Biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer

Takayuki Iwamoto[1], Yukiko Kajiwara[1], Yidan Zhu[1], Shigemichi Iha[2]

[1]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; [2]Department of Breast Oncology, Miyake Ofuku Clinic, Okayama, Japan

Contributions: (I) Conception and design: T Iwamoto, S Iha; (II) Administrative support: T Iwamoto, Y Kajiwara, Y Zhu; (III) Provision of study materials or patients: T Iwamoto; (IV) Collection and assembly of data: T Iwamoto, Y Kajiwara; (V) Data analysis and interpretation: T Iwamoto; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Takayuki Iwamoto. 2-5-1, Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Email: tiwamoto@md.okayama-u.ac.jp.

Abstract: The improvement of tumor biomarkers prepared for clinical use is a long process. A good biomarker should predict not only prognosis but also the response to therapies. In this review, we describe the biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer, considering different breast cancer subtypes. In hormone receptor (HR)-positive/human epidermal growth factor 2 (HER2)-negative breast cancers, various genomic markers highly associated with proliferation have been tested. Among them, only two genomic signatures, the 21-gene recurrence score and 70-gene signature, have been reported in prospective randomized clinical trials and met the primary endpoint. However, these genomic markers did not suffice in HER2-positive and triple-negative (TN) breast cancers, which present only classical clinical and pathological information (tumor size, nodal or distant metastatic status) for decision making in the adjuvant setting in daily clinic. Recently, patients with residual invasive cancer after neoadjuvant chemotherapy are at a high-risk of recurrence for metastasis, which, in turn, make these patients best applicants for clinical trials. Two clinical trials have shown improved outcomes with post-operative capecitabine and ado-trastuzumab emtansine treatment in patients with either TN or HER2-positive breast cancer, respectively, who had residual disease after neoadjuvant chemotherapy. Furthermore, tumor-infiltrating lymphocytes (TILs) have been reported to have a predictive value for prognosis and response to chemotherapy from the retrospective analyses. So far, TILs have to not be used to either withhold or prescribe chemotherapy based on the absence of standardized evaluation guidelines and confirmed information. To overcome the low reproducibility of evaluations of TILs, gene signatures or digital image analysis and machine learning algorithms with artificial intelligence may be useful for standardization of assessment for TILs in the future.

Keywords: Biomarker; chemotherapy; breast cancer; gene expression

Submitted Dec 11, 2019. Accepted for publication Jan 13, 2020.
doi: 10.21037/cco.2020.01.06
View this article at: http://dx.doi.org/10.21037/cco.2020.01.06

Biomarkers and subtypes of breast cancer

Breast cancer is not a single disease. Clinically, breast cancer has been known to have distinct prognosis and response to chemotherapies based on the immunohistochemical (IHC) subtypes [e.g., estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2)] (1,2). hormone receptor (HR)-positive (ER and/or PgR-positive)/HER2-negative breast cancers have a good response to hormone therapy and favourable prognosis. HER2-positive and triple-negative (TN: ER, PgR and HER2-negative) breast cancers have poor baseline prognosis, and good response to HER2 targeted therapy and chemotherapy, respectively. In 2000, molecular subtypes (luminal A, luminal B, HER2 enriched, and basal) in breast cancer were reported (3). mRNA expression patterns in a

set of 65 surgical samples of human breast cancers provided a distinctive molecular subtype of each cancer (3). Tumor grade divides HR-positive/HER2-negative tumors into luminal A and B. This discrimination serves to determine the indication of chemotherapy. Gene expression patterns in HR-positive/HER2-negative tumors have been used to improve the genomic markers that may have better predictive power over classical pathological biomarkers (4). On the other hand, an additional clinical value in HER2-positive or TN subtypes is small due to close resemblance to IHC ER, PgR and HER2. Many of these breast cancer subtypes represent biologically distinct disease entities, indicating that each subtype has a distinct prognosis and response to chemotherapy (1,2). These observations lead to the theory that each subtype should have a distinct biomarker (5). Almost twenty years have elapsed since the molecular subtypes were established by Dr. Perou (3); but, how many additional next-generation biomarkers after IHC ER, PgR and HER2 have been available in routine clinical use for early-stage breast cancers in the adjuvant setting?

