**Review Article**

Indian J Med Res 146, November 2017, pp 563-571
DOI: 10.4103/ijmr.IJMR_1354_17



# Prognostic & predictive factors for planning adjuvant chemotherapy of early-stage breast cancer

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Received October 6, 2017

**Breast cancer is a heterogeneous disease and may present with different clinical and biological characteristics. At present, breast cancer is divided into molecular subgroups besides its histopathological classification. Decision for adjuvant chemotherapy is made based on not only histopathological characteristics but also molecular and genomic characteristics using indices, guidelines and calculators in early-stage breast cancer. Making a treatment plan through all these prognostic and predictive methods according to risk categories aims at preventing unnecessary or useless treatments. In this review, an attempt to make a general assessment of prognostic and predictive methods is made which may be used for planning individualized therapy and also the comments of the guidelines used by the oncologists worldwide on these methods.**

**Key words** Adjuvant chemotherapy - early-stage breast cancer - predictive - prognostic

## Introduction

Breast cancer is the most common cancer type among women worldwide and consists of 25 per cent of newly diagnosed cancer cases[1]. It is also the most common cause of cancer-related deaths[2]. Breast cancer is a heterogeneous disease complex in structure[3]. While invasive carcinoma of no special type (commonly known as ductal carcinoma not otherwise specified) and invasive lobular carcinoma make up the vast majority of breast cancers, more than 20 different histopathological subtypes are also defined[4].

Breast cancer has been divided into intrinsic molecular subtypes together with the developments in genomic analyses in the recent 10 years[5]. Breast cancer was divided into five molecular subtypes in St. Gallen Consensus[6]. These subtypes are luminal A-like [oestrogen receptor (ER)+/progesterone receptor (PR)+, human epidermal growth factor receptor 2 (HER2)−, Ki-67 low]; luminal B-like [luminal HER2− (ER+/PR+, HER2− or Ki-67 high), luminal HER2+ (ER+/PR+, HER2+)]; HER2+ (ER−/PR−, HER2+) and triple-negative breast cancer (TNBC) (ER−/PR−, HER2−)[7].

Prognostic and predictive indices, guidelines and calculators have been developed for determining the relapse risk, making a decision for adjuvant therapy and determining the benefit from the adjuvant therapy

in early-stage breast cancer[8]. The aim of this effort is to prevent over-treatment.

## Prognostic and predictive methods

Prognostic factors usually predict the relapse risk. Age of the patient, menopause status, histopathological tumour size, lymph node status, tumour grade, immune histochemical (IHC), ER, PR, HER2 and Ki-67 expression parameters are necessary for making treatment plan and determining prognosis[9-12]. Various clinicopathological risk categories have been determined; indices, guidelines, online tools and multi-gene analyses were created using these prognostic factors.

### *Clinicopathological risk categories*

One of these risk categories is Nottingham prognostic index (NPI) which was created in 1978[13,14]. This scale determines a score using tumour size, lymph node stage and histological grade, and five-year survival is determined according to this score[14].

Thereafter, St. Gallen Consensus determined a risk scale for determining prognosis and aid treatment algorithm. Different from NPI, ER/PR, HER2 and Ki-67 levels were included in this scale which was created in 2009[15]. In the disease which is divided into molecular subtypes, while a favourable prognosis is expected in luminal A-like group, an unfavourable prognosis is expected in TNBC and HER(+) group. A less favourable prognosis is expected in luminal B-like group compared to luminal A-like group[16,17].

Another guidelines were developed by the National Comprehensive Cancer Network (NCCN)[18] together with various cancer centres worldwide. The NCCN guidelines are evidence-based, consensus-driven recommendations made by the NCCN guidelines panels. These include services from the Enhanced Resources Framework and additional services that provide minor improvements in disease outcomes[18].

### *Risk calculators (online tools)*

Except these indices and guidelines, some online tools were developed for risk calculation[19-21]. Adjuvant Online programme is the best known and frequently used programme by oncologists[22]. Adjuvant Online is a free web programme created for determining prognosis. This tool aims at providing information for health professionals about the benefits of adjuvant therapies applied after the operation in patients with early-stage breast cancer[23].

Adjuvant Online uses patient age, comorbidity, ER status besides tumour size, tumour grade and lymph node status used in NPI[24]. However, it does not include PR, HER2 and Ki-67 status, a limitation of the programme.

