Prognostic Outcomes and Decision-Making for Local-Regional Therapy After Neoadjuvant Chemotherapy: Pretreatment Clinical Staging or Posttreatment Pathologic Staging?

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Presurgical chemotherapy is increasingly implemented as it improves breast conservation rates and may reveal novel information about therapeutic response. However, neoadjuvant therapy raises questions about prognosis and decision making for adjuvant local-regional therapy. Current prognostic information and therapeutic treatment planning is typically based on American Joint Committee on Cancer staging information for patients treated with adjuvant therapy. This information is not readily applicable to patients treated with neoadjuvant chemotherapy, however, as neither pretreatment clinical staging data nor post-treatment pathologic data alone accurately reflect disease status. This review summarizes the implementation of a new staging system for patients receiving neoadjuvant therapy. This system combines clinical and pathologic staging factors with biologic markers to refine the prognostic assessment of patients treated with neoadjuvant therapy. Controversies related to neoadjuvant therapy and sentinel lymph node biopsy, postmastectomy radiation therapy, and breast conservation are also discussed.

Introduction

Neoadjuvant therapy is an integral part of the management of locally advanced breast cancer. In locally advanced disease, preoperative therapy often facilitates a decrease in tumor volume that makes subsequent operative treatment possible without the use of skin grafts or tissue flaps. Furthermore, axillary dissection can be more safely undertaken if bulky nodal volume is reduced before surgery. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial further investigated the role of neoadjuvant therapy in breast cancer management for patients with operable disease [1]. This trial examined the impact of neoadjuvant doxorubicin and cyclophosphamide on tumor response to therapy, outcomes, and breast conservation rates. Results of this trial showed that outcomes were the same for patients treated in either the neoadjuvant or adjuvant setting, though breast conservation rates were increased. The NSABP trial B-27 then examined whether adding docetaxel to the neoadjuvant doxorubicin and cyclophosphamide regimen led to improvement in patient outcomes [2]. This trial also revealed that neoadjuvant treatment did not affect overall patient outcomes, though the incidence of local recurrence decreased. Subsequently, it was found that patients who experienced a pathologic complete response (pCR) in the breast and axillary lymph nodes (ALN) to neoadjuvant therapy had an improved disease-free survival [3]. Additional work has also shown that neoadjuvant treatment safely resulted in higher breast-conservation rates [4,5]. Further, researchers are working to obtain new information about tumor biology that may be gained from neoadjuvant therapy. Tumor tissue can be studied before, during, and after the completion of treatment to assess for the dynamic expression of several biomarkers. This information may then be used to predict long-term response to therapy, establish new treatment plans, and identify patients who have a higher likelihood of recurrence. By applying these data and implementing therapies based on personal biomarker profiles, novel treatment regimens may also be explored.

More widespread use of neoadjuvant therapy has also created new questions regarding the best way to stage patients, determine prognosis, and plan for adjuvant

therapy. Patients treated with neoadjuvant therapy do not fit into the traditional breast cancer staging methodology. Outcomes for these patients are likely a hybrid of both presenting clinical stage and the impact that chemotherapy has had on final pathologic stage. Therefore, neither pretreatment clinical staging nor posttreatment pathologic staging may provide the best prognostic information regarding outcomes and decision-making for local-regional therapy after neoadjuvant treatment. Consequently, a combined staging system that incorporates data from both presenting clinical stage and final pathologic stage may help to provide prognostic information for patients treated in the neoadjuvant setting. A combined clinical–pathologic staging approach may also help address current controversies pertaining to sentinel lymph node biopsy (SLNB) and axillary dissection, postmastectomy radiation therapy, and breast conservation for patients treated with neoadjuvant therapy.