It takes a long time to introduce a biomarker into daily clinic, due to the lack of consistent evidence, inadequate validation of the biomarker, inadequate evidence of clinical significance, operational barriers to clinical implementation, and inadequate evidence of operational effectiveness or impact in clinical care (6). A biomarker refers to a measurable variable that is associated with the cancer outcome. There is a giant confusion regarding the distinction between a predictive and a prognostic biomarker (7). A prognostic biomarker informs about a likely cancer outcome (e.g., cancer recurrence, cancer progression, and death) impartial of treatment received. If a biomarker is prognostic and therapy is efficacious, the therapeutic benefit is similar for both biomarker-positive and biomarker-negative patients; though the biomarker will nonetheless be associated with a differential outcome, depending on whether it is present or absent. On the other hand, a biomarker is predictive if the therapeutic effect is unique for biomarker-positive patients compared to biomarker-negative patients. In this review, we describe biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer taking prognostic and predictive response to chemotherapy into consideration.

First-generation genomic signatures

Several first-generation genomic signatures highly associated with cell cycle and proliferation have been described for HR-positive/HER2-negative and node-negative breast cancer. Two of these (the 21-gene recurrence score: Oncotype DX, Genomic Health and the 70-gene signature: MammaPrint, Agendia Inc.) were tested by prospective randomized and controlled trials to assess their ability to predict prognosis and chemotherapy response. They are now increasingly used in clinical practice. An encouraging finding is that first-generation genomic signatures showed similar overall performance despite the limited overlap of genes (8). Several common features of TN and HER2-positive tumors had excessive expression of tumor-differentiation genes, together with numerous cell-cycle and proliferation genes (9). In contrast, the HR-positive combined luminal A and luminal B subtypes were not homogeneous (3). Since HR status and histologic grade are predictors of prognosis and response to chemotherapy or even endocrine therapy, and those features are associated with large scale gene expression differences, the first-generation genomic signatures invariably included many genes that capture the clinical phenotype (i.e., HR status and histologic grade) (10). Another critical and consistent finding in the field of genomic prognostic markers is the tumor size and nodal status. Although these have strong prognostic power, they have no powerful gene signatures inherently associated with them. In almost all research, these anatomical pathological variables continue to be statistically significant and independent predictors of prognosis (9,11,12). However, neither tumor size nor nodal status has a strong and consistent association with therapeutic sensitivity (i.e., probability and quantity of response to therapy).

The 70-gene signature has been developed using cDNA microarray analysis on primary breast cancer samples of 117 patients, which applied supervised classification to identify a gene expression signature predictive of breast cancer prognosis (13). The phase 3 randomized MINDACT (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) study, including 6,693 patients with early-stage breast cancer, aimed to provide prospective evidence of the clinical benefits of adding the 70-gene signature to classical clinical-pathological variables in choosing patients for adjuvant chemotherapy. It showed that approximately 46% of breast cancer patients with high clinical risk might not need chemotherapy (14). Based on the results of the MINDACT study, ASCO guidelines were updated, stating that the 70-gene signature can be used for patients at high clinical risk to decide whether to withhold adjuvant chemotherapy. This method can help identify a good-prognosis population,

who would get limited benefit from chemotherapy, among HR-positive/HER2-negative and lymph node-negative patients (15). On the other hand, for patients in the low clinical risk category, the 70-gene signature does not have clinical benefits because they did not benefit from chemotherapy, irrespective of the risk group.

