STUDY PROTOCOL

Validation of CPS+EG, Neo-Bioscore, and modified Neo-Bioscore staging systems after preoperative systemic therapy of breast cancer: Protocol of a retrospective multicenter cohort study in China

Ling Xu[1] , Zhuo Zhang[2], Qianxin Liu[2], Bin Zhou[1], Yinhua Liu[1], Qian Xiang[2], Sainan Zhu[3], Xuening Duan[1*] & Yimin Cui[2*]

1 Department of General Surgery, Breast Disease Center, Peking University First Hospital, Beijing, China
2 Department of Pharmacy, Peking University First Hospital, Beijing, China
3 Statistics Department, Peking University First Hospital, Beijing, China

Correspondence
Xuening Duan, Department of General Surgery, Breast Disease Center, Peking University First Hospital, No. 8 of Xishiku Street, Beijing 100034, China.
Tel: +86 10 8357 5053
Fax: +86 10 6655 2566
Email: xuening666@126.com

Yimin Cui, Department of Pharmacy, Peking University First Hospital, No. 8 of Xishiku Street, Beijing 100034, China.
Tel: +86 10 6611 0802
Fax: +86 10 6611 0908
Email: cui.pharm@pkufh.com; bdyyyljd@126.com

*These authors contributed equally to this work.

Abstract

Prognostic assessment after preoperative systemic therapy (PST) is critical to develop a therapeutic strategy for breast cancer management. Currently, a clinical–pathologic staging system that incorporates ER status and nuclear grading (CPS + EG), and the Neo-Bioscore system that includes HER2 status into CPS + EG, are used to predict outcomes in patients with breast cancer after PST. While HER2-positive is recognized as a favorable factor in the Neo-Bioscore system based on results in patients administered one year of trastuzumab as anti-HER2 therapy, most HER2-positive cases have difficulty accessing anti-HER2 treatment in China. Therefore, it is crucial that a modified Neo-Bioscore staging system is developed that incorporates an additional factor of poor prognosis, HER2-positive status without trastuzumab treatment, to determine accurate prognosis. We propose a retrospective multicenter cohort study in China to validate CPS + EG, Neo-Bioscore, and the modified Neo-Bioscore system and determine the accuracy of prediction. Primary breast cancer patients without metastasis treated with PST and surgery in academic institutions or hospitals of provincial level in China will be included. Disease-free, disease specific, and overall survival will be calculated using the Kaplan–Meier Method, stratified by CPS + EG, Neo-Bioscore, and the modified Neo-Bioscore staging system. Areas under the curve of each staging system will be calculated. Multivariate analysis using Wald testing and maximum likelihood estimates in a Cox proportional hazards model will be conducted.

Introduction

Preoperative systemic therapy (PST) has become a part of standard treatment for patients with locally advanced breast cancer, and thus has become more common in clinical practice. While chemotherapy reduces tumor size, rendering large tumors operable, and permits breast conservation, PST has also been used to evaluate the prognostic response of breast cancer to anti-cancer drugs.

Several studies have demonstrated that the degree of reduction in tumor burden after PST does benefit disease-free survival (DFS) and overall survival (OS). A recent pooled clinical trial by Von Minckwitz et al. demonstrated that patients who achieved a pathological complete response (pCR), defined as the histological absence of invasive cancer cells in the breast and axillary nodes, had significantly superior DFS after PST compared to patients with residual

disease.[1] However, how to improve the prognosis of non-pCR patients still needs to be determined. Masuda *et al.* recently carried out a phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after PST. Their results revealed that postoperative adjuvant use of capecitabine significantly improved DFS and OS in patients with pathologically proven residual invasive disease after standard PST of anthracyclines and/or taxanes.[2] However, not all pCR patients were able to complete six or eight cycles of capecitabine treatment after surgery; some were treated with a reduced dosage of the anticancer drug or withdrew from the regimen. This raises the question of whether all non-pCR patients should be administered postoperative chemotherapy. Thus, a more refined staging system is needed to improve prediction and develop better therapeutic strategies for postoperative treatments.

