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Prognostic Indicators in Breast Cancer Patients

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Abstract

Numbers of clinicopathological factors predict the outcome of breast cancer in terms of risk of recurrence and death from cancer depending upon tumor and patients characteristics. Traditional prognostic factors are number of positive lymph nodes, size of tumor, histologic grade of tumor, lymphatic and vascular invasion and hormone receptor (HR) positivity. Prognostic factors help the clinicians to select appropriate therapy for the patients in such a manner that they will potentially benefit for prevention of recurrence of tumor.

The role of classical prognostic markers like the stage of the disease, presence of metastasis at the time of initial diagnosis, lymph node invasion, age of the patient, HR status, Human Epidermal growth factor 2 (HER-2) and Ki67 expression is well established to assess outcome and response to the treatment.In addition to the traditional prognostic factors, with advances in the field of genetics and molecular biology several promising prognostic factors are emerging. In the present era of personalized medicine, prognostic factors play an important role in selection of patients at risk for recurrence for administration of appropriate adjuvant therapy.

Keywords: Breast cancer; Prognosis; Classical factors; Novel factors

Background

Breast cancer is a heterogeneous malignancy observed frequently among women. If it is diagnosed at the early stage, relatively it turns into favorable outcome. Numbers of clinicopathological factors predict the outcome of breast cancer in terms of risk of recurrence and death from cancer depending upon tumor and patients characteristics. Traditional prognostic factors are number of positive lymph nodes, size of tumor, histologic grade of tumor, lymphatic and vascular invasion and hormone receptor (HR) positivity. Estrogen-receptor (ER) and progesterone receptor (PR) positive tumors have about 70% chance to respond endocrine treatment, while ER and PR negative tumors have less than 5% chance of endocrine response [1]. Human Epidermal growth factor (HER-2) is also an important prognostic factor for response to trastuzumab.

Prognostic factors help the clinicians to select appropriate therapy for the patients in such a manner that they will potentially benefit for prevention of recurrence of tumor. In detail knowledge about pathophysiology of progression of breast cancer disease improved risk assessment, targeted therapies and individualized treatment [2]. Hence estimation of individual patient's risk of recurrence of breast cancer using prognostic factors is helpful to plan management. Prognostic factor is any measurement at the time of surgery, which correlates with disease-free or overall survival irrespective of systemic adjuvant therapy and correlate with the natural history of the disease. Predictive factor is any measurement associated with response to a given therapy. Hence, they are associated with the sensitivity or resistance to the treatment. HR status and HER-2 act as both, prognostic and predictive factors [3]. Independent prognostic factors are lymph node status, tumor size and ER/PR status [4]. Because of limitations of traditional factors to predict risk of recurrence, mRNA and DNA based markers and gene signatures are under evaluation for prognostication of the disease.

Prognostic Factors for Breast Cancer

In addition to traditional well-established prognostic factors, various novel factors are emerging to select appropriate therapies for patients with breast cancer. These factors are indicators of aggressiveness, invasiveness, extent of spread of the disease and correlate with survival independent of treatment [5].

Classical Prognostic Factors

Stage at the time of initial diagnosis

The stage of breast cancer at the time of diagnosis is the most important prognostic factor. Early

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stage breast cancer has a favorable prognosis in comparison with the late stage diagnosis. If diagnosed at late stage with distant metastasis, obviously there are more chances of recurrences resulting in poor outcome. Presence of metastasis at the time of initial diagnosis is a significant risk factor for recurrence of the disease. Bone marrow micro metastasis has also been proposed as prognostic factor associated with tumor size, nodal status and grade of the tumor [6].

Size of the tumor

At the time of diagnosis, if tumor size is large, they are more likely to recur resulting in less favorable prognosis. Tumor size is a good prognostic marker for distant relapse among node-negative patients, although patients with small tumor having size less than 1cm if not treated have 12% chance of relapse of the disease [7]. Size of tumor correlates with the presence and number of involved axillary lymph nodes. It is also independent prognostic factor for distant recurrence rates especially among node-negative cases [8].

Spread to lymph nodes

Involvement of lymph node is very important prognostic factor for breast cancer. Nodal status including number of positive lymph nodes affects the prognosis of the disease in terms of disease-free and overall survival. Still 30% of node-negative cases may develop recurrence by 10 years [8]. Lymphatic invasion is especially useful prognostic factor among patients with borderline tumor size.

Tumor grade

Histological grade of the tumor is a subjective assessment that is based on the degree of differentiation and consists of tubule formation, nuclear pleomorphism and mitotic activity. Low-grade tumors are likely to have less aggressive behavior, while high-grade tumors progress aggressively. Tumor grade is a strong prognostic factor which itself act as a molecular signature and if analyzed properly it could add information superior to currently existing commercial molecular methods [9].

Hormone receptor (HR) status

Hormone receptor-positive tumors (Estrogen receptor- ER, Progesterone receptor PR) are often less aggressive, low grade and have low risk of metastasis and recurrence. So they have the good prognosis and respond well to the treatment. ER and PR are dimeric, gene regulatory proteins. Recently the role of ER as a negative and HER2 as a positive indicator for chemotherapy has been recognized. Female sex steroid hormones often regulate growth of breast cancer [10]. Hence, determination of ER and PR in the tumor continues to be used as prognostic markers for potential benefits anti-hormonal therapy.

HER2 status

Amplification of HER-2 proto-oncogene that encodes for tyrosine kinase glycoprotein plays a significant role in breast cancer pathogenesis. Its overexpression is associated with the poor DFS rate in patients with axillary node-positive breast cancer cases. HER2 positive breast cancer is aggressive and spread fast compared to HER2 negative type of tumor. Overexpression of HER2 strongly indicates likelihood to respond to anti-HER2 therapies in the form of trastuzumab or laptatinib [11].

