**Original Investigation**

**Personalizing Breast Cancer Staging by the Inclusion of ER, PR, and HER2**

Sanjay P. Bagaria, MD; Partha S. Ray, MD; Myung-Shin Sim, MS, DrPH; Xing Ye, MS; Jaime M. Shamonki, MD; Xiaojiang Cui, PhD; Armando E. Giuliano, MD

**IMPORTANCE** Nonanatomic factors, such as histologic grade and biomarkers, can guide breast cancer management but are not included in the current TNM staging system.

**OBJECTIVE** To use as an example the triple-negative phenotype (TNP) defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) to examine whether such inclusion improves the prognostic accuracy of TNM staging for breast cancer.

**DESIGN, SETTING, AND PARTICIPANTS** Women diagnosed with primary invasive ductal breast cancer from January 1, 1991, through December 31, 2008, were identified from a prospective institutional database. Excluded were patients who received neoadjuvant therapy, those whose staging information was incomplete, or those whose tumor lacked ER, PR, and HER2 data. Breast cancers were categorized by TNM stage and by the presence or absence of TNP.

**MAIN OUTCOMES AND MEASURES** Overall survival at 5 years.

**RESULTS** Database review identified 1842 consecutive eligible patients with breast cancer. When patients were stratified by TNM stage, overall survival curves for those with TNP breast cancer matched those for patients whose non-TNP breast cancer was 1 TNM stage higher. Multivariable analysis showed that TNP status was a powerful prognostic variable, and the likelihood ratio test revealed that the prognostic accuracy of the TNM staging system that incorporated TNP was superior to the current TNM staging system (P < .001). A TNM staging system that incorporated TNP reduced early-stage compression by 15%.

**CONCLUSIONS AND RELEVANCE** The internationally recognized and easily reproducible examination of ER, PR, and HER2 status exemplifies how nonanatomic factors can improve the prognostic accuracy of breast cancer staging.

Published online December 4, 2013.

Anatomic factors are the cornerstone for American Joint Committee on Cancer (AJCC) staging of breast cancer.¹ Tumor size (T), regional nodal involvement (N), and distant metastases (M) are prognostic factors used to represent the anatomic extent of disease and to partition patients with cancer into stages with comparable outcomes. The AJCC's TNM staging system affords clinicians a common language to discuss the prognosis of patients with newly diagnosed breast cancer and provides a framework for reporting and comparing treatment outcomes.

As our understanding of breast cancer has improved during the past half century, the pendulum has swung from the radical mastectomy to breast-conserving therapy and personalized systemic therapy based largely on prognostic and predictive biologic factors expressed by the primary tumor. Many of these changes are reflected by revisions in the AJCC's TNM staging criteria. However, the current TNM staging system still is based strictly on anatomic factors; it does not consider the prognostic impact of tumor biology.

The relevance of the TNM staging of breast cancer in the era of biomarkers, genomic analysis, and personalized medicine is becoming increasingly limited. The emergence of tumor biology as an essential component to breast cancer care has allowed clinicians to understand why patients who are staged similarly using the TNM staging system have significantly different outcomes based on tumor biology. Nonanatomic factors, such as histologic grade, lymphovascular invasion, and biomarkers, have become vital in identifying patients whose cancer has an aggressive tumor biology and may not respond well to adjuvant systemic agents.
The AJCC's Breast Cancer Task Force acknowledged the importance of tumor biology and strongly considered adding a “B” category (for biology) to TNM staging. But the Breast Cancer Task Force decided that its inclusion in the TNM system was not feasible. Histologic tumor grade has been shown to have prognostic value, but its reproducibility was questioned and was therefore excluded from TNM staging. The task force also reasoned that multigene expression assays are complex and expensive and that their inclusion into TNM staging would be difficult because lower-income countries may not have the resources to perform such assays and therefore would be unable to use such a proposed B-TNM staging system.

We hypothesized that biologic features would have a significant effect on TNM staging outcome. We added the internationally used biomarker profile for the triple-negative phenotype (TNP) to the TNM staging system to examine the effect of a B category on TNM accuracy. Triple-negative phenotype breast cancers are a prognostically distinct subgroup identified by negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). We recognize that many nonanatomic factors play a role in breast cancer prognosis, such as histologic grade, lymphovascular invasion, and multigene assays. However, we decided to study the inclusion of TNP status because (1) immunohistochemical examination of tumors for expression of ER, PR, and HER2 is simple and performed nearly worldwide; (2) assessment of TNP status is inexpensive and routinely performed and therefore would not incur additional cost; and (3) the inclusion of TNP status would not complicate the current AJCC TNM staging system.

