS prediction model and 0.811 for OS prediction model, which indicated a good model performance.

When dividing the patients into four subgroups (luminal A, luminal B, HER2, and triple-negative), based on ER, PR, HER2 status,[16] AJCC response criteria was valid in each subgroups (Fig. 2).

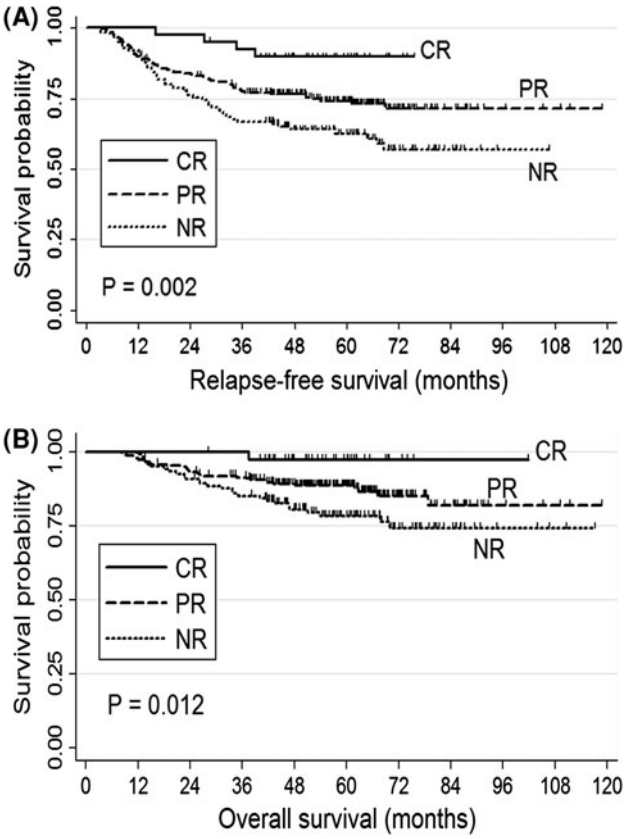


**FIG. 1** Relapse-free survival (**a**) and overall survival (**b**) by AJCC response criteria

## DISCUSSION

In the present study, we demonstrated clinical usefulness of AJCC response criteria for NAC in breast cancer. AJCC response criteria was not only correlated with radiologic response but also having a prognostic value for survival. AJCC response criteria can discriminate among the patient subgroups with respect to survival.

Even though pCR after NAC is the single most important prognostic factor and surrogate marker for survival, binary response classification in "pCR" or "non-pCR" is too simple and it sacrifices valuable response information.[5–8] Non-pCR contains broad spectrum of various response and needs to be classified with more sophisticated categories. To date, several response criteria have been proposed for these reasons.[9–12] Symmans et al. [9] proposed residual cancer burden (RCB) index to measure the residual disease after NAC. RCB index was calculated as a continuous index, which combines the pathologic measurements of tumor (size and cellularity) and lymph node involvement. RCB index have independent prognostic value and have been externally validated.[27] However, RCB index calculation requires a careful quantitative pathology review, including cellularity fraction of invasive cancer, and correction of DCIS component. RCB index does not take the initial tumor size into account, resulting initial small tumor and bulky tumor is regarded as the same.

Hence, other simple criteria also have been proposed. Rodenhuis et al.[12] invented neoadjuvant response index (NRI). The NRI was defined as the sum of the breast

**TABLE 3** Comparison between AJCC response criteria, and RECIST criteria by paired breast MRI and chest CT

| | AJCC criteria | | | |
|---|---|---|---|---|
| $N = 337$ | CR | PR | NR | $P$ value |
| RECIST criteria | | | | <0.001 |
| CR | 8 (44.4 %) | 7 (38.9 %) | 3 (16.7 %) | |
| PR | 27 (10.7 %) | 168 (66.7 %) | 57 (22.6 %) | |
| SD | 0 (0.0 %) | 30 (47.6 %) | 33 (52.4 %) | |
| PD | 0 (0.0 %) | 1 (25.0 %) | 3 (75.0 %) | |

**TABLE 4** Univariate and multivariate Cox proportional hazard regression analysis—between clinicopathologic variables and relapse-free survival

