Current Breast Cancer Reports (2019) 11:185–189
https://doi.org/10.1007/s12609-019-00325-3

LOCAL-REGIONAL EVALUATION AND THERAPY (DM EUHUS, SECTION EDITOR)

Pathology Meets Biology: the New Era of Breast Cancer Staging

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Published online: 16 August 2019

Abstract

Purpose of Review Breast cancer is now recognized to be a very heterogeneous disease. This complexity was recently reflected in the newest American Joint Committee on Cancer (AJCC) breast cancer staging, implemented in 2018. Although it seems very daunting, the new staging is based on both the anatomical extent of the disease and the prognostic factors such as hormonal and HER2 status, grade of the tumor, and genomic assays providing information regarding risk of recurrence. The purpose of this review is to illustrate the reasoning for the change in previous, solely an anatomically based breast cancer staging system and to report the updates.

Recent Findings The research showed that evaluation of breast cancer through immunohistochemistry and utility of genomic assays provides substantial prognostic information.

Summary The combination of anatomic and prognostic factors has a tremendous impact on outcome predictive abilities of the staging system for each affected individual.

Keywords Breast cancer staging · Biomarkers · Intrinsic subtypes · Genomic assays · Prognostic factors

Introduction

Recent updates in the understanding of breast cancer biology as well as improved response to treatment, have allowed the medical community to enhance and to redefine breast cancer staging. Since its creation, the TNM system (primary tumor (T), regional lymph nodes (N), distal metastases (M)) was based purely on the anatomic information. It was used for decades to provide an estimate of disease severity with the increasing stage correlating to decreased survival [1••, 2•]. When the American Joint Committee on Cancer (AJCC) instituted the new TNM staging system in the 1950s, the effective systemic therapies were nonexistent, and local treatments were limited to radical surgical procedures [1••]. These extensive surgeries were supported by the idea that cancer cells follow an orderly progression from the breast, through different lymph node regions and to the metastatic disease [1••]. TNM staging allowed development of a common language of communication among the providers. It also established a means to spare selected patients from extensive surgery, if the patient had an elevated, perceived risk of death within a short period of time despite aggressive local treatment [1••].

Since the 1950s, there has been tremendous progress in unlocking and advancing the understanding of breast cancer. As a result, potent systemic therapies have been developed to help control the disease. New evidence regarding the tumor spread has also challenged the previously established orderly progressive cancer escalation dogma. Today it is known that some invasive cancers have the potential for metastatic spread even in the absence of lymph node involvement [1••]. This paradigm shift in thinking, paired with the discovery of effective adjuvant therapies, has allowed recent treatment methods to de-escalate the extent of surgical intervention in the breast and in the axilla, which resulted in less postsurgical complications, such as lymphedema, and better cosmetic outcomes [1••].

Biological Factors

In January 2018, breast cancer staging was updated for the eighth time. During the development of the AJCC sixth and

This article is part of the Topical Collection on *Local-Regional Evaluation and Therapy*

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seventh editions, various emerging associations between breast cancer prognosis and biological factors, like grade or hormone receptor expression, were preliminarily observed [1••]. These associations, however, were not included in those editions of breast cancer staging because strong evidence supporting their utility was still lacking [1••]. For several decades, the importance of hormonal receptor status was recognized and used to a certain degree in evaluation of breast cancer. However, it is within the last 15 years population-based registries began to collect information about estrogen and progesterone [1••]. Similarly, human epidermal growth factor 2 (HER2) was not universally documented in cancer databases, like SEERS (Surveillance, Epidemiology, and End Result), or NCBD (National Cancer Database), prior to the last decade [1••]. As these biological markers were initially being incorporated into the evaluation of breast cancer, it was noted that certain tumors behaved differently than others with regard to response to the treatment, the rate of recurrence, and overall survival. Because of these observations, three major groups of breast cancer were delineated based on cancer's immunohistochemistry. These groups include hormone receptor-positive and HER2-negative tumors, HER2-amplified tumors, and tumors that were not expressing either human epidermal growth factor 2 or hormonal receptors [1••]. Additional analysis of the HER2-amplified group resulted in the realization that there were even other differences in behavior between tumors that were hormone positive and those which were hormone negative. All those discoveries lead to the development of an individually tailored approach to treatment for each subclass of breast cancer. At this point, breast cancer began to be seen as a very heterogeneous disease, varying in its molecular characteristics and survival outcomes [3, 4].

Intrinsic Types of Breast Cancer and Genomic Assays

As more research was done on breast cancer molecular profiling, several distinct subtypes were identified using microarray-based gene expression analysis and hierarchical clustering [5]. These subtypes included luminal A, luminal B, basal-like, claudin-low, normal-like, and HER2-enriched categories [5–7].