Methods

This study identified women from the John Wayne Cancer Institute database who underwent treatment for primary invasive ductal breast cancer between January 1, 1991, and December 31, 2008. All cancers were staged according to the seventh edition of the AJCC staging manual. Exclusion criteria included receipt of neoadjuvant therapy, incomplete staging data, and incomplete ER, PR, and HER2 data. Lobular carcinomas were not included because of the low likelihood of TNP. Clinical management was at the discretion of the patient and the physician. Most patients diagnosed with TNP were treated with systemic adjuvant chemotherapy due to a lack of effective targeted therapies. The study was performed with institutional review board approval from the John Wayne Cancer Institute.

A board-certified, specialty-trained breast pathologist (J.M.S.), who remained masked to the clinical data, reviewed immunohistochemical (ER, PR, and HER2) slides from randomly selected study cohort patients. Approximately 20% of all slides were randomly reviewed to ensure that ER, PR, and HER2 status was consistent for the entire study cohort. This internal quality control measure found no change in the biomarker profile in the 360 sets of slides evaluated. Immunohistochemical staining was scored using criteria from published guidelines. The American Society of Clinical Oncology/College of American Pathologists revised immunohistochemical testing guidelines for ER and PR in 2010 and recommended that ER and PR assays be considered positive if immunostaining was seen in more than 1% of tumor nuclei. Since this study was conducted between 1991 and 2008, ER and PR status was considered positive if immunostaining was seen in more than 5% of tumor nuclei. Because ER- and PR-positive status defined as 1% to 5% ER and/or PR positivity by immunohistochemistry is rare, the revision is unlikely to have affected our results significantly. HER2 status was considered positive if immunostaining was scored as 3+ according to HercepTest (Dako) criteria. For an equivocal result (2+), HER2 status was considered positive if the fluorescent in situ hybridization assay revealed an HER2 to chromosome 17 amplification ratio of 2.2 or higher. Triple-negative phenotype status was defined by negative expression of ER, PR, and HER2.

All statistical analyses were performed using SAS (version 9.1.3; SAS). Categorical variables were analyzed using the χ² test, and continuous variables were analyzed using the t test. Overall survival (OS) was the primary outcome. Survival time was calculated from the date of diagnosis until the date of death. Univariate survival curves were generated by the Kaplan-Meier method, and significance was determined using the log-rank test. Multivariable analysis was performed using the Cox proportional hazards regression analysis. Multivariable models were constructed to evaluate the prognostic significance of TNM and B-TNM. The 2 nested multivariable models were compared using the likelihood ratio test. All tests were 2-sided, and P < .05 was considered statistically significant.

Results

Of 1972 patients with primary invasive ductal breast cancer, 130 were excluded from analyses because 118 had incomplete staging information and 12 received neoadjuvant therapy (Figure 1). All cancers had biomarker (ER, PR, and HER2) expression information available. Of the remaining 1842 patients, 280 (15.2%) were diagnosed with TNP breast cancer (Table 1). There was no statistically significant difference in age at diagnosis between patients with TNP and non-TNP. Patients with TNP were less likely to have stage I disease.

Figure 2 plots the survival curves of 1842 patients stratified by stage and TNP status. Median follow-up was 4.3 years (range, 0-17.5 years). The survival curves for patients with TNP diminished to a level similar to that for patients with non-TNP at the next higher stage. That is, the 5-year OS for stage I TNP was similar to stage II non-TNP (92.2% vs 93.4%; P = .63). The 5-year OS for stage II TNP was similar to stage III non-TNP (83.9% vs 78.5%; P = .57). The 5-year OS for stage III TNP approached stage IV non-TNP (58.4% vs 34.6%; P = .76). The 5-year OS for stage IV TNP was 14.3%.

We then investigated the prognostic accuracy of a proposed B-TNM staging system that considers the presence of TNP as an upstaging biologic factor. For example, in the B-TNM system, a TNM stage I TNP breast cancer would be upstaged to stage II, a TNM stage II TNP breast cancer would be upstaged to stage III, and a TNM stage III TNP breast cancer would be upstaged to stage IV. A patient diagnosed with a stage IV TNP breast can-
would be considered to have stage IV disease in the B-TNM system. Table 2 shows the distribution of patients stratified by stage for TNM and B-TNM staging systems. Approximately 15% of the patients in the original TNM staging system migrated to a higher stage in the proposed B-TNM staging system. Bowker’s test of symmetry demonstrated that the B-TNM staging system significantly decompresses the number of patients with early-stage breast cancer (P < .001).