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age (years) | | | | | | |
| <35 | 1 | | | 1 | | |
| ≥35 | 0.608 | 0.367–1.007 | 0.068 | 0.608 | 0.361–1.026 | 0.062 |
| Initial clinical stage | | | | | | |
| IIA,IIB | 1 | | | 1 | | |
| IIIA | 3.599 | 1.718–7.538 | 0.001 | 3.782 | 1.798–7.957 | <0.001 |
| IIIB | 5.357 | 2.406–11.929 | <0.001 | 5.394 | 2.398–12.131 | <0.001 |
| IIIC | 6.113 | 2.720–13.736 | <0.001 | 7.528 | 3.298–17.18 | <0.001 |
| AJCC response | | | | | | |
| CR | 1 | | | 1 | | 1 |
| PR | 2.714 | 0.986–7.47 | 0.053 | 2.915 | 1.051–8.088 | 0.040 |
| NR | 4.372 | 1.575–12.138 | 0.005 | 8.250 | 2.881–23.621 | <0.001 |
| Estrogen receptor | | | | | | |
| Negative | 1 | | | 1 | | |
| Positive | 0.536 | 0.364–0.787 | 0.001 | 0.461 | 0.302–0.703 | <0.001 |
| Ki67[a] | | | | | | |
| Continuous | 1.014 | 1.005–1.023 | 0.003 | 1.015 | 1.005–1.025 | 0.002 |

*HR* hazard ratio, *CI* confidence interval

[a] Ki67 as continuous variable

**TABLE 5** Univariate and multivariate Cox proportional hazard regression analysis—between clinicopathologic variables and overall survival

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age (years) | | | | | | |
| <35 | 1 | | | 1 | | |
| ≥35 | 0.534 | 0.277–1.029 | 0.061 | 0.622 | 0.310–1.247 | 0.181 |
| Initial clinical stage | | | | | | |
| IIA,IIB | 1 | | | 1 | | |
| IIIA | 5.444 | 1.286–23.038 | 0.021 | 4.902 | 1.151–20.887 | 0.032 |
| IIIB | 14.040 | 3.256–60.535 | <0.001 | 13.113 | 3.019–56.960 | 0.001 |
| IIIC | 15.661 | 3.579–68.522 | <0.001 | 20.142 | 4.506–90.032 | <0.001 |
| AJCC response | | | | | | |
| pCR | 1 | | | 1 | | |
| PR | 5.050 | 0.689–37.043 | 0.111 | 5.845 | 0.788–43.370 | 0.084 |
| NR | 8.629 | 1.172–63.555 | 0.034 | 22.42 | 2.936–171.226 | 0.003 |
| Estrogen receptor | | | | | | |
| Negative | 1 | | | 1 | | |
| Positive | 0.328 | 0.182–0.589 | <0.001 | 0.284 | 0.151–0.535 | <0.001 |
| Ki67 | | | | | | |
| Continuous | 1.018 | 1.006–1.030 | 0.002 | 1.017 | 1.005–1.030 | 0.007 |

response score (changes of T stage) and the axillary response score, which is divided by the sum of the achievable points. It is simple and easy to use but has not yet been externally validated, and thus, the optimal cutoff was not determined. Jeruss et al. proposed a novel scoring system, named CPS + EG score, which had been externally validated.[10,11] This score system reflects biologic tumor markers, as well as clinical and pathologic staging.