The CPS + EG staging [3,4] and updated Neo-Biosocre[5] scoring systems incorporate aspects of tumor biology into staging. The CPS + EG score has been valuable for predicting the survival of patients after PST, although this system was developed before the routine use of trastuzumab therapy in adjuvant and neoadjuvant settings in breast cancer. The Neo-Bioscore system was developed to validate the CPS + EG staging system using a new definition of ER positivity (ER positive if ≥ 1% tumor cell nuclei are immunoreactive), and also incorporated HER2 status into the previously developed CPS + EG staging system. Treatment of HER2-positive tumors with trastuzumab has been shown to improve survival in both adjuvant[6,7] and neoadjuvant settings;[8–10] thus, HER2-negativity is considered an unfavorable prognostic factor as patients with HER2-positive tumors routinely treated with trastuzumab yield better prognoses in the Neo-Bioscore prognostic stratification system. However, the health care system in China greatly differs from that in the United States. Most HER2-positive patients are not treated with trastuzumab because of the high cost in China. Data from our center revealed that only 24.4% of HER2-positive breast cancer patients in adjuvant and neoadjuvant settings received trastuzumab treatment during 2008–2011.[11] Although health insurance has covered half of the cost of trastuzumab therapy since 2012, only 50–60% of HER2-positive patients can obtain trastuzumab therapy. Because both the CPS + EG and Neo-Bioscore systems do not incorporate HER2-positive patients not treated with trastuzumab, the potential to predict outcomes in such patients is limited.

Herein, we describe the protocol for a retrospective multicenter cohort study in patients with primary invasive breast cancers treated with PST and surgery, which will be conducted to validate the CPS + EG, Neo-Bioscore, and modified Neo-Bioscore systems and determine the accuracy of prediction. The primary objective is to test the hypothesis that the modified Neo-Bioscore staging system has the potential to provide a reliable prognosis for patients with primary invasive breast cancer. The secondary objective is to test the hypothesis that the modified Neo-Bioscore staging system is superior to CPS + EG and Neo-Bioscore systems for prediction including a specific population of HER2-positive breast cancer patients who did not receive trastuzumab therapy.

Methods

Study design

We intend to conduct a retrospective multicenter cohort study of patient data from hospital databases from 2006 to 2015. All breast cancer patients who meet the following inclusion criteria will be included in the study: (i) women aged between 18 to 75 years; (ii) invasive breast cancer confirmed by histology at stage I, IIA, IIB, IIIA, IIIB, or IIIC; (iii) underwent PST before surgery; (iv) information on ER, PR, HER2, and menopausal status and histological grade available; (v) lymph nodes evaluated by fine needle biopsy (FNB) if clinically positive, or by sentinel lymph node biopsy (SLNB) if clinically negative or FNB-negative before PST; (vi) underwent complete surgical resection of the primary breast cancer after PST: either lumpectomy or mastectomy with SLNB or axillary dissection, with clear margins for both invasive and ductal carcinoma in situ (DCIS); (vii) no evidence of metastatic disease outside the breast and its regional lymph nodes prior to PST; and (viii) with a record of baseline bilateral breast B-type ultrasound.

Patients who meet any of the following criteria will be excluded: (i) bilateral breast cancer; (ii) history of severe hypersensitive reaction to chemotherapy drugs or formulation; (iii) history of heart failure, uncontrolled angina, severe uncontrolled arrhythmias, pericardial disease, or electrocardiographic evidence of acute ischemic changes; (iv) a major organ allograft or condition requiring chronic immunosuppression (i.e. kidney, liver, lung, heart, bone marrow transplant, or autoimmune diseases), except patients who received corneal transplants or cadaver skin or bone transplants; (v) a serious uncontrolled intercurrent medical or psychiatric illness, including serious infections such as clinically defined acquired immune deficiency syndrome (AIDS), bacterial and fungal infection, history of uncontrolled seizures, diabetes, or central nervous system (CNS) disorders; (vi) active hepatitis B or C with abnormal liver function tests (LFTs) or human immunodeficiency virus (HIV) positive; (vii) history of other malignancy within the last five years that could affect the prognosis or assessment of any of the study drugs (except cured basal cell carcinoma of skin, carcinoma in situ of uterine cervix, DCIS); (viii) breast cancer during pregnancy; (ix) any abnormal laboratory values before PST: absolute neutrophil