CancerMath.net is another online tool[25]. This programme adds HER2 status and predicts 15-yr mortality rate in addition to Adjuvant Online. Another online programme is the PREDICT which is a mathematical model accessed by the internet and has been designed for health professionals to help them decide on the ideal course of treatment following breast cancer surgery[26]. It is one of the first models of this type of programmes to include tumour HER2 and Ki-67 status. This programme enables to estimate five-yr and 10-yr survival rates[26].

### *Multi-gene analyses*

ER, PR and HER2 status are used for determining the benefit from adjuvant chemotherapy in early-stage breast cancer. The following are the popular questions: Are other biomarkers required for making a decision for adjuvant chemotherapy in early-stage breast cancer patients in whom hormone receptor status and HER2 status are known? What should these markers be? What should be the systemic adjuvant therapy[27]?

Oncotype DX was created by analyzing 21 genes selected from fixed, paraffin-embedded tumour tissues by real-time, reverse transcriptase-polymerase chain reaction (RT-PCR) method in patients with ER/PR(+), HER2(−) and lymph node involvement negative status. While 16 of 21 genes are related with cancer genes, five are reference genes. The patients are given a recurrence score (RS) according to expression levels of these genes and divided into low-, intermediate- and high-risk groups[28].

Benefit from chemotherapy is predicted with 21-gene RS in ER/PR(+), HER2(−) and lymph node(−) patients; 10-yr distant metastasis risk and survival are also calculated and therefore, it seems as the single predictive and prognostic method[29]. While adjuvant endocrine therapy (tamoxifen) is more beneficial in low RS, it is opposite in high RS[28-30]. Results of the TAILORx (Trial Assigning Individualized Options for Treatment) trial which is a prospective study are awaited for making a decision for chemotherapy versus endocrine therapy in the intermediate RS[31].

RS analysis was found to be a prognostic tool for disease-free survival (DFS) and overall survival (OS) in Southwest Oncology Group 8814 study in which

21-gene RS was used in ER/PR(+), HER2(−) and lymph node(+) post-menopausal patients and to predict the benefit of chemotherapy in high-RS patients. In addition, anthracycline-based chemotherapy was reported not to be useful in low-RS patients despite being node positive[32].

The RxPONDER trial which investigates the benefit of chemotherapy in RS≤ 25 and 1-3 lymph node(+) patients is still continuing[33]. While the previous studies used tamoxifen as an endocrine treatment, aromatase inhibitors (AIs) which have a wide range of use in post-menopausal patients, were investigated in another study. This study has revealed that RS is predictive for recurrence in ER/PR(+), HER2(−), lymph node(−) or (+) patients receiving anastrozole treatment[30]. The RS results consistently predict the risk of recurrence and survival in node-positive, ER-positive patients as shown in multiple studies[30,32,34].

While the American Society of Clinical Oncology (ASCO) guidelines strongly recommend adjuvant systemic treatment using RS in ER/PR(+), HER2(−) and lymph node(−) patients, in the case of lymph node-positive patients, there is a recommendation not to use this method (moderate recommendation)[27].

In St. Gallen 2017 Consensus, the Oncotype DX low-risk lymph node(−) group received 87.6 per cent of the votes, whereas the lymph node(+) group received 55.6 per cent of the votes for no chemotherapy[35].

MammaPrint[36] method was first used in lymph node(−) breast cancer patients. Patients were classified as low risk and high risk. Relationship with one-year and five-year distant metastasis was analyzed and the results were obtained as a prognostic model[37].

In the prospective Microarray in Node-Negative and 1-3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial, genomic risks of the patients were specified both with clinicopathological risk (Adjuvant! Online) and with MammaPrint gene-signature method, and the five-year distant metastasis risk was analyzed[38]. In MINDACT trial, patients with low clinical and genomic risk did not receive chemotherapy while patients with high clinical and genomic risk received chemotherapy. The patients who had discordant risk status (high/low or low/high clinical and genomic risk) were randomly designated to chemotherapy or to no chemotherapy arms[38].

