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Review Article

Prognostic and predictive factors in deciding the use of chemotherapy for hormone receptor positive, Herceptin 2 negative breast cancer

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ABSTRACT

Women suffering from hormone receptor positive, Herceptin 2 receptor (HER2) negative and node negative early breast cancer (EBC) receive adjuvant endocrine treatment as part of systemic treatment. The need for adjuvant chemotherapy in this patient group, regarding treatment benefit, can be assessed using validity of prognostic and predictive factors. A review was performed to assess the clinical validity with controversies of predictive and prognostic factors in use of adjuvant chemotherapy in early breast cancer (EBC). The cost effectiveness and turnaround time of genomic test also discussed. Retrospective cohort studies ranging from 2009 to 2024 were searched. Primarily tumour stage is the most important prognostic indicator, along with patient factors, preference and performance status. Considering intermediate group of breast cancer T1b to T3 node negative, ER positive, HER2 negative, the recurrence score (RS) is used to guide the decision of adjuvant chemotherapy. Although RS is well validated, other assays may also be acceptable. Women with newly diagnosed EBC should undergo hormone receptor and HER2 overexpression testing. Gene expression studies have identified several distinct breast cancer subtypes that differ markedly in prognosis. Further studies on genomic data derived from breast cancer specimen is going on. The circulating tumour cells (CTCs), a non-invasive, liquid based prognostic marker along with other liquid biopsy techniques are awaiting clinical validity.

Keywords: Oestrogen receptor, Human epidermal growth factor 2, Oncotype DX recurrence score, Early breast cancer, Circulating tumour cells

INTRODUCTION

Endocrine treatment is the mainstay of systemic treatment in women with oestrogen receptor (ER) positive, human growth factor receptor 2 (HER2) negative breast cancer. However, some of these cancers also benefit from adjuvant chemotherapy. Chemotherapy benefits depend upon the risk of recurrence, which is mainly estimated from stage and grade of tumour and the biological features of the tumour including gene expression. Adjuvant systemic therapy has reduced mortality from breast cancer. Unfortunately, some patients are over treated & some are undertreated. It is valuable to have reliable prognostic factors to help select those patients most at risk of recurrence.[1] Clinically applicable predictive factors would help in deciding adjuvant therapies most likely to benefit the patient, sparing them the unnecessary exposure to potentially toxic and expensive therapies.

Authors review prognostic and predictive factors relevant to decision making in patient diagnosed with hormone receptor positive, HER2 negative breast cancer. Prognostic factors provide information on clinical outcome at the time of diagnosis independent of therapy, considering usually growth, invasion and metastatic

potential. Predictive factors provide information of response to a given therapeutic modality. Despite being two separate terms, several factors in breast cancer are both prognostic and predictive, such as epidermal growth factor 2HER2.[2,3]

Predictive and prognostic factors must have analytic validity, clinical validity and clinical utility, to be of clinical use. Identification of clinically useful predictive markers has not been as successful as identification of prognostic markers in breast cancer. The most effective predictive marker in breast cancer is estrogen receptor (ER) for endocrine therapy and human epidermal growth factor receptor 2HER2, for HER2 directed therapy.[4,5] Predictive role of several prognostic biomarker assay (Gene expression profile) to guide decision on adjuvant systemic therapy in hormone receptor positive HER2 negative breast cancer is available (Table 1).

The American society of clinical oncology supports the use of Oncotype DX 21 gene recurrence score (RS), Endo Predict (EP), Predictor analysis of microarray 50 (PAM 50) and the Breast cancer Index. Additionally, the Amsterdam 70 gene profile (MammaPrint) may be useful in select cases.

Prior to discussing these prognostic assays, it is vital to understand the basic concept of gene expression also referred as gene expression profiling. Gene expression is the process by which the information encoded in DNA is turned into mRNA. This process can be triggered by environmental signals, often in cell type or in timing specific manner ultimately leading to synthesis of specific proteins. Messenger ribonucleic acid (mRNA) represents a functional bridge between DNA and protein. Any alteration in mRNA either serve as markers activation known as Expression or markers inhibition known as Repression of a particular gene. These two processes in gene either allow the cells to adapt their phenotype by turning on (Activation) or turning off (Repression) of specific functions that DNA encodes. Gene expression is measured by assaying mRNA.

Table 1: Breast cancer tissue molecular prognostic biomarkers.