Another genomic assay, the 21-gene recurrence score, exemplifies the candidate-gene approach to predict the outcome. It measures the expression of ER and HER2, as well as that of ER-regulated transcripts and several proliferation-related genes, by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) (11). The 21-gene recurrence score measures these variables into a recurrence score, which can be used as a continuous variable to predict the probability of recurrence in ten years and to group patients into low, intermediate, and high risk groups (11). Patients who had HR-positive/HER2-negative and lymph node-negative breast cancer with a recurrence score of 11–25 were randomized to receive hormone therapy alone or in combination with chemotherapy (16). For a recurrence score of <11, patients received hormone therapy, and for a recurrence score of >25, patients received a combination therapy. For a patient with a recurrence score of <11, the 5-year disease-free survival (DFS) was 93.8% [95% confidence interval (CI), 92.4 to 94.9] and the overall survival (OS) was 98.0% (95% CI, 97.1 to 98.6) (17), indicating clinicians may offer hormone therapy alone. For the patients with intermediate-risk, recurrence score of 11 to 25 had a similar efficacy between adjuvant endocrine therapy and chemo-endocrine therapy (18). For the patients with a high score of 26 to 100, who received adjuvant chemotherapy, the estimated 5-year DFS was 93% better than that expected with endocrine therapy alone (19). Based on this evidence, NCCN guidelines Version 3.2019 recommends using 21-gene recurrence score for NCCN category "1" disease as a prognostic and a predictive marker (20). There is no other method that is recommended both as a prognostic and a predictive marker in these guidelines (20). If a patient has HER2-positive or TN breast cancer, the physicians should not use the 21-gene recurrence score to make decisions on adjuvant systemic therapy (21).

The role of the first-generation signature for HR-positive/HER2-negative and node-positive breast cancer is another challenging area. Nodal status in breast cancer is a prognostic but not a predictive marker (9). Typically, patients with HR-positive and node-positive breast cancer should be prescribed not only hormone therapy but also chemotherapy, because they have a poor prognosis regardless of the sensitivity to chemotherapy. Albain *et al.* reported that the 21-gene recurrence score is prognostic for hormone-treated node-positive patients and predicted a significant benefit of chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil in breast cancers with a high recurrence score in the retrospective data set of 367 patients with breast cancer (22). Stemmer *et al.* showed the 5-year DFS of patients treated with N1 (1–3 positive lymph nodes) with a recurrence score <18, who received hormone therapy alone, to be 2.7% (95% CI, 1.4–5.1%) in the retrospective analysis of a prospectively designed study (23). The prospective phase 3 PlanB trial showed that the 21-gene recurrence score is prognostic for hormone-treated node-positive patients and their 5-year DFS with a recurrence score ≤11 is 94.4% (95% CI, 89.5–99.3%) (24). A phase 3, randomized clinical trial, RxPONDER, to assess the significance of chemotherapy for patients with N1 and recurrence score ≤25 is in progress (ClinicalTrials.gov Identifier: NCT01272037). This trial should provide evidence if the 21-gene recurrence score can predict the efficacy of chemotherapy for patients with N1 and HR-positive/HER2-negative breast cancers. NCCN guidelines v3.2019 states that multigene assays are prognostic, but not predictive, for patients with pN1. We are looking ahead to the consequences of phase 3 RxPONDER trial.

In summary, prospective randomized controlled trials for first-generation signatures, especially the 70-gene signature and the 21-gene recurrence score have been conducted and had met the primary endpoint that HR-positive/HER2-negative and node-negative patients with intermediate-risk can safely skip unnecessary chemotherapy. The node-positive setting is being tested for its predictive value for the multigene assay in a prospective randomized phase 3 trial. These assays will be more frequently used in the future.