count (ANC) < 1.5×10^9/L, platelet count < 75×10^9/L, hemoglobin < 90g/L, total bilirubin > 1.5 × the upper limit of normal (ULN), aspartate transaminase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) > 2.5 × ULN or > 5 × ULN with liver metastasis (patients with bone metastasis may not have elevated ALP as an exclusion criterion, as judged by the researchers); (x) failure to complete PST caused by various reasons before surgery; and (xi) failure to complete one year of trastuzumab therapy after PST.

Participant information

Participant information including age; menopause status; variables related to the cancer diagnosis; histological grade; ER, PR, and HER2 status; trastuzumab therapy; Ki 67; pre-treatment clinical stage (CS); and post-treatment pathologic stage (PS) will be retrieved from medical records by multi-center tumor registrars. The clinical stage is determined based on physical examination, mammography, ultrasonography and/or dynamic contrast-enhanced magnetic resonance imaging (MRI) of the breast and regional nodal basins at presentation. CS and PS are scored according to the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. ER, PR, and HER2 status and histological grade will be obtained from each patient's diagnostic core needle biopsy and reported into the pathology record by two dedicated breast pathologists.

ER and HER2 status will be evaluated using standard procedures, as previously reported.[12,13] Consistent with Mayo Clinic validation cohort,[14] the medical record of histological grade rather than the nuclear grade will be used in this study because this grading is more widely used. Briefly, the histological grade is evaluated according to Elston–Ellis modification of the Scarff–Bloom–Richardson grading system.[15] The tumor grade is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature and adding the scores for all three categories. A combined score of 3–5 points is grade 1 (G1), 6–7 points is grade 2 (G2), and 8–9 points is grade 3 (G3).

Treatment and standard procedures

Baseline investigation

Complete examination (e.g. routine blood test, biochemical test, electrocardiogram, echocardiography) of all consecutive patients with primary non-metastatic breast cancer is required to confirm the presence of any PST contraindications. Ultrasonography and/or dynamic contrast-enhanced MRI are used to examine breast tumors and axillary lymph nodes prior to PST. Lymph nodes are evaluated by FNB or by SLNB.

Treatment

All breast cancer patients are administered first-line taxane (T) and/or anthracycline (A) based neoadjuvant regimens, such as dose-dense doxorubicin/cyclophosphamide (AC) followed by docetaxel, docetaxel/epirubicin (TA), and docetaxel/epirubicin/cyclophosphamide (TAC), etc. Some HER2-positive patients are administered trastuzumab therapy with docetaxel/carboplatin/trastuzumab (TCH), AC followed by T chemotherapy with trastuzumab (AC–TH), and dose-dense AC followed by paclitaxel with trastuzumab (Supplementary Appendix A). Prior to each cycle, complete examinations should be conducted to rule out chemotherapy contraindications. If a patient's blood count is low, granulocyte colony-stimulating factor can be administered after chemotherapy. An echocardiography should be performed before PST and 3, 6, and 12 months after the start of treatment to determine the left ventricular ejection fraction in all patients treated with trastuzumab. B-type ultrasound and/or MRI examinations should be conducted within 10–14 days after the first day of the second and fourth cycles of three-week treatment to evaluate the clinical significance of PST. Tumor response to PST is determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[16] (Supplementary Appendix B), and the tumor features are measured as per changes in time-signal intensity (T-SI) curves (Table 1). If MRI evaluation shows a partial response (PR) after four cycles, the patient should complete six cycles of treatment and subsequently undergo surgery. Should the evaluation demonstrate stable disease (SD), another needle biopsy should be taken and the Miller–Payne system[17] used to evaluate the response by comparing specimens taken before and after PST (Supplementary Appendix C). Patients with a pathologic evaluation of grade 1 are administered replacement chemotherapy with vinorelbine/cisplatin (NP) for four to six cycles before surgery or receive surgical treatment directly without therapeutic regimen adjustment. HER2-positive patients administered trastuzumab should continue anti-HER2 treatment, although their chemotherapy drugs are substituted (e.g. vinorelbine, cisplatin and trastuzumab).