Test	Tissue	Method	Target population	Recommendation (ASCO)
Oncotype Dx	FFPE	21- gene RT-PCR	ER/PR+, HER2-, LN-	Strong
Mamma print	FF, FFPE	70-gene Microarray	ER/PR+, HER2-, LN- or 1-3 LN+	Strong
ProSigna (PAM50)	FF, FFPE	50-gene RT-PCR	ER/PR+, HER2-, LN-	Strong
Breast cancer index	FF, FFPE	11-gene RT-PCR	ER/PR+, HER2-, LN-	Moderate
Endo predicts	FFPE	12-gene RT-PCR	ER/PR+, HER2-, LN-	Moderate
uPA and PAI-1	FF	2-protein Elisa	ER/PR+,HER2-, LN-	Weak
Mammostrat	FFPE	5-protein IHC	ER/PR+,HER2-, LN-	No
IHC-4	FFPE	4-protein IHC	ER/PR+,LN- or 1-3 LN+	No

ASCO, American Society of Clinical Oncology; ELISA, enzyme-linked immunosorbent assay; ER, oestrogen receptor; FF, fresh-frozen, FFPE, Formalin-fixed paraffin-embedded, HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LN, lymph node, PR, progesterone receptor; RT-PCR, reverse-transcriptase chain reaction.

Table 2: Comparison of methods of quantify gene expression.[3-6]

Test	Amount of starting RNA required	Sensitivity of test	Analytic requirements	Information obtained from the test	No. of targets	Relative cost	Advantages	Disadvantages
RT-PCR	Low	High	Low to moderate	Relative Gene expression	Few to several hundred	Low	Straight forward higher sensitivity	Needs careful primer selection
RNA in situ hybridization	High	Low to moderate	Low	Presence and spatial localisation of RNA of interest	Few	Low	Spatial localisation in a tissue section or a cell	Low sensitivity Qualitative not quantitative
Microarrays (Oligonucleotide arrays)	Low to moderate	Moderate to high	Moderate to high	Relative gene expression	Thousands	Moderate	Simultaneous detection of thousands of genes Higher resolution	Analysis limited to known Genes. Decreased sensitivity for lowly expressed transcripts
Custom microarrays	Moderate	Moderate to high	Moderate to high	Relative gene expression between two conditions	Several hundred	Moderate	Simultaneous detection of hundreds of genes Direct comparison of two samples	Limited reproducibility

RNA: Ribonucleic acid, RT-PCR: Reverse transcription polymerase chain reaction.

The emergence of genomics which evaluate DNA and transcriptomics which evaluate RNA techniques can measure the expression of thousands of genes. The gene profiling test described are validated and are in clinical use. These tests rely on mRNA and are Reverse transcription polymerase chain reaction (RT-PCR) and microarray and sequencing technology (Table 2). Women with newly diagnosed breast cancer should undergo testing for hormone receptor expression and HER2 overexpression. This information is used to devise a tailored adjuvant treatment plan. Pathological factors like tumour stage considering tumour size, nodal status and presence or absence of metastasis are considered most important prognostic indicators. Gene expression has identified several distinct subtypes of breast cancer and their prognosis differ markedly. Major class among these are related to oestrogen receptor expression (Luminal), HER2 expression and unique cluster of genes known as Basal cluster.[3]

PROGNOSTIC FACTORS

Patient factors

Age and race

Age factor is worse in young & older patients at time of diagnosis; Variation depends on cancer subtype. African Americans are more affected than white due to socioeconomic reasons & tumour biology.[7]

Menopausal status

Prognosis is worse in premenopausal patients particularly in receptor positive cases.[7,8]

Smoking

Smoking before & after breast cancer carries a worse prognosis.[9]

Mammographic features

Screen detected breast cancers have a better prognosis. Multi-focality prognosis is debateable.[10]

Pathology factors

Tumour stage

Survival percentage for stage 1; 98 to100%, stage 2, 85 to 98%, stage 3; 70 to 95% (Table 3).[11]

Tumour size

Size>T2. But Multifocal and Multi quadrant is controversial.[11]

Nodal involvement

Nodal involvement is a negative prognostic factor. Macro metastasis is worse than micro metastasis and micro worse than no nodal involvement.[12]

Tumour morphology

Invasive ductal carcinoma (IDC) is worse than invasive lobular carcinoma (ILC). But ILC has higher risk of relapse. Worse prognosis is considered in metaplastic & micropapillary types.[13]

Tumour grade

Degree of tumour differentiation, Percentage of tubule formation, pleomorphism, mitotic activity increases towards worse prognosis.[13] Tissue markers including hormone receptors and HER2 expression Tumour singly receptor positive such as ER + PR- or ER- PR+ has a worse prognosis than tumour being ER+ PR+. HER2 positive tumour have worse prognosis than HER2 negative.[15]

Table 3: TNM Anatomical staging.

