Staging of Breast Cancer in the Neoadjuvant Setting

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Abstract

The use of neoadjuvant chemotherapy has become more prevalent in the treatment of breast cancer patients. The finding of a pathologic complete response to neoadjuvant chemotherapy (no evidence of residual invasive cancer in the breast and lymph nodes at the time of surgical resection) has been shown to correlate with improved survival. The current version of the American Joint Committee on Cancer (AJCC) staging for breast cancer has a pretreatment clinical stage designation that is determined by clinical and radiographic examination of the patient and a postoperative pathologic stage classification based on the findings in the breast and regional lymph nodes removed at surgery. Pathologic staging has not been validated for patients receiving neoadjuvant chemotherapy; thus, prognosis is determined for these patients based on the pretreatment clinical stage. We hypothesized that clinical and pathologic staging variables could be combined with biological tumor markers to provide a novel means of determining prognosis for patients treated with neoadjuvant chemotherapy. Two scoring systems, based on summing binary indicators for clinical and pathologic substages, negative estrogen receptor status, and grade 3 tumor pathology, were devised to predict 5-year patient outcomes. These scoring systems facilitated separation of the study population into more refined subgroups by outcome than the current AJCC staging system for breast cancer, and provide a novel means for evaluating prognosis after neoadjuvant therapy. [Cancer Res 2008;68(16):6477–81]

Background

Cancer staging systems provide both physicians and patients with a mechanism for placing disease into a specific context to aid in treatment planning and determining prognosis. Staging also allows for an ease of communication among treating physicians across multiple disciplines as patients undergo the multimodal management of disease. The significance of staging for patients tends to be an individual experience. Oncologists relay staging information to their patients to prepare them for the appropriate recommended treatments and to communicate directly about outcomes. This allows patients to plan and manage their personal and professional lives while undergoing what is often a complex and long period of treatment. Recent work has shown the importance of clear and open communication between oncologists and cancer patients (1, 2). Mack and colleagues (1) have found that although physicians may withhold prognostic information in an attempt to maintain patient optimism, conversely, overt discussion of outcomes, favorable or unfavorable, was more effective in sustaining patient morale. Furthermore, patients with an accurate understanding of prognosis can more appropriately process future quality of life expectations. If such information is withheld, this possibility may be lost (1). When oncologists respond to patient concerns with statements that facilitate the further discussion of these concerns, patients show decreased anxiety and depression and improved satisfaction and compliance (2). These findings show the significance of staging for patients with cancer. This is of increased importance in the neoadjuvant setting where clinical and pathologic response rates are known to provide additional prognostic information for breast cancer patients treated with chemotherapy before surgical intervention.

The implementation of staging as a routine part of patient assessment has also had a great effect on the management of cancer. There are now standard treatment guidelines published by the National Comprehensive Cancer Network that are based on individual stage designations. Traditionally, breast cancer has been staged using the tumor-node-metastasis, or TNM, system, revised most recently by the American Joint Committee on Cancer (AJCC) in 2003 (3). The TNM status is determined for each individual patient and corresponds to a specific stage grouping, which is then correlated to prognosis and a treatment plan. Breast cancer patients receive a clinical stage at initial diagnosis, before any surgical intervention, determined by physical examination, radiologic studies, and biopsy findings. The definitive breast cancer stage is based on pathologic information obtained at the time of surgical removal of the primary tumor and regional lymph nodes. A pathologist analyses the tissue to precisely establish the tumor size and extent of lymph node involvement. Tumors are graded as low grade (favorable), intermediate grade, or high grade (unfavorable), to provide a microanatomic perspective on the disease, using tissue and cellular phenotype as markers for cancer aggressiveness.

Multiple other variables can be determined from evaluation of the primary tumor including evidence of invasion into blood vessels or lymphatics, evidence of overexpression or amplification of oncogenes, deletion of tumor suppressor genes, proliferation status, and DNA ploidy. Biological markers that are routinely assessed in breast cancer specimens in pathology laboratories include estrogen (ER) and progesterone (PR) receptor expression, and HER-2/neu status. These markers can be assessed by several different techniques including immunohistochemical analysis and fluorescence in situ hybridization. Although there are several concerns regarding the lack of formal, standardized processing protocols for many of the biological markers currently being used.