After completion of PST, patients undergo either breast conserving therapy (lumpectomy) with whole-breast irradiation or mastectomy with or without post-mastectomy

Table 1 T-SI curve types and corresponding clinical significance

Clinical evaluation	Changes in the type of T-SI curves
Effective	Type III T-SI curve became Type T or Type II, Type II T-SI curve became type I
Stable	No change
Progressive	Type II T-SI curve became type III

T-SI, time-signal intensity.

radiotherapy (RT), and axillary dissection. The Miller–Payne grading system[17] is used to evaluate the PST pathological response by comparing the specimens taken from surgery and before PST (Supplementary Appendix C). We define a pathologic complete response (pCR) as the histopathological complete absence of invasive lesions in both breast and axillary lymph node specimens (ypTis/0ypN0). Patients with tumors > 5 cm before PST or pathological node-positive disease (including both FNB and CNB before PST) receive standard postoperative irradiation. No patients receive additional adjuvant chemotherapy. Both premenopausal and postmenopausal women with hormone receptor (HR)-positive breast cancer routinely receive a minimum of five years adjuvant endocrine therapy. Postmenopausal women can be treated with either tamoxifen (TAM) or aromatase inhibitor (AI), or a sequential regimen of TAM followed by AI. Endocrine therapy should commence within six weeks of the last dose of chemotherapy. Patients may be administered RT and endocrine therapy either concomitantly or sequentially. ER and/or PR positive patients with regular menstrual periods or whose estradiol reaches premenopausal levels during five years of endocrine therapy can be treated with TAM, or TAM combined with ovarian function suppression (OFS), such as a luteinizing hormone-releasing hormone (LHRH) analogue (e.g. goserelin) or bilateral oophorectomy, or AI combined with OFS. ER and/or PR positive premenopausal women who cannot tolerate or have a contraindication to TAM can be treated with LHRH analogues and AIs. HER2-positive patients treated with trastuzumab before surgery routinely complete one year of therapy.

Follow-up

Medical history, physical examinations, laboratory tests, and ultrasound of the breast, chest, and liver are carried out every six months after therapy. Chest X-ray or low dose chest computed tomography (CT) scans are performed every 6–12 months, while a bone scan is only required in certain patients. Bone mineral density is measured in women treated with an adjuvant AI annually or more often if necessary. Women who receive adjuvant TAM should have an annual gynecologic checkup for potential TAM-associated endometrial carcinoma. Patients are educated how to monitor and manage the lymphedema. Patients are also advised on the possible side effects of treatment, such as chemotherapy and endocrine therapy, and are encouraged to lead an active lifestyle (such as exercise, diet, nutrition) and manage their weight.

Analysis plan

The CPS + EG score and Neo-Bioscore will be determined for each patient, as previously reported.[3,5] Because HER2-positive patients not treated with trastuzumab