When T is ….	And N is …	And M is …	Then the stage group is …
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1 mi	M0	IB
T1	N1 mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB

Breast carcinoma TNM anatomical stage group AJCC UICC 8th edition.[11]

Ki-67

Early Breast cancer receptor positive HER2 negative T1-2, N0-1, Ki 67 Percentage target score of >30 indicate negative prognosis. High percentage reading in receptor positive HER2 negative tumours may need targeted treatment with Abemaciclib, a cyclin dependent kinase inhibitor.[14] Peritumoral lymphovascular invasion (LVI) is considered as a negative prognostic marker.[13]

Gene expression based and clinical prognostic profiles

Genomic DNA based and transcriptomics RNA based techniques evaluate thousands of genes help in identification of biology based prognostic profiles.[18]

Clinical risk prediction calculators

Different risk prediction calculators are in use, where Input of patient and tumour characteristics are submitted to gather prognosis. Tools available online are ESTIMATE, PREDICT, CTS5.[19,25]

Metastatic disease

Its presence is a negative prognostic marker.

Other prognostic factors

Tumour infiltrating lymphocytes

TILs are an adverse prognostic factor in luminal HER2 negative breast cancer. In contrast high levels of TILs in treated triple negative breast cancers carry a better prognosis.[20]

Global genomic profiling

Allows simultaneous measurement of the activity of thousands of genes in breast cancer cells but are not routinely applied in clinical care due to validity.[8,16]

Luminal subtypes of Luminal A and luminal B expressed genes assay

They express luminal cytokeratin 8 and 18. Most common subtype and are characterized by expression of ER, PR and other genes associated with ER activation.[16]

HER2 enriched subtype

10-15% of breast cancers with ER, PR negative and HER2 Positive show this. However, HER2 enriched subtype is not synonymous with histologically HER2 positive breast cancer.[16]

Basal subtype

Evident in 10 to 15% of breast cancers known as Triple negative characterized by low expression of luminal and HER2 gene clusters.[16]

IHC-4

Immunohistochemistry (IHC) of four standard markers ER, PR, HER2 and Ki-67 for analysing intrinsic breast cancer subtype. Some studies showed it is important in separating luminal A from luminal B subtype (Table 4).

Markers of proliferation

Proliferation of breast cancer has a prognostic significance. Methods include assessing mitotic count, S phase fraction, immunohistochemistry especially of nuclear antigen Ki-67.

Urokinase plasminogen Activator system

A serine protease important in cancer invasion & metastasis. High level of uPA, uPA (uPA receptor) PAI-1plasminogen activator inhibitor is associated with a shorter survival (Table 1).[21] Somatic tumour protein p53 (TP53). This somatic tumour protein is linked with invasion and metastatic potential. (Not usually analysed.) Data suggests patients with germline mutation of TP53 carry a worse prognosis.[21]

Disseminated of circulating tumour cells (DTSc/CTCs)

DTSc/CTCs play a role in development of distant metastasis in breast cancer. This is a liquid based non-invasive prognostic marker. Blood or bone marrow sample detect metastases much earlier than symptomatic presentation.[22,23]

Gene expression based prognostic biomarkers

Over last decade, commercially available genomic tests have been used to define the course of disease and in some cases to measure the response of specific treatment. The American society of clinical oncology (ASCO) supports the use of following biomarker assays to guide decision on adjuvant systemic therapy for women with early-stage invasive breast cancer. These include Oncotype DX 21gene recurrence score (RS), Endo Predict (EP), Predictor analysis of microarray 50 (PAM50), breast cancer index and Amsterdam 70- gene profile MammaPrint.[26,27] However, the national comprehensive cancer network is more conservative, validating RS in predicting the benefit of adding adjuvant chemotherapy to further reduce of recurrence, despite the availability of above mentioned several prognostic assays (Table 1 and 2).