Residual disease after neoadjuvant chemotherapy

Neoadjuvant chemotherapy is the standard therapy for locally advanced breast cancers and an alternative option for primary operable breast cancers. Neoadjuvant and adjuvant chemotherapy should clinically have a similar effect on the clinical outcomes, including DFS and OS (25). In one particular trial, there was no significant difference in DFS and OS (P value =0.99 and 0.83, respectively) among patients in the neoadjuvant and adjuvant chemotherapy-treated groups. Most patients were treated pre-operatively

before undergoing lumpectomy and radiation therapy post-operatively (67.8% versus 59.8%, respectively) (25). One purpose of the neoadjuvant chemotherapy is to be able to perform lumpectomy for cosmetic reasons and to have better clinical outcomes like a total mastectomy. Another purpose is to get clinical information on the response to therapies and provide additional therapies to improve clinical outcomes. Pathological complete response (pCR) after neoadjuvant chemotherapy is associated with long-term survival and has been adopted as the primary endpoint for neoadjuvant trials (25,26). Cortazar *et al.* reported the predictive value for survival by pCR after neoadjuvant chemotherapy (27). The prognostic value is the greatest in HER2-positive and TN subtypes (27), indicating that neoadjuvant chemotherapy provides an chance to observe the efficacy of a selected chemotherapy regimen directly. Patients with residual breast cancer after neoadjuvant chemotherapy are at a high-risk of recurrence of metastases, which make these patients ideal applicants for clinical trials. Two clinical trials, CREATE-X (28) and KATHERINE (29), have shown improved breast cancer outcomes with post-operative capecitabine and ado-trastuzumab emtansine treatment for patients who had either TN or HER2-positive breast cancer, respectively, who had residual cancer after neoadjuvant chemotherapy. Administering the additional agent for HER2-positive or TN patients with residual disease after neoadjuvant treatments may be a new framework to maximize a chance of survival (30).

In HR-positive/HER2-negative cancers, the clinical significance of pCR after neoadjuvant chemotherapy is not verified. Pooled analysis showed pCR was positively associated with event-free survival (HR 0.49, 95% CI, 0.33–0.71) and OS (0.43, 0.23–0.71), weaker than HER2-positive and TN breast cancers (27). As the adjuvant treatment, hormone therapies are prescribed to the majority of HR-positive patients. The correlation between pCR and survival is more complicated in HER2-positive and TN patients, because of the influence on hormone therapy, as showing in the following "Tumor-infiltrating lymphocytes" section.

Residual cancer burden (RCB) score that is measured as a continuous value combining pathologic measurements of the primary tumor (cellularity and size) and metastatic lymph node (size and number) may be a more powerful predictor than residual cancer after neoadjuvant chemotherapy (31). RCB can be prognostic for long-term survival after neoadjuvant chemotherapy not only in HER2-positive and TN breast cancers but also in the HR-positive/HER2-negative subtype (32).

Tumor-infiltrating lymphocytes (TILs)

There are no diagnostic multigene assays for HER2-positive and TN breast cancers. There is only classical clinical and pathological information (tumor size, nodal or distant metastatic status) for the decision making in the adjuvant setting in daily clinic. The extent of TILs by the assessment of hematoxylin and eosin (H&E)-stained tumor specimens is known to provide prognostic data, particularly in HER2-positive and TN breast cancers (33-35), but not in the HR-positive subtype, in the adjuvant setting. Loi *et al.* reported that a 10% increase in the stromal TILs is associated with a 15% reduced risk of recurrence (P value =0.025) and a 17% reduced risk of death in ER-negative/HER2-negative breast cancers, irrespective of the chemotherapy regimen (33). Similarly, 10% increased stromal TILs is associated with a 14% reduced risk of relapse or death (P value =0.02), an 18% reduced risk of distant relapse (P value =0.04), and a 19% of death (P value =0.01) in patients with TN breast cancer (34). In HER2-positive breast cancers, each 10% increase in TILs was significantly decreased recurrence in patients who received trastuzumab containing regimen (35). Furthermore, core needle biopsies from more than 3,000 breast cancer patients, before the treatment, have been evaluated to understand the predictive value of immune markers as a response to neoadjuvant chemotherapy (36). In a pooled analysis, the presence of higher TILs in pre-treated tumors was associated with favourable pCR rate to neoadjuvant chemotherapy (OR 3.93, 95% CI, 3.26–4.73) (36). The more, TILs expected higher pCR rates in TN (OR 2.49, 95% CI, 1.61–3.83) and HER2-positive (OR 5.05, 95% CI, 2.86–8.92), not in HR-positive (OR 6.21, 95% CI, 0.86–45.15) breast cancers (36). Similar analyses have reported that the higher levels of stromal TILs expected pCR (P value <0.001) in HER2-positive and TN breast cancers (37). Trastuzumab and pertuzumab containing regimen in HER2-positive breast cancers were also evaluated, where the high TIL levels in pre-treated tumors were significantly predictive of pCR in HER2-positive breast cancer (38). In summary, increased TILs can be a predictor of both response to chemotherapy and prognosis after chemotherapy for patients with HER2-positive and TN breast cancers, but not HR-positive breast cancers.