Multivariable models were then created for the TNM and B-TNM staging systems (Table 3). Age, T, N, and M were significant independent predictors for 5-year OS determined by the TNM staging system. Age, T, N, M, and B, as defined by TNP status, were significant independent predictors for 5-year OS determined by the B-TNM staging system. The likelihood ratio test revealed that the B-TNM staging system model significantly improved prediction of 5-year OS compared with the TNM staging system model (P < .001). The results did not significantly change when age was excluded from the multivariable analyses.

Discussion

The TNM staging system has been essential to the practice of solid tumor oncology for more than half a century and remains the most important tool in determining prognosis and standardizing treatment. The success of TNM staging depends on its ability to adapt to changes in oncologic care. During the past 3 decades, clinicians have witnessed the effect of nonanatomic factors, such as biomarkers, on breast cancer care. Despite their widespread use and clinical relevance, the AJCC has yet to incorporate biomarker status into the TNM breast cancer staging system. It relies on tumor burden to provide prognosis but does not consider the impact of tumor biology. The current breast cancer staging system is

Table 1. TNM Stage and TNP Status of Breast Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 1842)</th>
<th>TNP (n = 280)</th>
<th>Non-TNP (n = 1562)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.6 (14.1)</td>
<td>57.2 (15.3)</td>
<td>58.9 (13.9)</td>
<td>.06</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>942 (51.1)</td>
<td>121 (43.2)</td>
<td>821 (52.6)</td>
<td>.01</td>
</tr>
<tr>
<td>II</td>
<td>662 (35.9)</td>
<td>110 (39.3)</td>
<td>552 (35.3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>199 (10.8)</td>
<td>42 (15.0)</td>
<td>157 (10.1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>39 (2.1)</td>
<td>7 (2.5)</td>
<td>32 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TNP, triple-negative phenotype.

a Values are presented as number (percentage) unless otherwise indicated.

b TNP vs non-TNP.

The survival curves for patients with triple-negative phenotype (TNP) overlapped with the survival curves for patients with non-TNP of the next higher stage.
less than adequate in the era of personalized care, where tumor burden and biology are equally considered.

In the present study, we show that incorporating a biomarker profile in the TNM staging system improves the prognostic accuracy of breast cancer staging. The biomarker profile was defined solely by the lack of expression of ER, PR, and HER2—the so-called triple-negative breast cancers. Triple-negative phenotype status is a nonanatomic factor that serves to complement the anatomic grouping of the TNM staging system by upstaging cancers to the next stage. Stage is first determined by TNM, and the addition of TNP status determines the final stage. The results are not surprising. Triple-negative phenotype breast cancers account for 15% to 20% of all breast cancers and are associated with a poor prognosis.2,9 These patients are often younger, more likely to be of African descent, and more likely to harbor BRCA1 mutations.2,9-11 Studies have suggested that patients with TNP breast cancer have worse survival compared with patients with other biologic subtypes when controlled for anatomic factors.12-15 Effective therapy for TNP breast cancer remains elusive and is the subject of multiple clinical trials.

Multiple multigene expression assays provide valuable biologic information.14-17 However, they are complex and expensive. A major challenge for incorporating biomarkers into breast cancer staging is that not all countries have the resources to do so. The Breast Cancer Task Force was concerned that the inclusion of biomarkers could be costly and therefore prevent clinicians from low- and middle-income countries from adopting a biologic factor into their practice.1 We elected to study ER, PR, and HER2 because they are relatively inexpensive and readily available to clinicians worldwide. Low- and middle-income countries are more likely to adopt a B category if it involves standard immunohistochemistry as opposed to complex gene assays. The adoption of a B category defined by TNP status would not incur additional cost. Recent studies have shown that low- and middle-income countries do assess ER, PR, and HER2.20-21 It is hoped that efforts to implement standardized breast pathologic procedures in low- and middle-income countries, such as the guidelines developed by the Breast Health Global Initiative, will allow clinicians from low- and middle-income countries to adopt biomarkers into their practice.22

Other investigators have also proposed the inclusion of biomarkers into the AJCC breast cancer staging system.23-26 Verosini et al26 proposed a system that incorporates ER, PR, and HER2 status but did not test the proposal. Yi et al24 proposed a system that assigns values to pathologic stage, histologic grade, and ER status; calculates an overall staging score; and then stratifies patients. Although histologic grade has been shown to have prognostic significance, the Breast Cancer Task Force raised concerns regarding the inconsistency in grading and the prognostic significance of grade 2 in relation to grades 1 and 3 and, therefore, did not believe histologic grade merited inclusion in TNM breast cancer staging.7 We recognize that many important factors affect the prognosis of a patient with breast cancer. But we propose a system that includes TNP status to avoid the subjectivity of histologic grade and the expense of multigene assays, thereby taking advantage of the objectivity and inexpensive cost of determining TNP status worldwide.