Response to Neoadjuvant Therapy and Staging

Several studies have examined the impact of response to chemotherapy on patient outcomes, pr imarily emphasizing the association between pCR and improved overall survival. However, the prognosis for patients who achieve less than a pCR has not been rigorously addressed. Existing prognostic data are weighted toward final pathologic assessment of the amount of posttreatment residual disease found in the breast and ALNs. Patient outcomes have also been stratified by gradations of response, whereas others have compared pCR with no pCR [1,3,6–8]. Carey et al. [9] studied the utility of the 2003 American Joint Committee on Cancer (AJCC) breast cancer staging system to determine prognosis after neoadjuvant chemotherapy and found that application of final pathology to this staging system facilitated a more precise prediction of patient outcomes compared with previously proposed methods. Symmans et al. [8] has subsequently improved on the application of AJCC pathologic staging through a residual breast cancer burden index to determine outcomes after neoadjuvant therapy, based on measurements of both the residual primary cancer and number and size of axillary nodal metastases. Use of this pathologic analysis was predictive for outcomes regarding distant relapse-free survival, independent of AJCC pathologic staging [8].

Clinical and Pathologic Staging Variables to Define Outcomes

To help address the gap in knowledge regarding the impact of pretreatment clinical stage and posttreatment pathologic stage on overall prognosis, models for staging that incorporate clinical and pathologic substages, as well as data on biologic tumor markers, have recently been proposed [10•]. Using a database of prospectively collected clinical and pathologic information from patients treated at The University of Texas M.D. Anderson Cancer Center, patients who received neoadjuvant treatment were identified to create two novel staging models. The expectation was that by combining clinical, pathologic, and biologic markers, more precise prognostic information would be revealed, which could then better guide additional local and systemic treatment decisions, particularly as new therapeutic agents become available.

Based on results of a multivariate analysis, individual point values were assigned to all presenting clinical substages and final (postchemotherapy) pathologic substages (Table 1). An overall clinical pathologic score (CPS) was then determined by summing the points correlating to the patient's clinical and pathologic stages. This point total could then be correlated with distant metastasis–free (DMF) and disease-specific survival (DSS) (Table 1). Several patient and tumor factors were then examined and estrogen receptor (ER) negativity and grade 3 tumor pathology were found to be additional independent risk factors for poor outcomes for patients in the study cohort. Accordingly, the CPS system was further refined by the assignment of points for ER negativity and grade 3 tumor pathology (EG) to create the CPS-EG score. The CPS system stratifies patients into five different prognostic groups based on DMF and DSS, whereas the CPS-EG system stratifies patient outcomes into seven different prognostic groups (Table 2). These scoring systems are the only tools currently available that consider both clinical and pathologic factors to determine outcomes, and provide more refined prognostic information for patients treated in the neoadjuvant setting than the AJCC staging system for breast cancer.

Using the CPS-EG system, additional prognostic data can be obtained for patients who experienced a pCR. Implementing the CPS-EG system, patients who presented with early-stage disease (stage I or IIA) without associated adverse biologic markers were found to have the most favorable prognosis. Overall, more advanced presenting clinical stage correlated with poorer projected outcomes; this finding included patients who had attained a pCR in response to therapy. As expected, outcomes for patients were further negatively influenced by the presence of adverse biologic markers. Thus, data obtained from the incorporation of both clinical and pathologic staging parameters, as well as biologic markers, demonstrated that all patients who achieve a pCR are not the same biologically and should not be expected to have similar outcomes. Additionally, these findings emphasize the weighted significance of presenting clinical stage and biologic markers on DMF and DSS, implying that patient outcomes are largely determined by the primary biology of disease, despite currently available therapeutic interventions.

The importance of pCR in ALNs in response to neoadjuvant chemotherapy, independent of the response of the primary tumor, has been well documented [11–16]. This finding indicates that biological differences between the primary tumor and axillary metastasis have a significant impact on outcomes following neoadjuvant chemotherapy

Table 1. Implementation of the CPS and CPS-EG systems with associated 5-year outcomes

Clinical state	Score	Pathologic stage	Score	Tumor marker	Score
Stage I	0	Stage 0	0	ER negative	1
Stage IIA	0	Stage I	0	Nuclear grade	1
Stage IIB	1	Stage IIA	1		
Stage IIIA	1	Stage IIB	1		
Stage IIIB	2	Stage IIIA	1		
Stage IIIC	2	Stage IIIB	1		
		Stage IIIC	2		
CPS total score	**5-Year DMF survival, %**	**95% CI**	**CPS + EG total score**	**5-Year DMF survival, %**	**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	43	29–56
			6	22	3–51
CPS total score	**5-Year DSS, %**	**95% CI**	**CPS + EG total score**	**5-Year 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	57	42–70
			6	22	3–51

CPS—clinical pathologic score; DMF—distant metastasis–free; DSS—disease-specific survival; EG—estrogen receptor negativity and grade 3 tumor pathology; ER—estrogen receptor.