Table 2 CPS + EG, Neo-Bioscore, and modified Neo-Bioscore staging systems

Cancer stage	CPS + EG Score	Neo-bioscore (7 points)	Modified neo-bioscore (8 points)
Pretreatment clinical stage			
I	0	0	0
IIA	0	0	0
IIB	1	1	1
IIIA	1	1	1
IIIB	2	2	2
IIIC	2	2	2
Post-treatment pathologic stage			
0	0	0	0
I	0	0	0
IIA	1	1	1
IIB	1	1	1
IIIA	1	1	1
IIIB	1	1	1
IIIC	2	2	2
Tumor marker			
ER negative	1	1	1
Grade 3	1	1	1
HER2-negative		1	1
HER2-positive, no trastuzumab			2

therapy exhibit risk factors for poor prognosis, we will assign a score of 2 in our modified Neo-Bioscore staging system. Details of the staging systems are listed in Table 2. The Kaplan–Meier method will be used to calculate five-year DFS, disease specific survival (DSS), and OS in patient subgroups with multiple staging systems: (i) CS, (ii) PS, (iii) CPS + EG score, (iv) Neo-Bioscore, and (v) modified Neo-Bioscore. Within each staging system, DFS, DSS, and OS among the subgroups will be compared using the log-rank test. The area under the curve (AUC) will be calculated for the multiple staging systems and compared using the time receiver operating characteristic (ROC) package.[18] Wald tests and maximum likelihood estimates (MLE) in Cox proportional hazards model will be used to estimate hazard ratios with covariates of age; menopause; grade; ER, PR, HER2 groups (HER2-negative, HER2-postive with and without trastuzumab administration); Ki67; CS; and PS with DFS, DSS, and OS, respectively.

Research team and data collection

Data will be recorded by professional clinicians and double-checked by independent research staff for accuracy. All patients are educated and face-to-face consultation takes place two to three times a year to help patients understand the disease, recovery after surgery, and how to manage chemotherapy. The research team of this study

includes medical doctors, nurses, case managers, pharmacists, and other trained research staff. Retrospective data will be retrieved from hospital records and follow-up patient databases from multiple institutes or hospitals. Statisticians will perform statistical analyses. The sample size of this protocol is based on literature of the CPS + EG staging system. In the first report of the CPS + EG system in 2008, 932 patients were enrolled to establish the system.[3] In the three subsequent validation studies, the sample size ranged from 485 to 804.[4,14,19] In our protocol, we plan to develop a modified staging system (modified Neo-Bioscore) that incorporates insufficient anti-HER2 therapy into the previously developed Neo-Bioscore. Therefore, the sample size of this multicenter study should be approximately equal to the first report on the CPS + EG, rather than the lower sample sizes used in the validation studies.

Furthermore, this multicenter study will be conducted to reflect the real-world results of different situations of PST and anti-HER2 treatment in Chinese hospitals. In view of the accessibility of anti-HER2 therapy and the influence on peripheral medical systems, data will be retrieved from hospitals located in municipalities or provincial capitals, mainly in eastern and central parts of China. In our previous single center study, 30% of patients who received PST were HER2-positive and 61.2% received trastuzumab.[20] According to a preliminary survey, the proportion of HER2-positive patients who received PST in other centers is also approximately 30%, while the extent of anti-HER2 therapy varies widely. A recent real-world study in which 1017 early stage HER2-positive breast cancer patients were enrolled from 13 hospitals in Eastern China showed that 40.5% received trastuzumab.[21] In order to achieve a balance between the number of patients treated with and without trastuzumab, approximately 600 patients from external centers should be enrolled. Beijing hospitals will be included in this multicenter study to balance the difference in patient enrollment between Beijing and other provinces in China. Thus, our goal is to ensure that approximately 500 patients are enrolled from both Beijing and other provinces.

Outcomes

The primary outcome of this proposed study is DSS, which is calculated from the time of diagnosis to death as a result of breast cancer.

The secondary outcomes are DFS and OS. DFS is defined as the period from the time of post-PST breast cancer surgery to local recurrence; regional recurrence; distant metastasis; contralateral breast cancer (invasive or non-invasive); second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in

situ, or lobular carcinoma in situ of the breast); or death from any cause prior to recurrence or second primary cancer. OS is measured as the period from the date of diagnosis to the date of death of any cause.