Luminal A cancers were characterized by slow growth and a generally good prognosis [8]. These tumors were hormone receptor positive and HER2 negative. They also had a low Ki-67 index, which is a measurement of the cell proliferation rate. Luminal B cancers were also hormone receptor positive, but might be either HER2 positive or negative had a higher Ki-67 index [6, 8]. Luminal B tumors grew slightly faster and had a worse prognosis than luminal A [4, 5]. Normal-like tumors had similar gene expression to normal breast tissue and hence were named accordingly [9]. Basal-like tumors, also called triple-negative cancers, did not show expression of hormone receptor and HER2 [8, 10]. Usually, they also had a high Ki-67 index. The claudin-low subtype had low expression of genes for cell tight junctions and cell to cell adhesions [9]. Generally, it was also negative for hormone and HER2 expression and could be consider a subtype of a basal-like category [9]. It is important to mention that there were other subcategories of basal-like subtype such as mesenchymal, luminal androgen receptor, mesenchymal-steam like, or immunomodulatory types [11]. Finally, the HER2-enriched breast cancers were HER2 positive [8]. Each of these specific subgroups exhibited different disease-free and recurrence-free survival curves based on treatment targeting the unique characteristics of the tumor [5, 6]. The initial use of genome sequencing and microarray analysis was very costly [8]. Substantial work has been done to reduce cost as well as efficiently focus on key essential genes necessary for molecular profiling of breast cancer. In 2009, Parker and others developed a genomic assay testing 50 genes, called PAM50, to classify the intrinsic types of breast cancer [4]. PAM50 proved to have a good fidelity when compared with the assays utilizing a higher number of genes [4].

The fact that molecular assays become commercially available and relatively accessible revolutionized the world of breast cancer. After the success with PAM50, additional assays were developed. Those assays provided predictive and prognostic information for each tumor with regard to distal and loco-regional recurrence as well as information regarding sensitivity to chemotherapy. Assays, like Oncotype Dx or MammaPrint, have the most robust data supporting their use [1••]. Oncotype Dx is a 21-gene assay and is the oldest and the most studied genomic assay. It is used in hormone-positive cancers which have not metastasized to the lymph nodes [1••]. It should be noted that additional research is currently being done to validate this assay for lymph node-positive disease [12]. Initial data from Oncotype Dx analysis divided patients with hormone-positive breast cancers into three groups with regard to the recurrence risk score: low recurrence risk, intermediate recurrence risk, and high recurrence risk. Low recurrence risk patients did not need toxic chemotherapy and were shown to have excellent survival as long as they complied with their adjuvant endocrine therapy. In patients with a high score for risk of recurrence, chemotherapy was shown to be beneficial both in improving survival and in lowering the risk of the recurrence.

It was initially unclear if patients with intermediate risk of recurrence gain benefit from chemotherapy. Due to the lack of strong evidence advocating for the implementation of chemotherapy in this group, the treatment was left to the discretion of the physician and the patient's preference [13]. The National Comprehensive Cancer Network (NCCN) incorporated the Oncotype Dx results into the official guidelines in 2009

[14]. Additional research through the TAILORx trial provided greater clarification of the treatment options for the intermediate patient group. It also illustrated a correlation of patients' menopausal status to the recurrence risk score and estimated benefit from chemotherapy for both premenopausal and postmenopausal women. This further helped to reclassify intermediate patients to groups who would or would not benefit from chemotherapy.

Contrary to Oncotype Dx, a 70-gene assay called MammaPrint is not limited by hormonal status of the tumor and can be used in both hormone-positive and hormone-negative cancers. It was also validated for both lymph node-positive (up to three lymph nodes) and lymph node-negative cancers [15, 16]. The MINDACT trial demonstrated that MammaPrint was more precise in predicting clinical outcomes of women with early breast cancer over the clinical risk estimate based on tumor characteristics alone [1••]. Based on MINDACT data, 46% of women, who were thought to be at high risk of recurrence based on the clinical characteristics of tumor, could be spared from chemotherapy because their tumors had low-risk molecular profiles [17]. In addition to the most popular assays mentioned above, there are numerous others like EndoPredict or the Breast Cancer Index [1••].

New Staging

This monumental growth of information about the behavior of breast cancer and the coinciding evidence supporting the need of an individualized approach to a very heterogeneous disease have raised the question: does purely anatomically based TNM staging adequately reflect the true nature of the disease [1••]. This concern gave rise to the eighth edition of AJCC breast cancer staging, which combined the anatomy of the cancer with its biological behavior [1••]. This staging was intended for invasive carcinomas of the breast and in situ ductal carcinomas [1••]. A separate staging system is used for evaluation of the breast's sarcomas, phyllodes tumors, and lymphomas of the breasts.