Oncotype DX Recurrence Score Test Exact Sciences Laboratories, Madison, WI, USA

This test is based upon reverse transcriptase polymerase chain reaction (RT-PCR) assay of 21 genes out of which 16 are breast cancer related genes and 5 are reference genes, on a formalin fixed, paraffin embedded (FFPE) tissue. The genes analysed markers of proliferation, oestrogen signalling genes, invasion and HER2 related genes. Based on gene expression profile Recurrence Score is calculated using an algorithm. A higher score indicating increased risk of distant metastases at 10 years. Oncotype DX RS provides both prognostic and predictive information about the potential benefits of adjuvant chemotherapy in patients with ER/PR positive HER2 negative early-stage breast cancer. The RS is categorised as low risk (RS<18), intermediate risk (RS 18-30) and High risk (RS >31). RS is calculated in Hormone receptor positive HER2 negative node negative, as well as node positive (N1) (1 to 3 nodes), whilst taking in account the premenopausal, peri and post-menopausal status of the patient.[26,27]

PAM50 risk of recurrence score

The predictor analysis of microarray 50 (PAM50) is a 50 gene test that characterizes an individual tumour by intrinsic subtype. Results from PAM50 are used to generate risk of recurrence score (ROR), stratifying ER positive disease into high, medium and low risk subsets. The test can be performed on formalin fixed, paraffin embedded tissue with degree of analytic validity. The PAM50 was developed using microarray & quantitative reverse transcriptase polymerase chain reaction (PT-PCR) from a set of 190 prototype samples. Intrinsic subtypes defined by PAM50 and tumour size called the ROR score. Significantly predictive of prognosis with node negative breast cancer.[31]

Endo predicts

It is RNA based prognostic assay and utilizes RT-PCR of 11 genes to calculate prognostic score. EP appears to be useful in subgroup of patients with ER positive HER2 negative tumours that have very low risk of recurrence without adjuvant chemotherapy and appears to identify the patients at low risk of late recurrence. It is formalin fixed, paraffin embedded performed on core biopsies or surgical samples. No head-to-head comparison with other prognostic tests has been made prospectively.[31]

Breast cancer index

The breast cancer index (BCI) is combination of two profiles. The anti-apoptotic homeobox B13 (HOXB13) to interleukin 17B receptor (IL17BR) expression ratio (H:I ratio) and molecular grade index (MGI). This uses genome wide microarray analysis. Three differentially expressed genes are associated with increased risk of progression among ER positive patients treated with Tamoxifen. HOXB13 over expressed in tamoxifen non recurrent cases. Prognostic factors like age, tumour size. Tumour grade and lymph node status, the H:I ratio was significantly and independently correlated with outcome. Studies validated BCI as an accurate predictor of endocrine responsiveness suggesting who will benefit from extended treatment with tamoxifen.[28,30,31]

Amsterdam 70-gene profile (MammaPrint)

The Amsterdam 70-gene prognostic profile was the first gene expression array approved for commercial use. Initially used on unfixed frozen tissue, now current practice is to use formalin fixed paraffin embedded tissue. MammaPrint was developed using supervised DNA microarray assay. MammaPrint is useful in prognosis for those with high clinical risk, HR positive HER2 negative breast cancer with no or limited (1 to 3) lymph nodes regarding the decision to withhold chemotherapy. Data also suggests that MammaPrint identifies patients with a low chance of recurrence, independent of nodal status, tumour grade or hormone or HER2 receptor status.[30,31]

Aim

The aim of study is to assess the predictive & prognostic factors in hormone receptor positive HER2 negative breast cancer regarding the decision of adjuvant chemotherapy. Primary endpoint is to discuss the clinical validity, consensus and controversies related to this topic. The secondary endpoint is to look at cost effectiveness of genomic tests. The scope of the study is confined to decision making to administer adjuvant chemotherapy or not, in the context of Genomic assay test result. Chemotherapeutic agents/ regimes are beyond the scope of this study

REVIEW

Literature search and eligibility

The Following databases were searched; PubMed, Medline, Clinical key and clinical Trials.gov. Studies were included from 2009-2024.

Search strategy

Search term “Breast neoplasia”, “Hormone receptor”, “HER2 receptor”, “Prognostic factors”. Medical subject heading (Mesh) term were “breast neoplasia”, “Receptors” “prognostic factors”.

Inclusion criteria

The inclusion criteria for the current study were randomized prospective case control trials comprising Prognostic and Predictive factors in early receptor positive HER2 negative breast cancer. Female patient above the age of 18 years with biopsy proven Invasive

early breast cancer hormone receptor positive, HER2 negative with no or 1to3 axillary node involvement.