Ethics and confidentiality

The study protocol is in accordance with the Helsinki Declaration and has been approved by the central ethics committee at the Peking University First Hospital. Because of the retrospective design, all patient information will be stored in a secured electronic medical record system, identified only by number.

Discussion

Breast cancer stage is an important factor to assist physicians to develop treatment strategies. In 2017, the AJCC published the 8th edition Cancer Staging Manual, which included anatomic stage groups as well as prognostic stage groups. The updated staging system used for breast cancer was based on seven key pieces of information: tumor size; regional lymph node status; metastasis status; ER, PR, and HER2 expression; and cancer histological grade. In general, the higher the breast cancer stage, the poorer the prognosis. We previously evaluated the clinical prognostic value of this new staging system for different subtypes of breast cancer via a retrospective single center study.[11,22,23] We restaged patients based on the eighth edition of the AJCC cancer staging system and analyzed the prognostic value of anatomic and prognostic stage groups. We found that both staging methods had prognostic value in HER2-enriched subtype breast cancer. Another study found that staging breast cancer on the basis of prognostic stage is more accurate for the prediction and classification of survival than on the basis of anatomic stage.[24] The AJCC eighth prognostic staging system considers HER2-positive status a favorable prognostic factor for breast cancer on the basic assumption that all HER2-positive patients receive trastuzumab adjuvant therapy, while HER2-negative status is a poor prognostic factor. Although the prognosis of patients with HER2-positive breast cancer after trastuzumab treatment is better than for HER2-negative patients, an accurate prediction system for HER2-positive patients not administered anti-HER2 treatment needs to be developed.

Unlike the routine administration of trastuzumab for patients in the United States and other developed countries, most HER2-positive breast cancer patients in China are not treated with trastuzumab because of the expense and financial hardship. In addition, some HER2-positive patients initially treated with trastuzumab have to withdraw from therapy because of cardiac or non-cardiac

toxicity, a lack of compliance, or lack of response during PST.[25–27]

However, breast cancer patients are not always treated with anti-HER2 antibody therapy, even in developed countries. In the United States, for example, a retrospective study that enrolled 915 HER2-positive cases reported that 28% of such patients did not initially receive anti-HER2 therapy.[28] Another study reported that approximately 41% of 585 American women discontinued trastuzumab therapy at an early stage.[29] Thus, the number of HER2-positive patients that are not administered trastuzumab remains substantial. We plan to carry out a multicenter study using data from 12 top hospitals (Supplementary Appendix D) in China to validate CS, PS, and the CPS + EG and Neo-Bioscore staging systems by DSS, DFS and OS. We will assign HER2-positive patients not administered trastuzumab with a poorer prognostic factor of 2 points in the modified Neo-Bioscore staging system (Table 2) to test the reliability and accuracy of survival prediction. Our previous experience of retrospective analysis indicates that we will obtain reliable data from this large proposed sample of the Chinese population.

Previous validation studies from the MD Anderson Cancer Center and the Mayo Clinic were carried out with two distinctive cutoff points to define ER status.[5,14] According to 2010 American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP) guidelines, however, either a 1% or 10% cutoff can be used to define ER positivity in the CPS + EG staging system, with no significant difference.[12] For our study, we have chosen 1% as the cutoff and consider ER-negative status as a significant poor prognostic factor of breast cancer. In addition, we consider the histological grade of breast cancer an important prognostic factor, as described in AJCC eighth edition and in other publications.[30,31] As the Nottingham (Elston–Ellis) modification of the Scarff–Bloom–Richardson grading system (also known as the Nottingham grading system), is widely recommended and commonly used[30,32,33] and because the modified staging system renders lower interobserver and intra-observer variability than the nuclear grading system,[33] we propose to use histologic grade to validate the CPS + EG system in this study. We believe that histological grade is more feasible and does not compromise the extent of survival stratification. Furthermore, several studies have demonstrated that changes in Ki67 expression after PST are associated with outcomes of breast cancer. However, the cutoff value of Ki67 to predict treatment response and outcome of breast cancer after PST is still debated. In this study, we will use 14% as a cutoff or a threshold to distinguish subtypes Luminal A and Luminal B.[34–37]