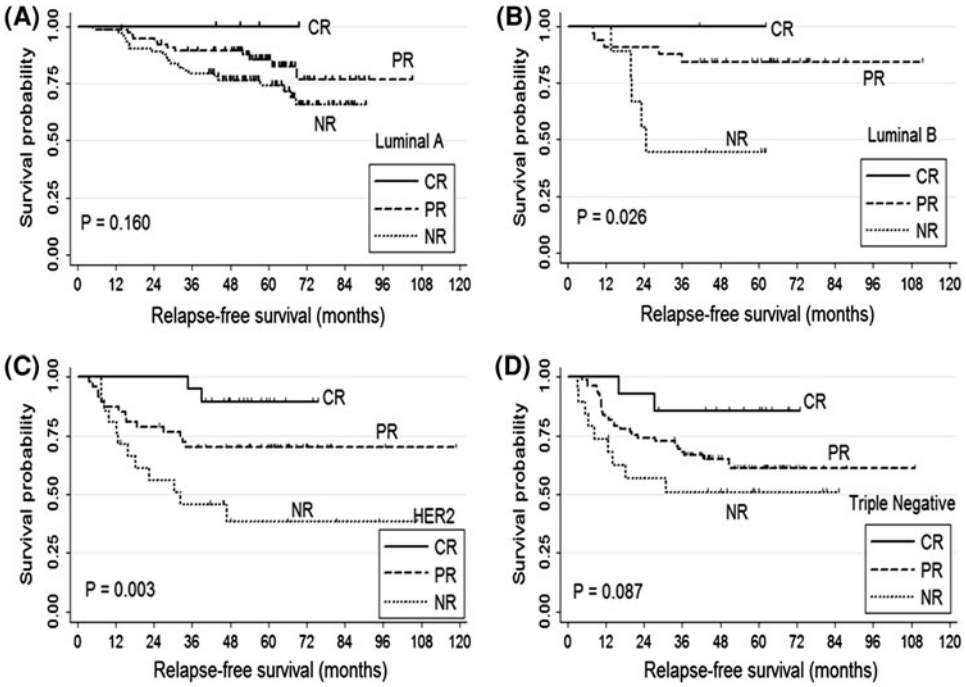


**FIG. 2** Relapse-free survival by AJCC response criteria in (a) Luminal A, (b) Luminal B, (c) HER2, (d) Triple negative subtypes

Recently, AJCC 7th edition tried to make more simple response criteria.[13] Response to NAC was divided into ternary: CR, PR, and NR. CR refers to prior pCR, and non-pCR was divided into PR and NR. This new AJCC criteria has only been proposed recently and not yet evaluated, nor validated. In our study, we evaluated the clinical usefulness of such proposed AJCC criteria. We found that the new AJCC criteria was well correlated with the radiologic response and also has an independent prognostic value for RFS and OS.

Molecular phenotype, based on ER, PR, and HER2 status, becomes more important to predict survival. In our results, AJCC response criteria was valid in four subgroups (luminal A/luminal B/HER2/triple-negative), and AJCC response criteria can be used regardless of subtypes. Even though ER, PR, and HER2 status are important prognostic factors, AJCC TNM staging system did not incorporate ER, PR, and HER2 status. This study was a validation study for AJCC response criteria, which reflect the downstaging in TNM.

Our study included some limitations. First, for non-pCR patients, we did not directly compare AJCC response with histopathologic response, which requires percentage of necrosis and cellularity.[28,29] Second, the pCR rate of our study (9.8 %) was relatively lower than that of another study, which used six or eight cycles of NAC.[30,31] This was because only three cycles of NAC were performed and the tumor size was relatively large. We designed this protocol in 2001, when optimal cycle of NAC had not reached a consensus, and the main purpose of NAC was converting locally advanced breast cancer to operable breast cancer instead of obtaining pCR. Potential limitation of this study was low pCR rate due to short cycles of NAC. It is not yet confirmed that AJCC response criteria would be valid in six or eight cycles. However, AJCC response criteria, which basically reflect downstaging, were valid after three cycles, associated with lower downstaging rate than six or eight cycles. This suggests that clinical significance of AJCC response criteria can be translated into six or eight cycles of NAC. Third, AJCC response criteria do not reflect a decreased cellular differentiation that characterizes high histologic grade lesions, which has been shown to correlate with several markers of increased proliferation.[32,33] Basically, AJCC response criteria mainly depend on decreasing tumor size and involvement of the lymph node. Fourth, fine needle aspiration was not routinely performed for the axillary node prior NAC, and this could be a limitation of our study. Fifth, prognostic significance of nodal isolated tumor cells post-treatment (ypN0(i+)) is not certain.

However, despite these limitations, our study also had much strength. This study was the first study that explored the clinical usefulness of AJCC response criteria for NAC. We performed an accurate initial clinical staging with chest CT and breast MRI. Pre- and post- NAC paired with chest CT and breast MRI allow us to perform an exact radiologic response evaluation. Pathologic review was done by one pathologist (PIA) to avoid potential bias and maintain consistency. Moreover, AJCC response criteria are very simple to implement to clinical practice.

## CONCLUSIONS

AJCC response criteria for NAC in breast cancer have clinical usefulness in the evaluation of the response of NAC, as well as predicting survival. AJCC response criteria may provide more information for risk stratification to select a high-risk patient and to determine additional postoperative treatment.

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**CONFLICT OF INTEREST** The authors declare that no conflict of interest exists.

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