Supplementary File

Clinical Practice Guidelines for Multigene Assays in Patients with Early-Stage Breast Cancer: Chinese Society of Breast Surgery (CSBrS) Practice Guidelines 2021

The MINDACT trial provided high-level evidence of the clinical use of the 70-gene (MammaPrint®) assay in assisting chemotherapy decisions. This was a randomized prospective phase 3 clinical trial approved by the European Organization for Research and Treatment of Cancer (EORTC). It included 6693 patients from 112 medical institutions in nine countries from 2007 to 2011. All patients were diagnosed with early invasive breast cancer with 0–3 lymph node metastases. The clinical risk was determined by Adjuvant! Online and genetic risk was determined by the 70-gene signature (MammaPrint®). The patients were divided into four main groups, according to their clinical (C) and genomic (G) risk: C-low/G-low risk, which included 2745 patients (41.0%), C-low/G-high risk (592 patients, 8.8%), C-high/G-low risk (1550 patients, 23.2%) and C-high/G-high risk (1806 patients, 27.0%). Patients in the C-low/G-low risk group did not receive chemotherapy but received endocrine therapy according to their hormone receptor (HR) status. All patients in the C-high/G-high risk group received chemotherapy. Patients with discordant results (C-high/G-low risk and C-low/G-high risk) were randomly assigned to receive chemotherapy or not. The primary endpoint was designed to test whether, among patients with C-high/G-low risk who did not receive chemotherapy, the lower boundary of the 95% confidence interval (CI) for the rate of five-year distant metastasis-free survival (DMFS) would be 92% or higher. Secondary endpoints were the proportion of patients who received chemotherapy according to the clinical risk compared with the genomic risk, as well as the overall survival (OS) and disease-free survival (DFS).[1]

In the initial analysis in 2016, the percentage of patients with five-year follow-up was 60%. The results showed that the five-year DMFS rate of patients in the C-high/G-low risk group was 94.7% (95%CI 92.5%–96.2%), reaching the primary endpoint. Among patients in the intention-to-treat (ITT) population with C-high/G-low risk at enrollment, the five-year DMFS was 95.9% in the chemotherapy group and 94.4% in the non-chemotherapy group. This shows that in high clinical risk patients, the 70-gene assay can determine that the genomic risk is low, and not receiving chemotherapy only reduces the benefit of the five-year disease control by 1.5% compared with chemotherapy. This suggests that patients with C-high/G-low risk can be exempted from chemotherapy.[1] A secondary analysis with a median follow-up of 8.7 years was reported at the 2020 American Society of Clinical Oncology (ASCO) conference. Ninety percent of patients were followed up for at least 5 years and 70% for at least 8 years. The analysis reported an updated five-year DMFS rate for the PT population of C-high/G-low patients with no chemotherapy of 95.1% (95% CI 93.1–96.6%), far exceeding the preset threshold. Exploratory analysis suggested that it was safe for patients >50 years-old to be exempted from chemotherapy (eight-year DMFS difference of 0.2% ± 2.1%). For patients <50 years, the eight-year DMFS of patients receiving chemotherapy was 5.0% (±2.8%) higher than that without chemotherapy.[2] However, this result is only an exploratory analysis, not the main object of this study, and we also cannot rule out whether the effect was related to the benefit of ovarian inhibition caused by chemotherapy. But we still should be cautious about the decision of patients <50 years with C-high/G-low risk to avoid chemotherapy. Among patients at C-low/G-high risk, the five-year DMFS was 95.8% (95% CI, 92.9%–97.6%) in the chemotherapy group and 95.0% (95%CI, 91.8%–97.0%) in the non-chemotherapy group. It has been suggested that patients with C-low risk do not derive clinical benefit from chemotherapy based on whether accompanied by G-high risk according to the genetic test. However, the genetic test cannot be used as a reference for the decision for chemotherapy.

The 21-gene assay (Oncotype Dx®) is currently the most widely used multigene panel and prognosis analysis

method for HR-positive breast cancer patients in the USA. In 2004, Paik et al first proposed the concept of the 21-gene assay[3]. These authors tested 16 tumor-related and 5 housekeeping genes using RT-PCR to calculate the RS score, which has a range of 1–100. The patients were divided into three groups: low recurrence risk (RS < 18), moderate recurrence risk (RS 18–31), and high recurrence risk (RS ≥31). The findings were subsequently verified by samples from the NSABP B14 trial, resulting in a 10-year distant metastasis risk rate for the three groups of 6.8%, 14.3%, and 30.5%, respectively[3]. Analysis of patients enrolled in the NSABP B20 trial also showed a significant benefit from chemotherapy in the high-risk group.[4] Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with RS ≥31 should receive chemotherapy.[5] The TAILORx study used a lower threshold for three risk groups: RS <11 representing low risk, RS 11–25 middle risk, and RS ≥26 high risk. From April 7, 2006, to October 6, 2010, the study enrolled 10 253 women aged 18 to 75 years with HR-positive, HER2-negative, node-negative breast cancer with tumors of 1.1 to 5.0 cm in the greatest dimension (or 0.6 to 1.0 cm in the greatest dimension and intermediate or high tumor grade). The low-risk group only received endocrine therapy, and the moderate-risk group was randomly divided into an endocrine treatment group and a chemotherapy combined with endocrine treatment group. The high-risk patients received chemotherapy combined with endocrine therapy. The primary trial endpoint was invasive disease-free survival (iDFS). In low-risk patients, the five-year iDFS was less than 1%, and any risk of recurrence was less than 2%, suggesting that endocrine therapy alone is sufficient for patients with RS <11.[6] After 7.5 years of follow-up, the trial reached the prespecified primary endpoint and found that endocrine therapy alone was not inferior to the combination of endocrine and chemotherapy (nine-year iDFS 83.3% vs. 84.3%) among women with an RS score of 11–25. The rates of nine-year DFS, distant recurrence, and OS were also similar in both groups. In total, the benefit of chemotherapy in patients with moderate risk is not obvious, and the avoidance of chemotherapy can be considered. Further subgroup analysis showed that patients >50 years with RS <15 had a low risk of recurrence and received no obvious benefit from chemotherapy, while patients with RS 16–25 could have some benefit from chemotherapy. The benefit of chemotherapy in patients >50 years was not significant. The recurrence rate of patients with RS >26 was still as high as 13% even receiving endocrine therapy combined with chemotherapy.[7] This suggests that these patients still need to explore more effective treatment methods. The result of the TAILORx study provides high-level evidence for the clinical application of the 21-gene assay in practice.

References

1. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016; 375 (8): 717-729. doi: 10.1056/NEJMoa1602253.
2. Fatima C, Laura van 't V, Coralie P, Josephine LC, Suzette D, Jean-Yves P, et al. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. J Clin Oncol 2020; doi: 10.1200/JCO.2020.38.15_suppl.506.
3. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351 (27): 2817-2826. doi: 10.1056/NEJMoa041588.
4. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006; 24 (23): 3726-3734. doi: 10.1200/JCO.2005.04.7985.
5. Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw

2020; 18 (4): 452-478. doi: 10.6004/jnccn.2020.0016.
6. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015; 373 (21): 2005-2014. doi: 10.1056/NEJMoa1510764.
7. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2018; 379 (2): 111-121. doi: 10.1056/NEJMoa1804710.