In the chemotherapy arm, the five-year distant metastasis-free survival (DMFS) was 95.9 per cent [95% confidence interval (CI), 94.0%-97.2%] versus 94.4 per cent (95% CI, 92.3%-95.9%) in no chemotherapy arm. The difference between these groups was 1.5 per cent, with an adjusted hazard ratio of 0.78 (95% CI, 0.50-1.21; *P*=0.27). In the group with high clinical and low genomic risk who received chemotherapy, as per intention-to-treat population analysis, they reported that the DMFS rate was 1.5 percentage points (and 1.9%) higher; DFS was 2.8 percentage points (and 3%) higher; and OS was 1.4 percentage points (and 1.5%) higher compared to the group with no chemotherapy. Thus, a small and insignificant benefit with chemotherapy in patients who had high clinical risk and low genomic risk cannot be excluded[38].

When chemotherapy versus no chemotherapy arms were compared in patients at 'low clinical risk but high genomic risk', chemotherapy arm had a five-year DMFS of 95.8 per cent (95% CI, 92.9%-97.6%) versus 95.0 per cent (95% CI, 91.8%-97.0%) for non-chemotherapy arm. The adjusted hazard ratio for distant metastasis or death with chemotherapy compared to no chemotherapy arms was 1.17 (95% CI, 0.59-2.28; *P*=0.66). Hence, there was no chemotherapy benefit in women with tumours at low clinical risk irrespective of their genomic subtype[38].

The ASCO guidelines were updated for MammaPrint assay in 2017 according to the results of MINDACT trial[39]. According to the updated guidelines, "if a patient has hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. The MammaPrint assay should not be used in those with low clinical risk as per the MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because women in low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer. If a patient has hormone receptor-positive, HER2-negative and node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit of chemotherapy cannot be

excluded, particularly in patients with greater than one involved lymph node. The MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk as per the MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population"[39]. The guidelines do not recommend MammaPrint assay use in TNBC and HER2(+) group (strong recommendation for triple(−) patients, moderate recommendation for HER2(+) patients).

In the St. Gallen 2017 Consensus, the MammaPrint low-risk lymph node(−) group was not voted for no chemotherapy, while 55.1 per cent in the lymph node(+) group received a yes vote[35].

**PAM50 risk of recurrence (ROR) score (Prosigna)**

Prosigna was developed based on the PAM50 gene-signature, which measures the expression of 50 genes[40]. Gene expression data are weighed with clinical variables to determine a score from 0 through 100 (ROR/Prosigna score) indicative of the probability of distant recurrence. ROR is based on the similarity of the gene expression profile to intrinsic subtypes, proliferation score and tumour size. Assay requires the input of gross tumour size and nodal status[41].

Prosigna is used to predict the risk of distant recurrence for post-menopausal women within 10 yr of diagnosis of early-stage, hormone-receptor-positive disease with up to three positive axillary lymph nodes after five years of hormonal therapy[42-44]. PAM50 ROR score was found to be significantly associated with the likelihood of distant recurrence within 10 yr of median follow up and more significant compared to conventional clinical prognostic data in all patients [ER(+), lymph node(−/+), HER2(−)]. It has been reported that chemotherapy may be administered in the high-risk group according to PAM50 ROR score. In the studies comparing RS calculated using Oncotype DX and PAM50 ROR score, ROR was found more prognostic than RS in ER(+) lymph node(−) group; it was also found to be better to differentiate between intermediate- and high-risk groups[43,45].

HER2(+) breast cancer is biologically heterogenous[46]. All HER2(+) breast cancer patients do not benefit from anti-HER2 therapy[47-49]. PAM50 ROR proliferation (RORP) score was used in NOAH study designed for predicting HER2(+) patients who could benefit from anti-HER2 therapy[50]. This study has revealed that HER2(+)/RORP-high group benefited more from trastuzumab treatment.

In the ASCO guidelines, while adjuvant systemic chemotherapy is strongly recommended in ER/PR(+), HER2(−) and lymph node(−) patients through using PAM50 ROR score together with clinicopathological variables, it is also recommended not to be used in lymph node(+) patients (moderate recommendation). The guidelines strongly recommend not to use PAM50 ROR score for making a decision for adjuvant therapy in TNBC and HER2(+) breast cancer patients[27].

In the St. Gallen 2017 Consensus, the PAM50 ROR score low-risk lymph node(−) group was not voted for no chemotherapy, while 30.8 per cent in the lymph node(+) group received a yes vote[35].