Association between immune functions and HR-positive breast cancer is another interesting topic. Although chemotherapy may be prescribed based on the clinical, pathological, and genomic risk, hormone therapy may

be given to the majority of the patients with HR-positive invasive breast cancer, regardless of the clinical and pathological risk. Even if patients with HR-positive breast cancer achieve pCR after neoadjuvant chemotherapy, indicating they have a good response to chemotherapy, pCR cannot be an indicator of favorable prognosis after surgery. Prediction of prognosis in HR-positive breast cancers treated with hormone therapy should take into consideration the response not only to chemotherapy but also to hormone therapies. Dunbier *et al.* showed that a higher expression of immune-associated genes such as *SLAMF8* and *TNF* as well as TILs is associated with a poor response to hormone therapies (P value <0.001) (39).

So far, we know that TILs cannot be used to either withhold or provide chemotherapy in the TN subtype or trastuzumab therapy in the HER2-positive subtype, because of the absence of standardized guidelines and limited evidence concerning reproducibility and clinical validity (40). A group of experts for TILs evaluation (the International TIL Working Group), reported recommendations to improve the consistency of TILs scoring and detailed suggestions for annotating TILs (41); however, it is not widely used in daily clinic. Kochi *et al.* reported the genomic signature related to TILs could be prognostic and potentially predictive as a response to chemotherapy in some breast cancer subtypes to overcome the low reproducibility of evaluations of TILs (42). The measurement of TILs by digital image analysis and machine learning algorithms with artificial intelligence might be useful for standardization of assessment for TILs in the future.

Conclusions

The improvement of tumor biomarkers ready for clinical use is a long process. A good biomarker should be a predictor of not only prognosis but also the response to therapies. Any new scientific intervention can be adopted into clinical practice only in the putting of level 1 evidence, and though costly, such evidence is provided in a prospective randomized clinical trial. Majority of the evidence to change the guidelines have come from the prospective randomized phase 3 trials. Simon *et al.* advocated that "prospective-retrospective" designs and archived samples from datasets with high-quality might be more efficient (43). In the future, clinical trials with a more efficient design are needed.