Exclusion criteria

Studies that were excluded from search pregnant or lactating patients, Male patients with breast cancer, patients with N2 lymph node status, Metastatic breast cancer.

RESULTS

For women with early oestrogen receptor ER positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer, adjuvant endocrine therapy is the mainstay of systemic treatment. Some of these cancers also stand to benefit from adjuvant chemotherapy. The benefit from chemotherapy depends upon the risk of recurrence which may be estimated from clinical features including stage and grade of tumour, biological features of tumour including gene expression. Cancers which are ER positive, HER2 negative, node negative less than 1 cm and particularly less than 0.5 cm have a good prognosis with endocrine therapy alone. They do not typically require adjuvant chemotherapy. At the other end of risk spectrum stage 3 breast cancer requires adjuvant chemotherapy to avoid the risk of recurrence and benefit from chemotherapy. The majority of hormone receptor positive and HER2 negative breast cancer cases fall in between these two extremes. Decision making regarding adding chemotherapy to adjuvant endocrine therapy depends upon patient and disease factors. Evidence suggested Oncotype DX RS test supported the prognostic outcome in patients of intermediate group.[30]

Node negative disease

Patients with Stage T1b to T3 node negative, HR positive, HER2 negative disease require Oncotype DX 21 gene assay recurrence score (RS) to guide adjuvant chemotherapy decisions. This is a common practice as RS is well validated and widely used assay. Other assays like PAM50 and MammaPrint may also be acceptable.[1,2] Women of any age with RS equal to or less than 15 do not require adjuvant chemotherapy. Women of age greater than 50 with recurrence equal or less than 25 do not require chemotherapy. However, in women who are 50 or less than 50 years of age with RS of 16 to 25, experts may suggest ovarian suppression along with endocrine therapy for premenopausal subset who have factors for high risk of recurrence, instead of adjuvant chemotherapy. Another group of experts suggest adjuvant chemotherapy to this select premenopausal patients particularly who have high intermediate RS 21 to 25 or high clinical risk. Patients who are of any age with RS equal or above 26 experts suggest adjuvant chemotherapy, noting that supporting data is strongest for RS greater than 30. It is important to recognised that other variables may also affect the decision of adjuvant chemotherapy such as patient preference & performance status, tumour features including size and tumour grade, instead of solely relying on Oncotype RS.[1-4]

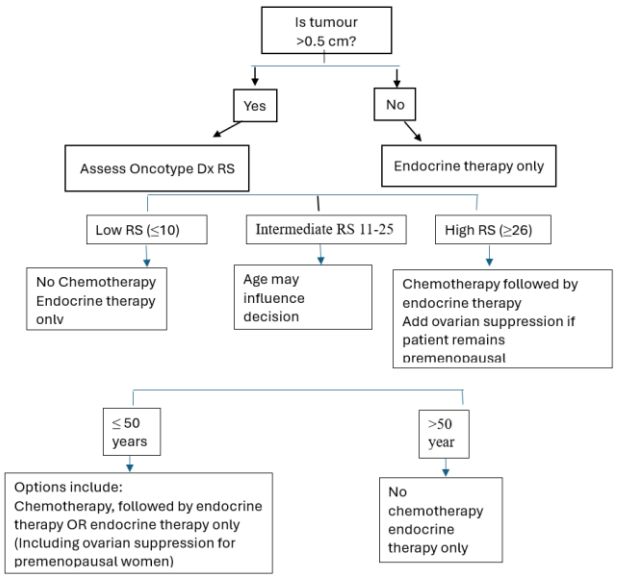

Figure 1: Adjuvant therapy using oncotype DX recurrence score in hormone receptor positive, HER2 negative, node negative early breast cancer.[1,4,11]

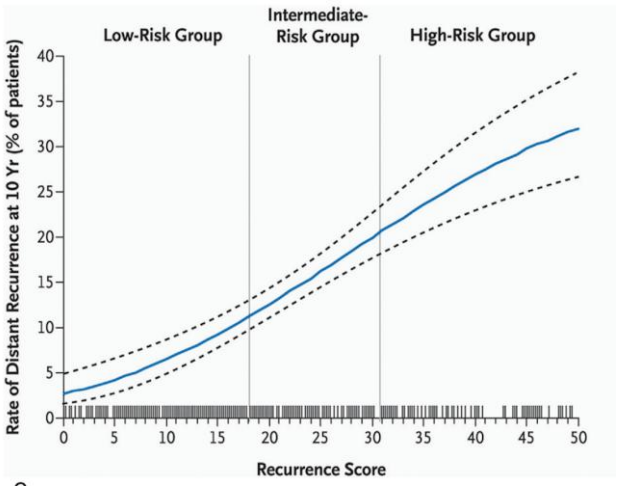

Figure 2: Relationship of distant recurrence at 10 years period with recurrence score. Bowel project (NSABP) B-14 trial.[11]