This study provides 3 empirical arguments for including a biomarker profile, such as TNP status, into the staging system. First, Figure 2 illustrates that the incorporation of TNP status can better partition patients into cohorts with similar survival outcomes. In each instance, the survival for patients with TNP remarkably decreased to that of patients with non-TNP of the next higher stage. Second, stage compression is a factor known to reduce the accuracy of a cancer staging system.27 The proposed B-TNM staging system reduces early-stage compression by shifting 15% of all patients to later stages and, as a result, improves the predictive accuracy of the breast cancer stag-

---

### Table 2. Distribution of Patients According to the Current TNM and the Proposed B-TNM Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>B-TNM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>942 (51.1)</td>
<td>821 (44.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>II</td>
<td>662 (35.9)</td>
<td>673 (36.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>199 (10.8)</td>
<td>267 (14.5)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>39 (2.1)</td>
<td>81 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Models for the TNM Staging System and B-TNM Staging System for 5-Year Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>TNM</th>
<th>B-TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>χ²</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>60.0</td>
</tr>
<tr>
<td>T</td>
<td>1</td>
<td>17.7</td>
</tr>
<tr>
<td>N</td>
<td>1</td>
<td>13.4</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>23.8</td>
</tr>
<tr>
<td>B (TNP vs non-TNP)</td>
<td>1</td>
<td>26.5</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

* Likelihood ratio test compared the models and demonstrated that B-TNM performs better than TNM in predicting 5-year overall survival (P < .001).
ing system. And third, multivariable analysis showed that the B category defined by TNP status was a significant prognostic indicator. Comparison of multivariable models of TNM and B-TNM demonstrated that the B-TNM staging system is superior to the TNM staging system in predicting survival.

The incorporation of nonanatomic factors into the TNM staging system is not without precedent. Examples include grade for sarcoma, mitotic rate for gastrointestinal stromal tumors, Gleason score for prostate cancer, and lactate dehydrogenase level for melanoma. Each of these nonanatomic factors was considered to have a significant prognostic value that overrode concerns of additional complexity. The incorporation of TNP status into breast cancer staging is feasible and may need similar consideration.

In the era of personalized medicine, the challenge to the medical community will be to take results from commonly measured nonanatomic factors and incorporate some aspects of a B category into the TNM staging system. TNM staging must reflect modern medicine while maintaining a connection with the past. To sustain a link with the past by ignoring tumor biology, TNM staging is in jeopardy of becoming obsolete in the 21st century, where an experienced clinician is more likely to relate to a colleague that a patient has a poorly differentiated triple-negative or HER2-positive breast cancer than he or she is to indicate that the same patient has stage II disease. Stage reclassification that incorporates TNP status can be a first step in recognizing the importance of nonanatomic factors in the staging of breast cancer and could help clinicians provide better cancer care. This study provides a preliminary proof of principle that the breast cancer staging system could be improved by the inclusion of biomarkers that complement TNM and are available worldwide.

ARTICLE INFORMATION
Accepted for Publication: April 18, 2013.

Author Contributions: Drs Bagaria and Giuliano had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bagaria, Ray, Sim, Cui, Giuliano.

Acquisition of data: Bagaria, Ray, Shamonki.

Analysis and interpretation of data: Bagaria, Ray, Sim, Ye, Shamonki, Giuliano.

Drafting of the manuscript: Bagaria, Ray, Ye, Cui, Giuliano.

Critical revision of the manuscript for important intellectual content: Bagaria, Ray, Sim, Shamonki, Giuliano.

Statistical analysis: Bagaria, Ray, Sim, Ye.

Obtained funding: Ray, Cui, Giuliano.

Administrative, technical, and material support: Ray, Shamonki, Cui.

Study supervision: Ray, Giuliano.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Drs Bagaria and Ray contributed equally to this work.

REFERENCES