Lobular carcinoma in situ (LCIS) was removed from the staging system and is now considered a benign lesion [1••]. Previously, LCIS was designated as an in situ carcinoma (Tis). Although it was extensively discussed, no additional category was created for a pleomorphic variant of LCIS with histologic features partially overlapping with ductal carcinoma in situ (DCIS) [2•]. Therefore, pleomorphic LCIS is not considered in situ carcinoma.

In general, new AJCC breast cancer staging is divided into two main groups: an anatomic stage and a prognostic stage. The latter is further subdivided into a clinical prognostic stage and a pathological prognostic stage, with a special subgroup reserved for patients treated in the neoadjuvant setting. One may wonder why the new staging system still incorporates a purely anatomically based category despite all the evidence pointing to an incomplete representation of the tumor-related prognosis. AJCC intends for the anatomic stage section to be used only in the parts of the world which do not have access to the analysis of biomarkers and the genomic assays. This anatomical classification, very similar to the seventh AJCC edition, is relevant worldwide and provides general information regarding the prognosis and advancement of disease in the absence of systemic treatment options.

Patients with access to the standard evaluation and treatment modalities of the developed world should be staged using the prognostic staging system [1••]. This new staging system intends to group tumors according to risk of distal recurrence and death. Even though anatomic staging provides general information regarding outcomes, patients with the same stage of disease can vary significantly in the rate of recurrences and survival. The inclusion of biological factors into the staging assessment provides a more accurate prediction of outcomes for individuals affected by the disease. Furthermore, adding the prognostic component to a well-established TNM system provides continuity with the past and allows researchers to compare groups of patients treated at various periods [2•].

The clinical prognostic stage is based on physical exam, imaging results, and information provided by the biopsy. In addition to the anatomical extent of the disease, this category also incorporates the tumor grade, HER2 receptor, estrogen receptor (ER), and progesterone receptor (PR). The pathological prognostic stage, as the name suggests, is used when the surgery has been completed. It integrates all the clinical information, biomarkers, and information obtained from surgery, including genomics of the tumor. The biological markers give both prognostic and predictive information to guide the therapy in patients newly diagnosed with breast cancer, those with recurrences, and those who have progressed to the metastatic disease [1••].

The new AJCC staging downstaged some tumors and upstaged others based on the biological markers. Using pathological prognostic staging, patients with hormone-positive and HER2- and lymph node-negative breast cancer that measure up to 5.0 cm, who have Oncotype Dx scores less than 11, or have low recurrence scores on other genomic assays are given stage IA. Previously, many of those patients would be classified as stage 2. Clinical prognostic staging also restaged numerous tumors based on their characteristics. These changes are illustrated in Fig. 1, based on AJCC eighth edition of breast cancer staging tables. Figure 1 represents tumors T2 N1 M0, which would be classified as a clinical stage II according to previous staging system. In the new staging system, those tumors range in clinical stage from IB to IIIB based on their biologic factors.

Both the AJCC staging system and the NCCN guidelines on treatment of breast cancer use Oncotype Dx due to stronger level 1 evidence available for this assay. At the same time, the