Node positive disease

Patients who have more than three lymph nodes involved and have not received neoadjuvant chemotherapy; the recommendation is adjuvant chemotherapy provided they have no contraindications. Patients with one to three nodes involved, RS is incorporated along with Menopausal status. For post-menopausal patients with one to three lymph nodes involved some experts recommend chemotherapy, while others apply RS, offering chemotherapy to those with RS equal to or greater than 26. Experts are divided in their approach for

pre-menopausal patients with one to three lymph nodes involved. The majority favour adjuvant chemotherapy due to demonstrated benefits by randomized trials and lack of available data for ovarian suppression as an alternative. Other groups of experts use gene expression profile to guide treatment decisions such as offering ovarian suppression with Aromatase inhibitors for RS equal to or less than 25 and chemotherapy for RS equal to or greater than 26.[11] The cost effectiveness of methods of gene expression along with other variables of these prognostic tests is shown (Table 1, 2 and Figure 1). The cost of test and turnaround time is discussed in the study and provided in (Table 5). Methods to quantify gene expression showed RT-PCR being most cost effective, advantages are high sensitivity, straight forward testing and moderate cost. Disadvantages are requiring careful selection. Cost of test (Table 5) discussed in this study revealed PAM50 and Endo Predict (EP) being the cheapest with their result availability ranging from 7 to 11 days. Oncotype DX is expensive, availability is normally 14 days but is widely accepted and clinically validated after data support. Turnaround time of Oncotype Dx is disadvantage.

Table 4: Intrinsic subtypes of breast cancer.[16,17]

Intrinsic subtype	IHC profile	Clinical classification
Luminal A	ER+, PR+, HER2-, Ki-67 low	HR- positive*
Luminal B	ER+, PR+/-, HER2-, Ki-67 high ER+, PR+/-, HER2+	HR- positive* HR- positive, HER2-positive
HER 2-enriched	ER-, PR-, HER2+	HER2-positive
Basal-like	ER-, PR-, HER2-	Triple-negative*
Normal-like	ER+, PR+, HER2-	HR-positive*

ER, Oestrogen receptor; HER2, human receptor growth factor receptor 2; HR, hormone receptor; PR, progesterone Receptor * includes patients with HER2-low disease.

Table 5: Cost and results availability of prognostic tests.

Test	Cost (USD)	Results available
MammaPrint	2400	After 10 days
Oncotype DX	3400	Within 14 days
ProSigna	2000	7 to 11 days
Endo Predict	2000	1 week
Foundation One	2965	3 to 4 weeks

Prognostic tests for breast cancer treatment that can be purchased.

Table 6: Tailorx trial.[1]

Trial	Total number of patients	Receptor and nodal status	Therapy	Results
TAILORx	10273	HR+, HER2-, N0	CET vs ET for patients with 21 Gene RS 11-25	ET non-inferior to CET for RS 11-25
				Small chemotherapy benefit in women <50 years with RS 21-25 or high clinical risk and RS 16-20
				Low DR with ET alone for RS 0-10
				Patients with RS >26 have better outcomes with CET than expected for ET alone

HR +, hormone receptor positive, HR-, Herceptin receptor negative, N0, Node negative, CET, chemo endocrine therapy, ET, endocrine therapy, RS, recurrence score, iDFS, invasive disease-free survival, DR, distant recurrence.

DISCUSSION

All women with newly diagnosed non metastatic breast cancer should undergo tumour testing for hormone receptor expression and HER2 overexpression. This can tailor individualized plans for adjuvant therapy. Prognostic pathological factors, tumour stage such as size, nodal status, metastatic or non-metastatic are important indicators. Gene expression studies have identified several distinct breast cancer subtypes which differ markedly in prognosis. The major clusters are related to estrogen receptor expression (Luminal clusters), HER2 expression and unique cluster of genes called basal clusters.