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then better guide additional treatment decisions, particularly as precise prognostic information would be revealed, which could help create two novel staging models. The expectation was that by patients who received neoadjuvant treatment were identified to at The University of Texas M.D. Anderson Cancer Center, 932 collected clinical and pathologic information from patients treated biological tumor markers (14). Using a database of prospectively overall prognosis, we have proposed new models for staging that disease (12, 13).

response through precise measurement of the residual burden of resection, and more recently by the assessment of pathologic system using final pathologic data obtained at the time of surgical application of the 2003 AJCC breast cancer pathologic staging neoadjuvant chemotherapy was shown to be determined best by (5, 6, 10–12). Up to this point, prognosis for patients treated with neoadjuvant therapy. These biological factors are also important predictors of response to neoadjuvant chemotherapy. The combination of clinical, pathologic, and biological factors resulting in a unifying CPS-EG score provided additional predictive value, and allowed for further expansion of the scoring system to 7 distinct 5-year DMFS and DSS subgroups. For the study cohort, 5-year DSS for AJCC clinical stages ranged from 67% to 98% and, for pathologic stages, ranged from 61% to 96%. Implementation of the CPS scoring system increased this 5-year DSS range from 48% to 99%, which was further improved with the CPS-EG scoring system, to a DSS range of 22% to 100%. Thus, we improved upon the prognostic value of the AJCC clinical or pathologic stage alone by combining clinical, pathologic, and biological factors resulting in a unifying CPS-EG system for the determination of patient outcomes. An example of this improved prognostic stratification was shown by application of the CPS-EG system to patients who were designated as pathologic AJCC stage IIA (n = 251) in the study population, predicted to have a 5-year DSS of 90% [95% confidence interval (95% CI), 85–93]. Through application of the CPS-EG scoring system to this stage IIA population, 5 prognostic groups were determined having the after DSS outcomes: score 1, 100%; score 2, 98%; score 3, 86%; score 4, 85%; and score 5, 64% (Fig. 1).

Impact

The scoring systems proposed in this study move beyond the traditional AJCC staging system to incorporate biological factors that can further aide in determining the prognosis of patients treated with neoadjuvant therapy. These biological factors are also important predictors of response to neoadjuvant chemotherapy. These scoring systems represent a novel means for using both pretreatment and posttreatment patient data to determine the effect of neoadjuvant chemotherapy on patient outcomes. The information obtained from the scoring systems has the capacity to provide patients and physicians with more precise information routinely in the clinic, much of the literature on these markers is consistent with the expected associated patient outcomes. The anticipation is that as more biological markers are characterized in terms of their prognostic or predictive abilities, they will be incorporated into the standard pathologic assessment and, thus, help facilitate a more refined molecular staging of disease.

Until recently, the majority of patients with breast cancer were treated with surgery first followed by chemotherapy, hormonal therapy, and radiation therapy as indicated by the pathologic findings. With this treatment paradigm, patients would typically receive a clinical stage shortly before obtaining a more definitive pathologic stage. Neoadjuvant therapy, or chemotherapy treatment preceding surgical removal of the tumor and lymph nodes, has been the standard treatment plan for patients with more advanced or inoperable breast cancers. Recently, the indications for neoadjuvant therapy have expanded to include patients with operable and early stage disease (4, 5). This neoadjuvant approach is based on the finding that most breast tumors will decrease in size by at least 50% when exposed to 3 to 4 cycles of cytotoxic chemotherapy, thus permitting breast conserving surgery over mastectomy. Another potential benefit of neoadjuvant therapy is the ability to assess primary tumor response to the individual treatment, with the notion that agents could be adjusted depending on response (6). Although current evidence from randomized neoadjuvant trials does not support changing agents for patients with stable disease, patients who show disease progression should be considered for surgical treatment, radiation therapy, or management with a different systemic agent (7–9).