For HR-positive/HER2-negative subtype, only two biomarkers, the 21-gene recurrence score and the 70-gene signature, have been tested in prospective randomized clinical trials (14,17,18). There are no diagnostic multigene assays for HER2-positive and TN breast cancers. TILs have been assessed to have a predictive value for prognosis and response to chemotherapy from the retrospective analyses. So far, TILs cannot be used to either withhold or provide chemotherapy based on the absence of standardized evaluation guidelines and confirmed information for HER2-positive and TN breast cancers. To overcome the low reproducibility of evaluations of TILs, gene signatures or digital image analysis and machine learning algorithms with artificial intelligence may be useful for standardization of assessment for TILs in the future.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Yutaka Yamamoto and Takayuki Ueno) for the series "Neoadjuvant/Adjuvant Treatment for Early Breast Cancer" published in *Chinese Clinical Oncology*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco.2020.01.06). This series "Neoadjuvant/Adjuvant Treatment for Early Breast Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418-23.
2. Iwamoto T, Bianchini G, Booser D, et al. Gene pathways associated with prognosis and chemotherapy sensitivity in molecular subtypes of breast cancer. J Natl Cancer Inst 2011;103:264-72.
3. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-52.
4. Iwamoto T, Kelly C, Mizoo T, et al. Relative Prognostic and Predictive Value of Gene Signature and Histologic Grade in Estrogen Receptor-Positive, HER2-Negative Breast Cancer. Clin Breast Cancer 2016;16:95-100.e1.
5. Coutant C, Rouzier R, Qi Y, et al. Distinct p53 gene signatures are needed to predict prognosis and response to chemotherapy in ER-positive and ER-negative breast cancers. Clin Cancer Res 2011;17:2591-601.
6. Pirmohamed M. Acceptance of biomarker-based tests for application in clinical practice: criteria and obstacles. Clin Pharmacol Ther 2010;88:862-6.
7. Ballman KV. Biomarker: Predictive or Prognostic? J Clin Oncol 2015;33:3968-71.
8. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355:560-9.
9. Iwamoto T, Lee JS, Bianchini G, et al. First generation prognostic gene signatures for breast cancer predict both survival and chemotherapy sensitivity and identify overlapping patient populations. Breast Cancer Res Treat 2011;130:155-64.
10. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med 2009;360:790-800.
11. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
12. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst 2006;98:1183-92.
13. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530-6.
14. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375:717-29.
15. Krop I, Ismaila N, Andre F, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol 2017;35:2838-47.
16. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol 2008;26:721-8.
17. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015;373:2005-14.
18. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2018;379:111-21.
19. Sparano JA, Gray RJ, Makower DF, et al. Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial. JAMA Oncol 2019;6:367-74.
20. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 3.2019. Available online: https://www.nccn.org/
21. Harris LN, Ismaila N, McShane LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016;34:1134-50.
22. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010;11:55-65.
23. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. NPJ Breast Cancer 2017;3:32.
24. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West

German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 2017;165:573-83.
25. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
26. Bonadonna G, Valagussa P, Brambilla C, et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J Clin Oncol 1998;16:93-100.
27. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
28. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 2017;376:2147-59.
29. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-28.
30. Pusztai L, Foldi J, Dhawan A, et al. Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. Lancet Oncol 2019;20:e390-6.
31. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414-22.
32. Symmans WF, Wei C, Gould R, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 2017;35:1049-60.
33. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 2013;31:860-7.
34. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 2014;32:2959-66.
35. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol 2014;25:1544-50.
36. Mao Y, Qu Q, Zhang Y, et al. The value of tumor infiltrating lymphocytes (TILs) for predicting response to neoadjuvant chemotherapy in breast cancer: a systematic review and meta-analysis. PLoS One 2014;9:e115103.
37. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol 2015;33:983-91.
38. Hwang HW, Jung H, Hyeon J, et al. A nomogram to predict pathologic complete response (pCR) and the value of tumor-infiltrating lymphocytes (TILs) for prediction of response to neoadjuvant chemotherapy (NAC) in breast cancer patients. Breast Cancer Res Treat 2019;173:255-66.
39. Dunbier AK, Ghazoui Z, Anderson H, et al. Molecular profiling of aromatase inhibitor-treated postmenopausal breast tumors identifies immune-related correlates of resistance. Clin Cancer Res 2013;19:2775-86.
40. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
41. Salgado R, Denkert C, Demaria S, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015;26:259-71.
42. Kochi M, Iwamoto T, Niikura N, et al. Tumour-infiltrating lymphocytes (TILs)-related genomic signature predicts chemotherapy response in breast cancer. Breast Cancer Res Treat 2018;167:39-47.
43. Simon RM, Paik S, Hayes DF. Use of Archived Specimens in Evaluation of Prognostic and Predictive Biomarkers. J Natl Cancer Inst 2009;101:1446-52.

Cite this article as: Iwamoto T, Kajiwara Y, Zhu Y, Iha S. Biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer. Chin Clin Oncol 2020;9(3):27. doi: 10.21037/cco.2020.01.06