Despite several prognostic assays are available to estimate recurrence risk consensus has been on Oncotype DX recurrence score RS, which has been validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence. New findings from TAILORx trial published in 2022 found the use of chemotherapy declined by 19% after RS funding was introduced and by an additional 23% after original TAILORx publication in 2006 (Table 6).[1]

Receptor status of ER and PR expression is generally associated with improved outcome, for at least over a short period. ER status should be used to determine if adjuvant endocrine therapy is indicated. Data suggest that overall survival (OS), distant disease-free survival (DFS) and time to treatment failure are all positively related to ER and PR levels. The annual recurrence rate for ER positive cancers is lower in first five years post treatment as compared to ER negative cancers. Studies suggest that it may be higher with longer term follow up.

A study of over 4000 patients with operable breast cancer, enrolled in Breast cancer study group clinical trial patients with ER positive breast cancer in comparison to ER negative disease during first five years the risk of recurrence came to be 9.9% versus 11.5%. ER positive has higher annual risk of recurrence during year 5-10, 5.4% versus 3.3%. 10-15 years 2.9% versus 1.3%. 15-20 years it is 2.8% versus 1.2%. Another study supported and showed that recurrence in ER positive early breast cancers continue to occur steadily after five years of endocrine therapy to at least 20 years. This risk of recurrence is strongly corelated to original cancer stage. This finding has given rise to interest in extended endocrine therapy courses.[28,30]

ER status also associated with specific site/s of metastatic spread, reason been unclear. ER positive tumours are likely to develop clinically apparent metastases in bone, soft tissue or reproductive / genital tract. In contrast ER negative tumours more commonly metastasize to brain & liver are associated with reduced survival.ER positive tumours are more likely to histologically well differentiated, less likely to be associated with mutation, loss of implication of breast cancer genes such as p53, HER2 and HER1, all of which are associated with poorer prognosis 87 %to 92% (Figure 1).[28,29] PR is independent of ER as prognostic marker. In a study of 1000 women with PR negative expression, ER positive node negative breast tumour treated with endocrine therapy, was associated with poorer prognosis for OS, BCSS and DFS. This is also supported by ER positive, PR negative disease having more aggressive subtypes of receptor positive breast cancer falling in luminal B subtypes. In general, tumours that are singularly receptor positive appear to have worse prognosis than those with both receptors positivity.

HER2 overexpression assay amplification is routine in diagnostic workup on all primary breast cancers. HER2 overexpression carries an unfavourable prognosis, particularly if patients are not treated with chemotherapy and HER2 directed agents. The main benefit of HER2 testing is its predictive value for appropriate patient to receive HER2 directed agents. In the absence of systemic therapy, HER2 overexpression is a marker of poor prognosis in both patients' group with lymph node positive and lymph node negative disease. Additionally, HER2 retains a prognostic value even in tumours of 1 cm or less.

Gene expression based and clinical prognostic profiles have led to genomics (DNA bases) and transcriptomic (RNA based) techniques which simultaneously measure the expression of thousands of genes leading to identification of biology based prognostic profiles. Several of which have been validated for clinical use. The Oncotype DX recurrence score RS and tests like PAM50, MammaPrint are better at prognostication than clinical-pathological features such as grade or Ki67. This field is under development and aim is to define clinical utility and indication for each of the prognostic profile in routine practice.

Additionally clinical risk prediction calculators exist allowing the user to input patient and tumour characteristics to garner prognostic information. Few examples are ESTIMATE online tool.[19] It estimates the residual cumulative risk of breast cancer specific mortality (BCSM) and non BCSM to year 20 after initial diagnosis. This tool was derived from registry of 264,000 women with invasive non metastatic breast cancer. PREDICT tool estimates risks of recurrence based on clinical features and predicts benefit of therapy.[25]

CTS5 categorizes patients who have been disease free for five years into low, Intermediate and high risk for developing distant recurrences between 5 and 10 years. One study suggest that it overestimates the risk in high-risk patients. Prognostic factors in routine clinical use like age, showed patients aged less than 35 have worse overall survival (OS) and recurrence free survival (RFS). In patients with predominantly ER negative disease who presented at a later stage treated despite aggressive treatment: The five-year survival rates were 75% versus women of 35-69 years of age. Irrespective of this the tumour stage, grade and ER status, treatment in the below 35 age group experience a relative increase in breast cancer mortality of at least 70%, indicating a more aggressive tumour biology in this group of patients. Age may be of a greater prognostic significance in patients with luminal cancers than other types of breast cancers. In a study of 17,500 women with stage I to 3 breast cancer women equal to or less than 40 years at diagnosis had increased breast cancer mortality relative to older patients. The most significant increase was seen in luminal A & B cancers with no difference seen in patients with HER2 subtypes. Several studies have shown increased breast cancer mortality in older patients aged greater than 65 years. This is attributed to later stage at

diagnosis, higher comorbidities and treatment discrepancies.[7,8]