***EndoPredict (EP)***

EndoPredict (EP) is a method which uses RT-PCR from formalin-fixed tissue for the prediction of metastasis risk that may develop from administering only endocrine therapy in ER/PR(+), HER2(−) breast cancer patients. The EP test measures the levels of 12 genes in breast cancer cells. These measurements are used to calculate an EP risk score which is combined with the cancer tumour size and lymph node status. The result is the EPclin score, which classifies cancer as having a high risk or a low risk for the distant metastases. The low-risk and high-risk categories of EPclin were pre-specified before the validation in the Austrian Breast and Colorectal Cancer Study Group (ABSCG)-6 and ABSCG-8 studies[51,52]. The EPclin identified a subset of ER-positive, HER2 negative, post-menopausal breast cancer patients with excellent prognosis when treated with endocrine therapy in the absence of chemotherapy. In EPclin, low-risk patients have good outcomes with endocrine therapy alone at 10 yr of follow up[52,53]. Data in ER-positive, HER2(−) and (+) breast cancer and TNBC patients do not support EP use[54]. Data are not available about the use of this method in HER2(+) breast cancer and TNBC patients.

While use of adjuvant systemic therapy using EPclin score in ER/PR(+), HER2(−) and lymph node(−) patients is a recommendation, this method is recommended not to be used in lymph node(+) patients in the ASCO guidelines. The guidelines strongly recommend not to use EPclin score for making a decision for adjuvant therapy in TNBC and HER2(+) breast cancer patients[27].

In the St. Gallen 2017 Consensus, the PAM50 ROR score low-risk lymph node(−) group was not voted for no chemotherapy, while 20 per cent in the lymph node(+) group received a yes vote[35]. In St. Gallen 2017 consensus, while EPclin score was not voted in low-risk lymph node(−) group in case of no chemotherapy, it was voted 20 per cent 'yes' in the lymph node(+) group[35].

***Breast cancer index (BCI)***

Breast cancer index (BCI) is a gene expression-based biomarker and created with algorithmic combination of two biomarkers defined as HOXB13:IL17BR ratio and molecular grade index[55-57]. BCI enables to predict distant metastasis risk[58]. Studies indicate that BCI is more favourable for the prediction of 0-10 yr of recurrence risk compared with clinicopathological factors[58,59]. Late relapses, developing five years after diagnosis of ER/PR(+) breast cancer are important problems. The Stockholm study, a prospective randomized study, conducted with ER/PR(+), HER2(−) and lymph node(−) patients treated with tamoxifen revealed the additional benefit of chemotherapy to 5-10 yr of hormonal therapy in high-risk patients after determining early and late recurrence risk with BCI[58,60,61]. No data are available for lymph node(+) or HER2(+) groups as BCI is an index developed for ER/PR(+), HER2(−) and lymph node(−) patients.

In the ASCO guidelines, while making a decision for adjuvant systemic therapy using BCI is a moderate recommendation, the use of BCI is strongly recommended in lymph node(+) patients. Using BCI for the adjuvant therapy is not recommended for TNBC and HER2(+) breast cancer patients[27].

***Mammostrat***

This genomic test was developed through measuring five genes specified IHC in ER/PR(+) early-stage breast cancer patients[62]. Patients were divided into three groups as low-, moderate- and high-risk according to distant metastasis risk. Risk category was used as a guide for making a decision for systemic therapy in addition to adjuvant therapy[63,64]. Mammostrat was detected to provide data for distant metastasis risk after treatment in a study conducted using aromatase inhibitor in post-menopausal, ER/PR(+), lymph node(−) or (+) early-stage breast cancer group[65]. In sub-group analyses, only 85 per cent of low-risk group patients were detected to be recurrence-free in 10 yr of follow up and the benefit from chemotherapy was significant[64]. Data are not available about HER2(+) breast cancer and TNBC group.

In the ASCO guidelines, use of Mammostrat is at moderate recommendation level in ER/PR(+), HER2(−) and lymph node(−) or (+) patients for making a decision for adjuvant systemic therapy. Not using Mammostrat is strongly recommended in TNBC and HER2(+) breast cancer patients[27].

***Immune histochemistry 4 (IHC4)***

IHC4 is a risk model developed through quantitatively evaluating and mathematically joining ER, PR, HER2 and Ki-67 which are used for specifying the prognosis of breast cancer. This mathematical risk model was shown to provide a more favourable prognosis data than provided separately by the prognostic markers[66]. When compared to Oncotype DX, the latter was shown to have a less prognostic value than IHC4[66]. When IHC4 and PAM50/ROR score were compared, they were reported to provide similar prognostic data; however, ROR score provided a better prognostic data in HER2(−) population[43]. Despite the availability of sufficient data about the use of IHC4, it has been examined and approved in only one research laboratory[43,66]. Data are not available about this method in HER2(+) breast cancer and TNBC patients.