Table 2. Local-regional treatment issues for neoadjuvant patients

Indications for postmastectomy radiation therapy
Stage III disease
T3 tumor
≥ 4 positive axillary lymph nodes
If so, consider for residual positive axillary lymph nodes after neoadjuvant therapy
Risk factors for local recurrence rate after breast conservation for neoadjuvant patients
Clinical N2-N3 disease
Lymphovascular invasion
Residual pathologic tumor size ≥ 2 cm
Residual pathologic multifocal disease

(*From* Buchholz et al. [27,29] and Chen et al. [41], with permission.)

[11]. Implementing the M.D. Anderson neoadjuvant CPS system, patients who presented with stage IIB or IIIA disease had similar projected outcomes [10•]. For patients in these groups who did not achieve a pCR or stage I final pathology, a stable or a partial response yielded outcomes that were moderately favorable, correlating to 5-year DMF and DSS of 72% and 83%, respectively. For those patients who presented with stage IIIB and IIIC disease and whose response to therapy resulted in stage II final pathology or higher, projected outcomes were significantly less favorable. These data demonstrate that whereas clearance of ALNs is important, the burden of disease at presentation and residual disease in the breast remain significant factors affecting patient prognosis. Overall, based on information obtained from the CPS and CPS-EG systems, the combined use of clinical and pathologic factors with biologic markers provides the most specific outcomes information to aid decision-making for local-regional therapy after neoadjuvant chemotherapy. Accordingly, patients with higher CPS and CPS-EG scores would likely benefit from additional therapy. A clinical tool to apply the CPS and CPS-EG systems can be found at http://www.mdanderson.org/postchemotherapystaging.

Sentinel Lymph Node Biopsy, Axillary Dissection, and Neoadjuvant Therapy

There are several questions about the appropriate timing of SLNB in the setting of neoadjuvant therapy. Two critical questions are 1) is SLNB accurate after neoadjuvant therapy and 2) would critical information be lost if SLNB were performed after chemotherapy? Comparable accuracy has been demonstrated for lymphatic mapping and SLNB whether it is performed before or after delivery of chemotherapy [17•]. However, posttreatment SLNB false-negative rates have ranged from 0% to 33% for patients treated in the neoadjuvant setting [17•,18,19]. The higher false-negative rates have been associated with larger primary tumor size and the possible fibrosis or scarring of lymphatic channels caused by chemotherapy. For patients who present with larger tumors (> 3.5 cm), the false-negative rate for postchemotherapy SLNB appears to be greater [20]. Thus, for this patient group, assessment of nodal involvement before treatment may be helpful for the most precise axillary staging and decision-making regarding the need for posttherapy axillary dissection [20]. For those patients who have smaller tumors, SLNB after chemotherapy appears to have an acceptable false-negative rate.

Some clinicians favor SLNB before neoadjuvant chemotherapy because they perceive this information may help guide a specific chemotherapy regimen or provide more accurate information for postmastectomy radiation therapy decision making. Others prefer to perform SLNB after neoadjuvant chemotherapy to possibly spare patients a second surgical procedure. Furthermore, patients may achieve a pCR in the nodal basin after therapy, and thus may have a higher chance of avoiding a completion axillary node dissection if the SLNB is negative [11,16,21]. In the NSABP B-18 study, where patients were randomly assigned to receive pre- or postoperative chemotherapy, patients in the neoadjuvant group had a lower percentage of positive nodes after treatment than those who underwent surgery first [22,23]. Several studies indicate that treatment with neoadjuvant chemotherapy resulted in eradication of nodal metastases in 22% to 30% of patients who presented with axillary nodal involvement at initial evaluation [11,16,18,24].