Premenopausal patients who received adjuvant chemotherapy, in whom lack of resumption of menstrual cycle due to chemotherapy induced amenorrhea, are associated with improved survival after control of standard prognostic variables, particularly hormone receptor positive disease (Figure 1). Multifocal and multicentric invasive breast cancers prognosis is controversial. Some studies suggest they are associated with poor prognosis while some suggest it does not influence prognosis. Despite this multifocality/multicentricity should not be included in decision regarding adjuvant therapy with newly diagnosed non metastatic breast cancer.[10]

Pathological factors (24) like tumour size (T) are important prognostic factors in breast cancer. Tumour size and nodal involvement are correlated, but prognostic value of the two are independent. In a study involving 62,000 patients with receptor positive node negative/ node positive breast cancer treated with endocrine therapy and disease free for 5 years, distant recurrence was correlated with original tumour size over 5-20 years period. The risk for distant recurrence for T1 versus T2 tumours, node negative was 13% versus 19%. Risks with T1-T2 tumours with one to three lymph nodes involved were given as 20% versus 26%.

Nodal involvement is a strong and independent negative prognostic factor. Lymph node macro metastasis is well established prognostic factor. The significance of micro metastasis (<2mm) is less clear. Patients with macro metastasis have worse outcome compared to node negative breast cancer. In a study of 3369 patients with breast cancer, patients with micro metastasis had significantly lower breast cancer specific five-year survival compared to node negative patients (80%-87%). However, there was no difference of survival.[12] National Surgical Adjuvant Breast and Bowel project (NSABP) B-32 trial, occult metastasis was independent prognostic factor for relapse but no meaningful effect on OS that is 94.6% versus 95.8% (Figure 2 and Table 6). Histological grade was found to be prognostic with worsened BCSS as the grade worsens. Peri tumoral lympho-vascular invasion (PLVI) is a poor prognostic indicator particularly in higher grade tumours. In a population study of 15,000 patients, PLVI is significantly associated with other adverse prognostic factors.[13] Factors like tumour, type, size, grade, nodal status, histology, ER negative are all associated with worse DFS. In absence these other factors PLVI had no effect on survival. At five years, 98% of patients without PLVI were alive versus 94.1% with PLVI.

Ki67 status prognosis in early breast cancer has been extensively studied. Ki67 has clinical validity, but clinical utility is for prognostic estimation in oestrogen receptor positive/ HER2 negative cancers in whom adjuvant chemotherapy was not needed (T1-2N0-1). The consensus was that Ki67 equal to or less than 5 or equal to or greater than 30 percent can be used to estimate prognosis. High Ki67 levels were associated with a higher risk of relapse and worse breast cancer survival in both node positive and node negative disease.[14] Disseminated and circulating tumour cells (CTC) and PIK3CA are liquid based (liquid biopsy) prognostic biomarker which are non-invasive techniques. PIK3CA mutation are among the most common genetic mutation alterations in breast cancer activating PI3K/AKT/mTOR signaling pathway promoting tumour growth and survival. 40% HR positive, HER2 negative cancers harbour this mutation. These mutations are resistant to endocrine treatment and can influence management strategy.[22,23]

CONCLUSION

The tissue-based biomarkers can be utilized to make precision/ personal treatment plans. High risk patients will receive the appropriate management and low risk will avoid unnecessary chemotherapy or prolonged hormonal therapy. Most of the biomarkers in clinical use have a target group of patients with ER/PR positive, HER2 negative Early breast cancer (EBC). Tissue biopsy based further genomic assays have been studied in clinical trials and have not been validated to the extent of ones in clinical use.

Prognostic factors like tumour infiltrating lymphocytes (TILs), global genomic profiling, luminal subtypes, basal subtypes, HER enriched, urokinase plasminogen activator system and disseminated and circulating tumour cells (CTC) are of great clinical interest and developing fast. Liquid biopsy based prognostic markers are extensively studied in recent years due to its non-invasiveness and easy to collect samples when compared to tissue biopsies. Some of these tests like CTC detection and PIK3CA mutation detection have been approved by FDA but not recommended by clinical guidelines due to lack of standardization and large cohort validity.

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