The broader use of neoadjuvant therapy has created a more complex scenario for breast cancer staging, as patients may present with an advanced clinical stage, and could have a much more favorable pathologic stage after the completion of neoadjuvant treatment and surgery. It is unclear whether the initial clinical stage or the final pathologic stage is more meaningful in terms of prognosis and further treatment decisions. Additionally, there is no current methodology for incorporating the information on clinical and pathologic response to the chemotherapy into the stage grouping. Because patients who experience a complete resolution of invasive disease in the breast and axilla, termed as a pathologic complete response (pCR), have more favorable outcomes, it would be useful to combine this information with the initial clinical stage (5, 6, 10–12). Up to this point, prognosis for patients treated with neoadjuvant chemotherapy was shown to be determined best by application of the 2003 AJCC breast cancer pathologic staging system using final pathologic data obtained at the time of surgical resection, and more recently by the assessment of pathologic response through precise measurement of the residual burden of disease (12, 13).

To help address the gap in knowledge regarding the effect of pretreatment clinical stage and posttreatment pathologic stage on overall prognosis, we have proposed new models for staging that incorporate clinical and pathologic substages as well as data on biological tumor markers (14). Using a database of prospectively collected clinical and pathologic information from patients treated at The University of Texas M. D. Anderson Cancer Center, 932 patients who received neoadjuvant treatment were identified to help create two novel staging models. The expectation was that by combining clinical, pathologic, and biological markers, more precise prognostic information would be revealed, which could then better guide additional treatment decisions, particularly as new therapeutic agents become available.

Results

We developed two systems to estimate the prognosis of patients treated with neoadjuvant chemotherapy. A Cox proportional hazards model with backward stepwise exclusion of factors, using a criterion of a P value of <0.05 for retention of factors in the model, was used to create the Clinical-Pathologic Scoring System (CPS) from all clinical and pathologic substages. Model performance was quantified using Harrell’s concordance index. After defining the CPS system, a second Cox proportional hazards model, with backward stepwise exclusion of factors and stratified on CPS, was used to test the added significance of ER and PR status, nuclear grade, HER-2/neu status, presence of lymphovascular space invasion, patient age at presentation, and chemotherapy cycle number (3 versus ≥4 cycles). The first model, the CPS system, used clinical stage greater than or equal to stage IIB or IIB and pathologic stage greater than or equal to stage pIIA or pIIIC to predict distant metastasis-free survival (DMFS) and disease-specific survival (DSS). Further analysis revealed that ER-negative disease and nuclear grade 3 tumor pathology were independent risk factors for poor prognosis. These variables were then added to the CPS system to create a second scoring system, the CPS-EG system. Points were assigned according to each presenting clinical stage, final (postneoadjuvant chemotherapy) pathologic stage, and the biological markers. By adding up the points, an overall CPS or CPS-EG score was determined (Table 1).

Through the CPS scoring system, patients were stratified into 5 groups with scores of 0 to 4. Increasing CPS scores were associated with decreasing 5-year DMFS and DSS. The addition of ER status and nuclear grade in the CPS-EG score provided additional predictive value, and allowed for further expansion of the scoring system to 7 distinct 5-year DMFS and DSS subgroups. For the study cohort, 5-year DSS for AJCC clinical stages ranged from 67% to 98% and, for pathologic stages, ranged from 61% to 96%. Implementation of the CPS scoring system increased this 5-year DSS range from 48% to 99%, which was further improved with the CPS-EG scoring system, to a DSS range of 22% to 100%. Thus, we improved upon the prognostic value of the AJCC clinical or pathologic stage alone by combining clinical, pathologic, and biological factors resulting in a unifying CPS-EG system for the determination of patient outcomes. An example of this improved prognostic stratification was shown by application of the CPS-EG system to patients who were designated as pathologic AJCC stage IIA (n = 251) in the study population, predicted to have a 5-year DSS of 90% [95% confidence interval (95% CI), 85–93]. Through application of the CPS-EG scoring system to this stage IIA population, 5 prognostic groups were determined having the after DSS outcomes: score 1, 100%; score 2, 98%; score 3, 86%; score 4, 85%; and score 5, 64% (Fig. 1).
regarding prognosis. More refined prognostic information may help facilitate improved decision making regarding postoperative treatment strategies and, therefore, have the potential to affect quality of life for patients with breast cancer. This risk-stratification is important because there are currently no treatment guidelines for determining the need for additional therapies in patients who receive neoadjuvant chemotherapy.