The study will devote significant attention to data quality at multiple stages, including case ascertainment, data extraction, and data management. However, the study will face some limitations that are common in retrospective design. First, the findings largely depend on the accuracy and completeness of the medical records and the extraction process. Second, there may be fewer patients in higher score groups because we intend to exclude cases who participated in aggressive chemotherapy with other regimens after PST, as they may have a poorer prognosis. Third, although we will include 12 hospitals and a large sample size (> 1000 cases) is anticipated, the data may still be insufficient because of a short follow-up period. If this is the case, we will recruit more hospitals/research centers for a larger patient sample. Finally, the findings of our retrospective study will need to be confirmed in a future prospective study.

Acknowledgment

Disclosure

No authors report any conflict of interest.

References

1 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**: 1796–804.

2 Masuda N, Lee SJ, Ohtani S *et al.* Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017; **376**: 2147–59.

3 Jeruss JS, Mittendorf EA, Tucker SL *et al.* Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. *J Clin Oncol* 2008; **26**: 246–52.

4 Mittendorf EA, Jeruss JS, Tucker SL *et al.* Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol* 2011; **29**: 1956–62.

5 Mittendorf EA, Vila J, Tucker SL *et al.* The neo-bioscore update for staging breast cancer treated with neoadjuvant chemotherapy: Incorporation of prognostic biologic factors into staging after treatment. *JAMA Oncol* 2016; **2**: 929–36.

6 Piccart-Gebhart MJ, Procter M, Leyland-Jones B *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353**: 1659–72.

7 Romond EH, Perez EA, Bryant J *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353**: 1673–84.

8 Mittendorf EA, Wu Y, Scaltriti M *et al.* Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. *Clin Cancer Res* 2009; **15**: 7381–8.

9 Buzdar AU, Valero V, Ibrahim NK *et al.* Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res* 2007; **13**: 228–33.

10 Buzdar AU, Ibrahim NK, Francis D *et al.* Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 2005; **23**: 3676–85.

11 Zhou B, Xu L, Ye J, Xin L, Duan X, Liu Y. The prognostic value of the 8th edition of the American Joint Committee on cancer (AJCC) staging system in HER2-enriched subtype breast cancer, a retrospective analysis. *Anticancer Res* 2017; **37**: 4615–21.

12 Hammond ME, Hayes DF, Dowsett M *et al.* American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. (Published erratum appears in *J Clin Oncol* 2010; **28**: 3543.). *J Clin Oncol* 2010; **28**: 2784–95.

13 Wolff AC, Hammond ME, Hicks DG *et al.* Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 2013; **31**: 3997–4013.

14 Abdelsattar JM, Al-Hilli Z, Hoskin TL, Heins CN, Boughey JC. Validation of the CPS + EG staging system for disease-specific survival in breast cancer patients treated with neoadjuvant chemotherapy. *Ann Surg Oncol* 2016; **23**: 3206–11.

15 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. *Histopathology* 2002; **41**: 154–61.

16 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

17 Ogston KN, Miller ID, Payne S *et al.* A new histological grading system to assess response of breast cancers to primary chemotherapy: Prognostic significance and survival. *Breast* 2003; **12**: 320–7.

18 Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013; **32**: 5381–97.

19 Choi M, Park YH, Ahn JS *et al.* Assessment of pathologic response and long-term outcome in locally advanced breast cancers after neoadjuvant chemotherapy: Comparison of pathologic classification systems. *Breast Cancer Res Treat* 2016; **160**: 475–89.

20 Xu L, Duan X, Zhou B *et al.* Validation of the CPS+EG and Neo-Bioscore staging systems after preoperative systemic therapy for breast cancer in a single center in China. *Breast* 2018; **40**: 29–37.

