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Review

Do online prognostication tools represent a valid alternative to genomic profiling in the context of adjuvant treatment of early breast cancer? A systematic review of the literature

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ABSTRACT

Introduction: Decision-making regarding adjuvant chemotherapy has been based on clinical and pathological features. However, such decisions are seldom consistent. Web-based predictive models have been developed using data from cancer registries to help determine the need for adjuvant therapy. More recently, with the recognition of the heterogenous nature of breast cancer, genomic assays have been developed to aid in the therapeutic decision-making.

Methods: We have carried out a comprehensive literature review regarding online prognostication tools and genomic assays to assess whether online tools could be used as valid alternatives to genomic profiling in decision-making regarding adjuvant therapy in early breast cancer.

Results and conclusions: Breast cancer has been recently recognized as a heterogenous disease based on variations in molecular characteristics. Online tools are valuable in guiding adjuvant treatment, especially in resource constrained countries. However, in the era of personalized therapy, molecular profiling appears to be superior in predicting clinical outcome and guiding therapy.

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1. Introduction

Breast cancer is the most common female cancer with 252,710 women estimated to be diagnosed with invasive breast cancer in 2017.[1] It is the second leading cause of death in the United States and is expected to become the leading cause of death within the next few years.[2] Despite this, survival rate has increased since the 1990s.[3] This is largely attributed to the advances in diagnosis and adjuvant therapy.[2] A major step has been the acknowledgement of the rather heterogenous nature of breast cancer based on substantial variety in molecular and clinical characteristics leading to diverse patient subpopulations.[4,5]

Breast cancer can be classified based on the histopathological characteristics into invasive ductal carcinoma not otherwise specified (IDC-NOS) and special types (lobular, tubular, medullary, and metastatic carcinoma). Furthermore, tumor grade, which is also determined histologically, plays an important role in prognostication tools.[4] An immunohistochemical profile based on the degree of expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2(Her2) and Ki-67 similarly identifies breast cancer subtypes.[6]

Further molecular profiling based on micro-array technology has identified five distinct intrinsic subtypes: luminal A, luminal B, Her2-enriched, basal-like, and normal breast tissue-like.[7] Thereafter, advances in gene expression studies have led to further subclassification of breast cancer into new molecular entities. Dawson et al. described 10 clusters of breast cancer integrating molecular information with the genomic and transcriptomic landscapes of breast cancer. Each of these clusters is associated with distinct clinical outcomes, thus providing new insights into the underlying biology and potential molecular drivers. Recognizing the heterogeneity of breast cancer with its implications for disease biology, behavior and relapse risk highlights the importance of individually tailored management rather than a “one-size- fits all” approach.[4]

The diagnosis of breast cancer is a distressing event.[8] Surgical resection for early breast cancer renders the patient free of overt disease.[9] Thereafter, a difficult decision has to be made regarding adjuvant therapy; including, hormonal therapy, chemotherapy, or both.[10] The goal of adjuvant therapy is the eradication of persistent microscopic disease, the assumption of which is based on data extrapolated from previous clinical trials whereby the lack of relapse is assumed to be reflective of the effectiveness of the treatment rather than the favorable prognosis of the disease. It is also assumed that the responsiveness to treatment is uniform between the primary disease and the micrometastases.[9] Adjuvant systemic therapy prolongs survival in the majority of breast cancer patients.However, it is frequently associated with significant side effects.[11,12]

Furthermore, even though its significance in early breast cancer is still undefined,[13] and the majority, especially node-negative patients, have favorable 10- year survival with locoregional treatment alone,[12] current guidelines still recommend chemotherapy in most node-negative patients exposing them to unnecessary overtreatment.[14]

2. Materials and methods

2.1. Search strategy

Relevant articles were identified using electronic database search PubMed database. Articles published up to February 2017 with no upper limit were included in the study. The following free text terms were used to search for relevant literature: “breast” AND “adjuvant” AND “online”, or “breast” AND “adjuvant” AND “multigene assay”. A total of 284 articles were identified. Only articles published in English were selected. Studies identified were screened for relevance. Reference articles in this review were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work. Our review yielded a total of 119 references.

3. Prognostication methods

The ability to predict which patients will benefit from the addition of chemotherapy is limited.[15] The art of prognostication, first elucidated by Hippocrates, is not static and rarely relies on a single factor. Therefore, estimates often use a combination of factors and are described as prognostic models, prognostic indices, prediction tools, or risk scores.[16–18] The decision to administer chemotherapy is currently based on clinical and pathologic parameters which analyze the primary tumor and estimate outcomes based on the assumption of residual microscopic disease. They include patient's age, menopausal status, histopathological features of the primary tumor (size, grade, nodal involvement, ER, PR, and more recently Her2 and Ki-67).[19–21]

3.1. Clinicopathological factors derived indices and guidelines

These prognostic factors were incorporated into prognostic indices like the Nottingham Prognostic Index (NPI) which was originally devised in 1978 by Blamey et al.,[22] described formally in 1982 by Haybittle*et al.*,[23] and updated in 2007. NPI was derived from data on symptomatic patients in the UK predating the screening era. It uses the following formula: maximum tumor size in centimeters x 2 + lymph node stage (1, 2, or 3) + histological grade (1, 2, or 3) generating a numeric score to provide 10- year survival estimates within specified prognostic groups.[8,22] Hence, these groupings assist in making clinical decisions based on balancing baseline risks and potential side effects of adjuvant systemic therapy.[24] Such a tool cannot be used globally as it is based on UK patient's data. Quintyne*et al.*[25] demonstrated that NPI underestimates the actual overall survival in a study done in Ireland reflecting the effect of different population makeup on the NPI results.

Guidelines like the St. Gallen Consensus and the National Comprehensive Cancer Network (NCCN) were also developed in order to guide the management of breast cancer patients. In 2009, the St. Gallen Consensus presented a new algorithm incorporating both risk assessment and therapy recommendations omitting patient's age and focusing on the diagnostic thresholds for consideration of systemic treatment. It incorporates standardized cut-offs for ER, PR, Her2, and Ki-67.[26,27] Limitations of such a guideline include the HER 2 false-negative or false positive IHC results, the assumption of homogenous Her2 expression throughout a tumor, different diagnostic thresholds to those used inmost reported adjuvant therapy trials, and the limited technical reproducibility and subjective interpretation of Ki-67 expression.[28–33]

The NCCN, which is an alliance of 27 of the world's leading cancer centers working together to develop treatment guidelines for most cancers, offers guidelines for decision making in the management of breast cancer. These guidelines are evidence-based, consensus-driven to ensure that all patients receive the optimal management with optimal outcome.[34] However, guideline-driven decisions may have several limitations since factors like treatment toxicity, performance status, quality of life, psychological well-being, and patient's perception of the treatment efficacy can play pivotal role in clinical decision making. All these factors are poorly captured by practice guidelines.[35–38]

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