Tumor proliferation rate

It is an important prognostic factor in breast cancer. It is estimated by various methods like S-phase fraction by flow cytometry, cell cycle related antigens by immunohistochemistry and expression of nuclear phosphoprotein mitocin. Ki67 is a nuclear non-histone protein antigen which is expressed only in the cells in the proliferative phases of cell cycle (G1, S, G2 and M phases). It is usually estimated as the percentage of tumor cells positively stained by the antibody with nuclear staining. Its expression is the most common criterion of proliferation index. Proliferation rate of tumor is a predictor of aggressiveness, especially in ER positive tumors. Ki67 has been found to be of prognostic value in breast cancer showing strong statistically significant correlation with clinical outcome such as DFS and OS [12]. Ki67 staining is useful as prognostic marker and technically easier laboratory test. Ki-67 strongly correlates with nuclear grade, age and mitotic rate of the tumor. If more than 50% of the cells show overexpression of Ki67, they are at high risk of developing recurrent disease [13]. The expression of Ki67 by immunohistochemistry is commonly used to assess the proliferation. Tumors showing high Ki67 expression, should receive systemic chemotherapy [14].

Site of recurrence of breast cancer

Local recurrence means tumor in breast after surgery and radiation therapy has a favorable prognosis. But in case of distant spread to various organs like lung, liver, brain, bone, prognosis is poor [6].

Age at diagnosis

Breast cancer among younger women age less than 35 years has a poor prognosis due to aggressive and high-grade nature of the tumor. While older women with breast cancer have a better prognosis. Age has been reported to be an independent prognostic factor among women with more than 35 years to show poor 10-year distant recurrence free survival [15,16].

Period of disease free interval

If recurrence is after 5 years of initial diagnosis, the prognosis is favorable. But recurrence within 2 years results in the poor outcome.

Presence of occult metastatic cells (OMC) and isolated tumor cells (ITC) in the bone marrow at the time of surgery and during follow-up have been studied as prognostic factors for subsequent relapse and death from breast cancer [17].

Novel Prognostic Factors

In addition to the traditional prognostic factors, with advances in the field of genetics and molecular biology several promising prognostic factors like urokinase-type plasminogen activator, plasminogen activator inhibitor 1, epithelial cell adhesion molecule and multigene profiles are under evaluation [18]. Angiogenic growth factors like vascular endothelial growth factors, platelet-derived endothelial cell growth factors and fibroblast growth factors have been identified to be of prognostic value for clinical utility [19]. The role of DNA aneuploidy has been investigated among node-negative breast cancer patients. It was reported to be useful prognostic factor for identification of high-risk patients who might benefit from additional adjuvant therapy [20].

New insights in breast cancer biology, genomic and transcriptomic landscape help to quantify the risk of progression of the disease and plan treatment accordingly. New high-throughput microarray technologies introduced novel multiple prognostic markers for breast cancer. Interest in the field of novel prognostic markers has been raised because of the fact that many patients harbor microscopic metastasis at the time of initial diagnosis of early stage breast cancer.

Analysis of specific mutations in clinical labs is also under

evaluation for its prognostic, predictive and therapeutic utility. Next generation sequencing (NGS) technology permits analysis of all the exomes or even entire gene that helps for individual risk assessment and identifies patients likely to respond to novel therapies. Base on NGS technology, variety of commercial panels are available for detailed analysis of mutations, rearrangement, amplifications and deletions or coding and non-coding RNA [21]. NGS assays are being clinically validated and used in clinical trials. Number of multigene prognostic markers like 21-gene assay, Mammaprint and 80- gene Blueprint gene tests, Breast cancer Index and PAM50-based Prosigna assays are available commercially. They have been assessed for their prognostic and therapeutic utility by several researchers. But most of them are useful in prognostication of ER+ tumors with limited use in prediction as response to therapy [9]. Some large trials proposed the role of gene signatures in the management of patients with node-negative breast cancer. Validation of gene signature as prognostic or predictive tool is under evaluation [1]. But the cost and availability of the resources for implementation of novel prognostic markers in routine clinical practice is a major challenging issue.

Prognostic factors are the key elements for selection of the potential individuals with early breast cancer at high risk of tumor relapse for adjuvant treatment. The role of classical prognostic markers like the stage of the disease, presence of metastasis at the time of initial diagnosis, lymph node invasion, age of the patient, HR status, HER2 and Ki67 expression is well established to assess outcome and response to the treatment. Numerous novel genetic and phenotypic markers like p53, $p14^{ARF}$, cyclin D1, cyclin E, TBX2/3, BRCA1/2 and vascular endothelial growth factors are emerging, but their role is still debatable for prognostication of the disease [5]. Careful evaluation of measurement of these markers with available therapeutic modalities is needed to ensure their clinical benefits. Many molecular markers can be used to expect therapeutic outcomes and plan the treatment strategy. In the present era of personalized medicine, prognostic factors play an important role in selection of patients at risk for recurrence for administration of appropriate adjuvant therapy.

Conclusion

Prognostic factors provide important information about clinical outcome of the patients at the time of diagnosis, independent of therapy. Such factors are indicators of growth, invasiveness of the tumor and its metastatic potential. Traditional prognostic factors include the tumor size, axillary lymph node status, and nuclear and histologic grade. HR statuses, overexpression of HER2 and Ki67 defined proliferation index are the most clinically relevant prognostic factors. To improve clinical decision-making, integration of clinical, histological and molecular prognostic factors need to be developed and validated for risk assessment with adequately powered prospective clinical trials.

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