The ASCO guidelines recommend the use of IHC4 at moderate level for making a decision for adjuvant systemic therapy in ER/PR(+), HER2(−) and lymph node(−) or (+) patients. Using IHC4 for making a decision for adjuvant therapy is strongly not recommended in TNBC and HER2(+) breast cancer patients[27].

***Urokinase plasminogen activator and plasminogen activator inhibitor type 1 (uPA/PAI-1)***

Tumour-related proteolytic factors urokinase plasminogen activator (uPA) and its type 1 inhibitor PAI-1, play important roles in tumour invasion and metastasis. uPA and/or PAI-1 are related with cell signalling, adherence, cell growth and survival[67]. uPA/PAI-1 protein detection has been done using ELISA method from fresh frozen primary tumour tissue obtained on surgery[68]. The lymph node(−) patients were classified as low risk or high risk according to uPA/PAI-1 and the 10-yr follow up outcomes were reported. A good prognosis was detected with treatment-free follow up in low-risk patients. However, this condition is insufficient when compared with survival benefits obtained from current

standard adjuvant hormonal therapies. Clinical benefit of chemotherapy was found to be insufficient in high-risk patients; however, these patients were also seen not to have received hormone therapy[69]. Data are not available about the use of this method in HER2(+) breast cancer and TNBC patients.

In the ASCO guidelines, making a decision for adjuvant systemic therapy using uPA/PAI-1 in ER/PR(+), HER2(−) and lymph node(−) patients is a weak recommendation. The guidelines weakly recommends not to use IHC4 for making a decision for TNBC and HER2(+) breast cancer patients[27].

### *Circulating tumour cells (CTCs)*

Circulating tumour cells (CTCs) are detected in the peripheral blood in studies conducted with metastatic breast cancer patients, and it was found to be related with poor progression-free survival and overall survival[70,71]. In the prospective SUCCESS study conducted with non-metastatic breast cancer patients (pT1-T4, pN0-N3,M0), peripheral blood CTC measurements were done before and after adjuvant chemotherapy, and these values were shown to be associated with a reduction in survival rates and to have prognostic value[72]. The potential of this prognostic value increases with higher CTC levels. Other studies have also indicated similar results[73-75]. However, no studies are available on making a decision for adjuvant systemic therapy using a CTC-based test.

The ASCO guidelines recommend not to use CTCs for making a decision for adjuvant systemic therapy (strong recommendation)[27].

### *Tumour-infiltrating lymphocytes (TILs)*

Tumour-infiltrating lymphocytes are detected through histopathological analysis of tumour tissue[76]. TILs detected in different tumour tissues were found to be related with better outcomes in many studies[77-81]. Neoadjuvant chemotherapy study revealed that TILs detected in tumour tissue was associated with improved response to chemotherapy[76].

In the studies conducted with TNBC and HER2(+) breast cancer patients, high TIL levels at the time of diagnosis were detected to be prognostic for reduced distant recurrence risk in TNBC patients and predictive for improved response to trastuzumab in HER2(+) breast cancer patients[82,83]. However, all these data were obtained from subgroup analyses. Sufficient data are not yet available for its widespread clinical use.

In the ASCO guidelines, the recommendation is not to use TILs for making a decision for adjuvant systemic chemotherapy in ER/PR(+), HER2(−) and lymph node(−) or (+) patients and in TNBC and HER2(+) breast cancer patients (strong recommendation)[27].

## Conclusion

Being aware of the prognostic status of the patient, predicting the benefit from therapy is the main component of individualized treatment goal when planning adjuvant therapy for early-stage breast cancer. While the excellent outcomes are aimed through the methods developed for this purpose, each method has some limitations. Though various prognostic and predictive methods have been developed, Oncotype DX is more commonly used. It is found in the international guidelines and online networks frequently used by oncologists. However, developing countries can experience difficulties due to the high cost of using these methods. The methods which provide maximum benefit to the patient should be determined and used. Though the currently available methods are encouraging but for the future more advanced researches are required.

***Conflicts of Interest*:** None.

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