Are outcomes the same for patients who are initially sentinel node negative and for patients who become node negative after chemotherapy? This question is difficult to answer and critical to consider when discussing SLNB either before or after neoadjuvant treatment to obtain information for local-regional therapy. The concern is that axillary information obtained after chemotherapy may result in the undertreatment of patients who were initially node positive and who might have benefited from further local and systemic treatments compared with those patients who were node negative at the outset. Ultimately, the rationale for pretreatment SLNB is to determine the most accurate clinical staging and precise count of positive SLNs for prognostic and therapeutic decision-making. Indications for postmastectomy radiation therapy include patients with T3 tumors or four or more positive ALNs. For those patients with smaller primary tumors and fewer than four positive SLNs before chemotherapy and no additional nodal involvement found after treatment, the benefit of postmastectomy radiation therapy remains unclear. Pretreatment SLN information will not contribute much information to therapeutic decision making in these cases. Often, decisions regarding postmastectomy radiation therapy can be based on primary tumor size or the number of positive nodes found on final (postchemotherapy) pathologic assessment. Additionally, all patients who undergo breast conservation will receive radiation therapy and can have their radiation treatment plan modified to include additional fields when indicated. Ultimately, therapeutic decision-making for patients treated in the neoadjuvant setting may be facilitated through the application of the neoadjuvant CPS and CPS-EG scoring systems that account for both pre- and posttreatment patient data. The strength of these scoring systems is increased by dedicated breast radiologists who can use ultrasound-guided biopsy of the ALNs to percutaneously derive much of the same information about axillary nodal status that is revealed from a prechemotherapy SLNB. A limit to pretreatment ultrasound-guided ALN assessment, however, is a shortage of breast radiologists who can accurately perform axillary ultrasound. Without proper technique, the false-negative rate of ultrasound-guided axillary assessment can be high [20]. Ultimately, a prospective clinical trial may be helpful to address the question of SLNB timing for neoadjuvant patients.

Completion Axillary Dissection After Positive Sentinel Lymph Node Biopsy

Currently, most centers recommend that patients with documented lymph node involvement before neoadjuvant therapy, either through pretreatment SLNB or ultrasound-guided biopsy, undergo a postchemotherapy completion ALN dissection. Consequently, few studies have attempted to define unique clinicopathologic factors for non-SLN involvement in patients with a positive SLN after neoadjuvant chemotherapy. Factors predictive of any persistent nodal involvement after neoadjuvant therapy include clinical and pathologic response of the primary tumor, tumor grade, estrogen receptor status, size of the primary tumor, and patient age [11,16,24,25].

One study examining the likelihood of additional nonsentinel disease after neoadjuvant therapy found 44% of patients who had a positive SLN after neoadjuvant chemotherapy had no additional axillary nodal disease [26•]. Thus, several patients in this series were exposed to the potential morbidity of a completion axillary dissection without a significant benefit. A nomogram derived at M.D. Anderson using this patient dataset and validated at the University of Michigan, provides a tool to predict the likelihood of

positive non-SLNs in patients with positive SLNs after neoadjuvant chemotherapy: http://www.mdanderson.org/postchemoSLNnomogram [26•]. Based on multivariate analysis of several patient and tumor factors, the nomogram includes five clinicopathologic factors to assess patient risk for additional positive nonsentinel ALNs: lymphovascular invasion (LVI), method of SLN metastasis detection, multicentricity, initial nodal status, and pathologic tumor size. These markers reflect pretreatment clinical staging and posttreatment pathologic staging information, as well as tumor markers, which again underscores the superiority of using data that combine both pre- and posttreatment information to obtain the most accurate outcomes information for patients treated in the neoadjuvant setting. The data derived from this neoadjuvant M.D. Anderson nomogram should be used in conjunction with the clinical context of individual patients to aid the surgical decision-making process regarding the need for completion ALN dissection. As the morbidity of axillary dissection is often a great concern for patients, use of this nomogram helps inform clinicians and patients regarding the potential necessity of axillary dissection in the setting of positive SLNs following neoadjuvant treatment. Whereas the standard of therapy continues to be a completion axillary dissection in all patients with positive SLNs, the ultimate goal is to individualize therapy so only patients who will benefit from a treatment are subjected to the possible associated morbidity.