Previous efforts to examine the predictive value of tumor response to neoadjuvant therapy focused primarily on the relationship between achieving a pCR and a corresponding superior overall survival. Whereas patients who experienced a pCR generally had improved outcomes, patients with a partial response to treatment can also have improved survival beyond what their initial clinical stage would indicate (10). Through the implementation of the CPS-EG system, patients who experienced a pCR are further risk stratified. Patients presenting with early stage disease (stage I or IIA) without associated adverse biological markers were found to have the most favorable prognosis. Overall, the more advanced the presenting stage, the worse the projected outcomes were despite attainment of a pCR. This was also true for patients who had achieved less than a pCR upon final pathology review. Outcomes for these patients were further negatively influenced if the patients presented with adverse biological markers. Our data therefore show that all patients who achieve a pCR are not the same biologically and cannot be expected to have similar outcomes. Additionally, our findings emphasize the weighted significance of presenting clinical stage on DMFS and DSS, implying that patient outcomes are largely determined by the primary biology of disease, despite currently available therapeutic interventions. This finding may be explained, in part, by the persistence of resistant cancer stem cells in those patients who present with more advanced disease (15, 16). The presence of these resistant cells may account for the greater likelihood of relapse and death in patient subgroups who initially responded favorably to neoadjuvant treatment.

Breast cancer cells with a high nuclear grade and low or negative hormone receptor expression are typically associated with more aggressive disease. The loss of normal cell-cell interactions, high mitotic count, nuclear pleomorphism, and loss of normal hormone receptor expression have also been associated with cell cycle abnormalities, including overexpression of cyclins and down-regulation of cyclin-dependent kinase inhibitors (17, 18). Thus, due to their more rapid cellular turn-over, high-grade, ER-negative breast cancers are more likely to respond to chemotherapeutic treatment with a decrease in tumor size, and are more likely to achieve a pCR (10, 19–23). Nevertheless,

### Table 1. Worksheet for implementation of the CPS and CPS-EG systems with associated 5-y outcomes

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Score</th>
<th>Pathologic stage</th>
<th>Score</th>
<th>Tumor Marker</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>0</td>
<td>Stage 0</td>
<td>0</td>
<td>ER Negative</td>
<td>1</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>0</td>
<td>Stage I</td>
<td>0</td>
<td>Nuclear Grade 3</td>
<td>1</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>1</td>
<td>Stage IIA</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>1</td>
<td>Stage IIB</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>2</td>
<td>Stage IIIA</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIIC</td>
<td>2</td>
<td>Stage IIIB</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CPS total score** 5- y DMFS (%) 95% CI  
0 97 93–99 0 98 88–100  
1 87 82–91 1 94 88–97  
2 72 66–77 2 87 82–91  
3 62 53–70 3 79 72–84  
4 46 26–64 4 63 54–70  
5 53 48–68 5 43 29–56  
6 57 3–20 6 22 3–51  

<table>
<thead>
<tr>
<th>CPS total score</th>
<th>5- y DSS (%) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99 96–100</td>
</tr>
<tr>
<td>1</td>
<td>93 89–96</td>
</tr>
<tr>
<td>2</td>
<td>83 78–88</td>
</tr>
<tr>
<td>3</td>
<td>76 68–83</td>
</tr>
<tr>
<td>4</td>
<td>48 27–67</td>
</tr>
</tbody>
</table>

**CPS total score** 5- y DSS (%) 95% CI  
0 99 96–100 0 100  
1 93 89–96 1 98 94–100  
2 83 78–88 2 96 91–98  
3 76 68–83 3 88 83–92  
4 48 27–67 4 72 64–79  
5 53 42–70 5 57 42–70  
6 57 3–20 6 22 3–51  