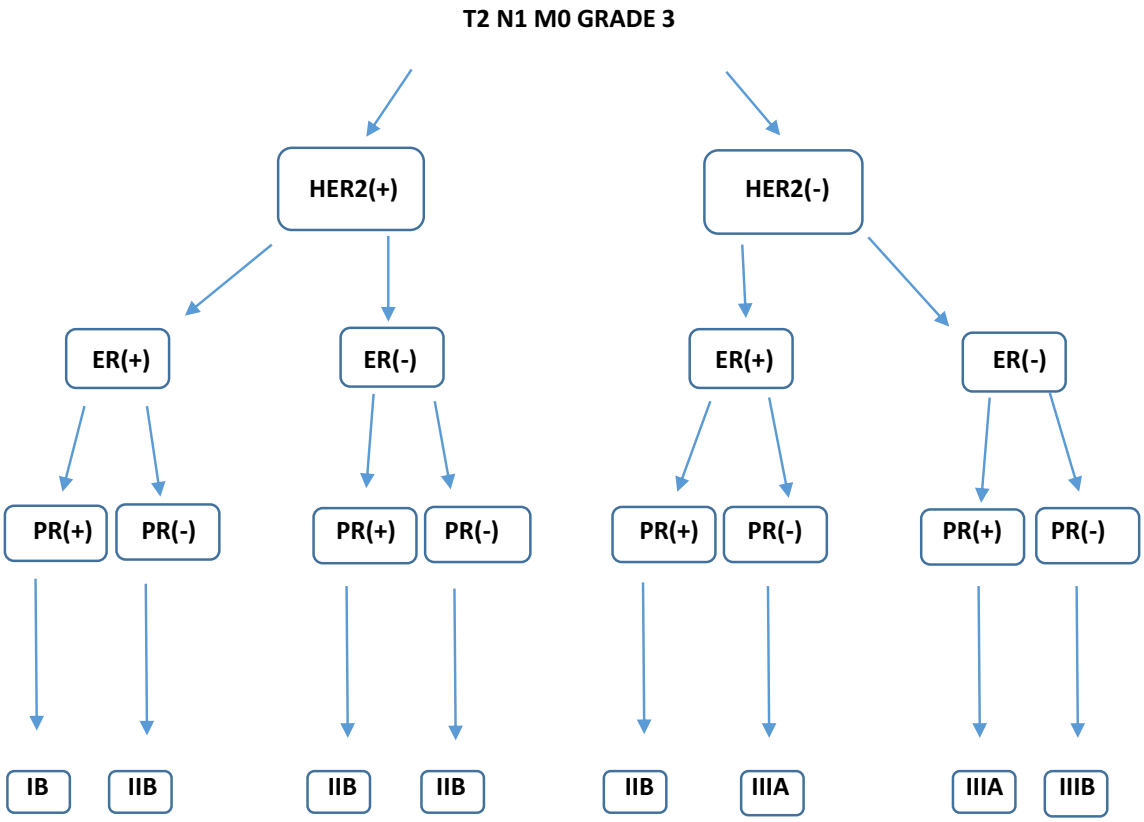

Fig. 1 Sample of clinical prognostic staging for T2 N1 M0 breast cancers [1••]. Used with permission from the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging Manual*, Eighth Edition (2017) published by Springer International Publishing

AJCC panel of experts did not want to endorse Oncotype Dx over the other genomic assays since all of them provide valuable prognostic information [1••].

Other updates available with the new staging of breast cancer are aimed at obtaining information regarding hormone receptors and HER2 status, along with the grade for all invasive carcinomas. Ductal carcinoma in situ (DCIS) also should have a nuclear grade assigned [1••]. The invasive tumor size should be rounded to the nearest millimeter except in the case of tumors between 1.0 and 1.5 mm. Rounding down to 1.0 mm would incorrectly classify that tumor as microinvasive (T1mi), which is defined as an invasive tumor foci equal or smaller than 1.0 mm. For multifocal disease, the newest staging system assigns designation "m." The sizes of multiple tumors should not be added together. Only the largest mass ought to be considered. The recurrences of breast cancer should be marked with "r" placed before the stage. The AJCC expert panel made category pM1 invalid and removed it from staging. The category cNx is restricted only to patients who had previous regional lymph node basin removal and whose lymph nodes cannot be assessed on clinical exam. If microscopic or molecular evidence of cancer cells is found at the distal site without clinical or image-based evidence of distal metastasis, then a category cM0(i+) is assigned to indicate isolated tumor cells [2•]. For every patient undergoing neoadjuvant chemotherapy (NAC), response to that treatment should be assessed. Pathological complete response (pCR) is precluded if there is any focus of residual invasive tumor noted. The fibrosis from the treatment effects is not included in tumor measurement after NAC [1••]. A special situation may occur where the tumor is eradicated from the entire tumor bed, but viable cells are identified within lymphatic vascular channels [2•]. If this event occurs, the tumor would not be classified as reaching a complete pathological response to the neoadjuvant treatment [2•]. It is important to remember that the newest staging is based on specific tumor characteristics and on the tumor's response to treatments. If the patient is noncompliant with the treatment or the treatment is not accessible, then the risk of recurrence and mortality varies significantly from the one estimated, based on the eighth edition of the AJCC breast cancer staging. The only way for the tumor pathology to meet tumor biology is to implement the treatment to which cancer will respond.

Breast Cancer Staging Tables and Phone Applications

For fast and efficient staging of breast cancer, the AJCC created clinical and pathological prognostic stage tables that are

available online. In the modern era of technology, these tables are also accessible in various cancer stage calculator applications available on phones and desktops. A quick search for "AJCC Staging" in the App Store will return numerous applications which are easy to use and can be very helpful. Additional information regarding the changes in the most recent AJCC breast cancer staging can be found in the article by Giuliano et al., "Breast Cancer-Major changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual" [2•].

Conclusion

In summary, the eighth edition of AJCC breast cancer staging incorporates anatomic and prognostic factors to provide more accurate estimates of tumor recurrence and mortality. Although work toward including tumor biologic factors started a few decades ago, strong evidence was missing. The molecular profiling and genomic assays providing risk of recurrence added substantial new information about breast cancer treatment and likely response to therapy. The growing body of evidence allowed to confidently include the prognostic factors into the staging system. The new system can be used worldwide even in places which do not have access to the newest technology. The addition of biologic factors provides a prognostic stage that is more predictive for the outcomes based on the treatment received. The new breast cancer staging, which may appear daunting at first, can be simplified tremendously by the use of online cancer staging calculators and various phone applications available in the App Store.

Compliance with Ethical Standards

Conflict of Interest The author declares that there are no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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