Postmastectomy Radiation Therapy After Neoadjuvant Therapy

Decisions regarding appropriate implementation of postmastectomy radiation therapy after neoadjuvant treatment are complex. Major concerns stem from data acquisition that will facilitate accurate decision-making and avoid under- or overtreatment of disease. Whereas postmastectomy radiation therapy may have a significant impact on local disease control, it is also associated with considerable morbidity, particularly for patients with limited reconstructive options. In the neoadjuvant setting, problems arise from the difficulty of precisely determining the primary tumor size or nodal status before treatment. As most tumors/lymph nodes have a favorable response to chemotherapy, information regarding primary disease status may be lost, making treatment decisions complicated.

Buchholz et al. [27] have noted that patients who present with locally advanced disease or residual positive axillary nodes after treatment were at higher risk for local-regional recurrence after neoadjuvant therapy and mastectomy alone. Additional work has found that patients presenting with T3 lesions, stage III disease, and more than four positive ALNs experienced a lower local recurrence rate (LRR) and improved DSS when treated with postmastectomy radiation therapy [28]. Results from the NSABP B-18 and B-27 trials have also shown a higher LRR for patients with residual positive lymph nodes after neoadjuvant therapy [2,22,23]. Thus, based on the information available, postmastectomy radiation has been recommended for patients who present with T3 lesions, stage III disease, or four or more positive ALNs, and should be considered for patients with any residual positive axillary lymph nodes after chemotherapy (Table 2) [27,29]. Furthermore, patients who present with stage III disease but have a pCR to neoadjuvant chemotherapy should also undergo postmastectomy radiation therapy, as LRR, DSS, and overall survival improved for patients who underwent this treatment [27,28,30].

In the adjuvant setting, data have shown a decrease in local recurrence and improved survival for stage II patients with one to three positive lymph nodes, (10-y LRR rates, 3% vs 13%) [31,32]. A retrospective analysis of stage II patients treated in the neoadjuvant setting who presented with T3 lesions, four or more positive nodes on final pathology, or age less than 40 had a higher incidence of LRR [33]. Those stage II patients who presented with clinical T1 or T2 lesions or who had one to three positive lymph nodes after chemotherapy were found to have a lower risk for LRR [33]. Patients younger than 35 who presented with stage IIB to stage III disease and who underwent anthracycline-based neoadjuvant chemotherapy and postmastectomy radiation therapy demonstrated improved local-regional control and overall survival compared with patients who did not receive postmastectomy radiation therapy [34]. Management questions remain for stage II patients who are found to be node negative at final pathology and for patients with one to three positive ALNs.

Several clinical and pathologic risk factors for LRR have been determined for patients treated with neoadjuvant therapy, mastectomy, and postmastectomy radiation therapy [35]. Clinical factors include presenting clinical stage, clinical T stage, ipsilateral supraclavicular nodal involvement, response to chemotherapy, and final clinical tumor size. Pathologic factors include the number of residual positive lymph nodes, fewer than 10 ALNs in dissection, multifocal/multicentric disease, LVI, extracapsular extension, skin involvement, and ER-negative disease [35]. Patients with several of these factors may be considered for additional experimental protocols beyond conventional treatment. Unresolved treatment questions regarding postmastectomy radiation therapy may also be optimally addressed by implementation of the CPS and CPS-EG systems, with which patients with higher scores may ultimately benefit most from additional radiation therapy.

Breast Conservation After Neoadjuvant Therapy–Increased Local Recurrence?

A major advantage of neoadjuvant treatment is the potential for patients to become eligible for breast conservation