NOTE: Based on the need to better address the prognostic determination for patients treated with neoadjuvant therapy, two scoring systems were devised. The CPS system includes both presenting clinical substage and posttreatment pathologic substage. The CPS-EG system uses the addition of biological markers to further improve the discrimination of the CPS system. Point assignments for the CPS and CPS-EG scoring systems are found in the worksheet above. Associated 5-y DMFS and DSS levels for patients based on scores from the CPS and CPS-EG system show how clinical, pathologic, and biological variables can be easily collated to derive outcomes for patients treated with neoadjuvant therapy.
despite the attainment of a pCR, patients with ER-negative, high-grade lesions have an overall poor prognosis (19). This paradox, that the same biological markers involved in chemotherapeutic response are associated with poor outcomes, underscores the significance of new marker discovery to improve both prognostic determination and subsequent treatment strategies and trial design.

Breast cancers are routinely evaluated by stage, which reflects the macroanatomic nature of disease, and pathologic grade, which reflects the microanatomic nature of cancer. The significance of stage and grade lies in their contribution to the determination of disease prognosis and treatment. Currently, the accuracy of stage and grade is not refined, which results in subsets of patients being undertreated and overtreated, either of which may lead to unnecessary morbidity or untimely death. New methods for evaluating breast cancer are necessary to bring critical refinement to the management of this disease. The addition of a molecular staging to the traditional stage and grade designations may help to facilitate this refinement. To this end, clinical trials are currently under way to examine the utility of signature gene profile DNA microarrays as a novel means for establishing breast cancer prognosis (24). The Oncotype DX assay, which uses 21 genes to predict breast cancer recurrence in patients with early stage breast cancer, is actively being incorporated into clinical practice and clinical trials to aid in prognosis determination and to evaluate the predictive ability of the assay (25).

The data presented emphasize the significance of the initial presenting clinical stage on patient outcomes. Thus, the detection of breast cancer at its earlier stages through breast cancer screening remains important, and cannot be overemphasized. The scoring systems described in this work, for the staging of patients treated with neoadjuvant therapy, show the effect that the addition of biological markers can have on the further clarification of patient outcomes. The potential for this more refined prognostic information to alter treatment strategies is currently being explored (26). Subsequent to the prospective validation of this work, data should be forthcoming to determine if changes in postneoadjuvant, postsurgical care will positively influence patient outcomes. Nevertheless, there is currently limited data available to determine if patient outcomes will be improved through the use of additional postoperative treatments in patients who receive neoadjuvant chemotherapy. Studies are being performed implementing molecular profiling to predict response to neoadjuvant regimens (27, 28). This may also be possible for patients who have residual disease after completion of neoadjuvant therapy. To this end, a multicenter study has been under way to examine the effects of bevacizumab alone or in combination with other chemotherapies for patients with residual disease after neoadjuvant treatment (29). The expectation that

Figure 1. DSS for pathologic stage IIA patients stratified by the CPS-EG scoring system. Through application of the CPS-EG scoring system to AJCC pathologic stage IIA patients, 5 prognostic groups were determined having the following 5-y DSS outcomes: score 1, 100%; score 2, 98%; score 3, 86%; score 4, 85%; and score 5, 64%.
new targeted therapies will soon be available, and that phase I trials are ongoing, demands a mechanism for better determining which patients would be best suited for further therapy (30, 31). The proposed scoring systems attempt to provide information for this purpose.

We anticipate that the prospective accrual of patients undergoing neoadjuvant treatment will lead to validation of our findings and add strength to the outcomes data presented. Furthermore, we are optimistic that through the addition of new molecular markers to the scoring system, improvements in patient care will be facilitated. A Web site has been created which will allow clinicians in any location to access and use the neoadjuvant scoring system prognostic calculator. This Web site can be found at http://www.mdanderson.org/postchemotherapystaging. Access to this Web site should help to expedite both prospective validation and further development of the scoring systems.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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