21 Li J, Wang S, Wang Y *et al.* Disparities of trastuzumab use in resource-limited or resource-abundant regions and its survival benefit on HER2 positive breast cancer: A real-world study from China. *Oncologist* 2017; **22**: 1333–8.

22 Xu L, Li JH, Ye JM *et al.* A retrospective survival analysis of anatomic and prognostic stage group based on the American Joint Committee on Cancer 8th edition Cancer Staging Manual in luminal B human epidermal growth factor receptor 2-negative breast cancer. *Chin Med J (Engl)* 2017; **130**: 1945–52.

23 Ye J, Wang W, Xu L *et al.* A retrospective prognostic evaluation analysis using the 8th edition of American Joint Committee on Cancer (AJCC) cancer staging system for luminal A breast cancer. *Chin J Cancer Res* 2017; **29**: 351–60.

24 Lee SB, Sohn G, Kim J *et al.* A retrospective prognostic evaluation analysis using the 8th edition of the American Joint Committee on Cancer staging system for breast cancer. *Breast Cancer Res Treat* 2018; **169**: 257–66.

25 Campiglio M, Bufalino R, Sasso M *et al.* Effect of adjuvant trastuzumab treatment in conventional clinical setting: An observational retrospective multicenter Italian study. *Breast Cancer Res Treat* 2013; **141**: 101–10.

26 Untch M, Rezai M, Loibl S *et al.* Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: Results from the GeparQuattro study. *J Clin Oncol* 2010; **28**: 2024–31.

27 Boons CC, Wagner C, Hugtenburg JG. Guideline adherence regarding the use of expensive drugs in daily practice: The examples of trastuzumab in breast cancer and bortezomib in multiple myeloma. *Oncol Res Treat* 2016; **39**: 417–22.

28 DaCosta Byfield S, Buck PO, Blauer-Peterson C *et al.* ReCAP: Treatment patterns and cost of care associated with initial therapy among patients diagnosed with operable early-stage human epidermal growth factor receptor 2-overexpressed breast cancer in the United States: A real-world retrospective study. *J Oncol Pract* 2016; **12**: 159–67.

29 Wang SY, Long JB, Hurria A *et al.* Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival. *Breast Cancer Res Treat* 2014; **146**: 411–9.

30 Rakha EA, Reis-Filho JS, Baehner F *et al.* Breast cancer prognostic classification in the molecular era: The role of histological grade. *Breast Cancer Res* 2010; **12**: 207.

31 Amin MB, Greene FL, Edge S *et al.*, eds. *AJCC Cancer Staging Manual*, 8th edn. Springer, New York 2016.

32 Simpson JF, Gray R, Dressler LG et al. Prognostic value of histologic grade and proliferative activity in axillary node-positive breast cancer: Results from the Eastern Cooperative Oncology Group Companion Study, EST 4189. *J Clin Oncol* 2000; **18**: 2059–69.

33 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. *Histopathology* 1991; **19**: 403–10.

34 Montagna E, Bagnardi V, Viale G et al. Changes in PgR and Ki-67 in residual tumour and outcome of breast cancer patients treated with neoadjuvant chemotherapy. *Ann Oncol* 2015; **26**: 307–13.

35 Jones RL, Salter J, A'Hern R et al. Relationship between oestrogen receptor status and proliferation in predicting response and long-term outcome to neoadjuvant chemotherapy for breast cancer. *Breast Cancer Res Treat* 2010; **119**: 315–23.

36 Sheri A, Smith IE, Johnston SR et al. Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. *Ann Oncol* 2015; **26**: 75–80.

37 Goldhirsch A, Wood WC, Coates AS et al. Strategies for subtypes–dealing with the diversity of breast cancer: Highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. *Ann Oncol* 2011; **22**: 1736–47.

Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Appendix A. Neoadjuvant chemotherapy regimen.
Appendix B. Response evaluation criteria in solid tumors.
Appendix C. Miller–Payne grading system.
Appendix D. Principal investigators and clinical sites.