who otherwise would require mastectomy. Data from the NSABP B-18 trial demonstrated that patients who became candidates for breast conservation after neoadjuvant therapy had an LRR of 15.9%, whereas patients who were breast conservation candidates at the outset of treatment had a lower LRR of 9.9% [36•,37]. Overall, there have been considerable discrepancies regarding local recurrence after breast-conserving therapy (BCT) in patients treated with neoadjuvant therapy, ranging between 10% and 20% [6,7,36•,38–40]. Based on this wide discrepancy, Chen et al. [41] developed a prognostic scoring system using four independently significant markers for local regional recurrence. Each marker was assigned one point and included both pre- and postoperative patient data: clinical N2-N3 disease, LVI, residual pathologic tumor size greater than 2 cm, and residual pathologic multifocal disease (Table 2) [41]. Huang et al. [36•] applied this scoring system to examine the LRR for patients treated with neoadjuvant therapy, either BCT or mastectomy, and radiation. Comparing LRR between patients treated with either mastectomy or BCT, for those patients who had low scores (0–1), the 10-year LRRs were not considerably different (score 0: 4% for mastectomy, 5% for BCT; score 1: 7% for mastectomy, 9% for BCT). In comparison, patients with a score of 2 had more of a difference in LRR (12% for mastectomy; 28% for BCT). Importantly, patients with scores of 3 to 4 who underwent BCT had a significantly higher LRR of 61% compared with patients who underwent mastectomy (19% for LRR) [36•]. Therefore, implementing this scoring system, patients with higher scores may be most effectively treated with mastectomy and radiation after neoadjuvant therapy. These data again point toward the importance of using pre- and posttherapy data to arrive at both prognostic information and to aid in surgical decision making subsequent to neoadjuvant therapy. Recent work from the 2005 Oxford Overview demonstrates the negative impact of local recurrence on survival and emphasizes the importance of durable local control from the outset of treatment [42]. In light of these findings, patients must be carefully selected for breast conservation after neoadjuvant therapy by considering both presenting disease stage and pathologic response to preoperative therapy [36•]. Finally, patients treated with neoadjuvant therapy for whom breast conservation is a possibility should undergo pretreatment clip placement. Oh et al. [43] have demonstrated decreased local recurrence for patients who underwent pretreatment tumor clip placement to allow for more precise tumor bed identification and optimal radiation therapy planning.

Patients With Residual Disease After Chemotherapy

There remains no clear answer regarding the best course of systemic treatment for patients who have residual disease after neoadjuvant therapy. One M.D. Anderson study included patients treated with neoadjuvant anthracycline-based therapy who were found to have more than 1 cm of residual disease. These patients were randomly allocated to receive or continue adjuvant treatment with vincristine, doxorubicin, cyclophosphamide, and prednisone, or to switch to vinblastine, methotrexate, leucovorin rescue, and fluorouracil. No significant differences were found among treatment groups, although a trend was seen favoring patients who received vinblastine [44,45]. The potential for more refined prognostic information to change and improve treatment planning is being explored [46]. Yet, limited information is available to determine if patients benefit from the use of additional postoperative systemic treatments after neoadjuvant chemotherapy. The utility of molecular profiling to predict response to neoadjuvant regimens is being examined [47,48]. Molecular profiling may also be possible for patients who have residual disease after neoadjuvant therapy. Recently, a multicenter study was designed to examine the effects of bevacizumab alone or in combination with other agents for patients with residual disease after neoadjuvant treatment [49]. The expectation that new targeted therapies will soon be available, and that phase 1 trials are ongoing, demands a mechanism for better identifying those patients who would be best suited for further therapy, local or systemic [50,51]. Currently, the use of additional (post-neoadjuvant) chemotherapy in the adjuvant setting is not recommended, regardless of residual pathologic tumor burden, unless given under the auspices of a clinical trial [44].

Conclusions

There is an ongoing trend toward less invasive surgical interventions to treat disease. Increasingly widespread use of chemotherapy before surgery may facilitate less extensive surgical resection of breast cancer. With this shift in treatment strategy comes a need for new methods of determining patient prognosis. Additionally, critical assessment of current practice patterns is required to best determine how to incorporate neoadjuvant therapy into the management of operable breast cancer. Greatest concerns involve the potential for either under- or overtreatment of disease, if accurate prognostic determinations cannot be made secondary to either the loss of crucial staging information or the inability to process newly available data regarding response to therapy. Implementation of the CPS and CPS-EG systems should help bridge the divide between pretreatment and posttreatment data and provide more precise information for prognosis and treatment planning. Thus, questions regarding the appropriate timing of SLNB, the use of postmastectomy radiation therapy, and the implementation of BCT may be best answered through a combined approach to disease staging and the outcomes of future prospective clinical trials.

Disclosure

No potential conflicts of interest relevant to this article have been reported.

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