Impact of Progression During Neoadjuvant Chemotherapy on Surgical Management of Breast Cancer

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ABSTRACT

Background. Although neoadjuvant chemotherapy (NCT) is standard therapy for locally advanced breast cancer, it remains controversial for early-stage disease due to concerns that disease progression may make breast-conservation therapy (BCT), or even operability, impossible. The goal of this study was to determine the impact of disease progression during NCT on surgical management.

Methods. We reviewed clinicopathological data on patients who received NCT for stage I–III breast cancer from 1994 to 2007. Chemotherapy regimens were anthracycline- and/or taxane-based as determined by the treating medical oncologist.

Results. Of 1,928 patients who received NCT, 1,762 (91%) had a partial or complete response, 107 (6%) had stable disease (SD), and 59 (3%) progressed (PD) while receiving at least one regimen. Of the patients with progressive disease, 40 (68%) patients underwent mastectomy, 12 (20%) underwent BCT, and 7 (12%) did not undergo surgery. In patients who underwent mastectomy, only three (8%) were BCT candidates before progression. Overall, disease progression changed the operative plan in 11 (0.5%) patients: 3 developed distant metastasis, 2 developed clinical lymphadenopathy, 3 required mastectomy instead of BCT, 2 became inoperable, and 1 required flap closure.

Conclusions. Disease progression while receiving NCT is infrequent (3%), but early identification may allow for change to other, potentially beneficial, therapeutic

interventions. Patients with breast cancer who receive NCT should be evaluated frequently for response to therapy. Overall, progression during NCT changes the surgical management in a small proportion of patients.

Neoadjuvant chemotherapy (NCT) is the standard of care for patients with locally advanced and inflammatory breast cancer, and its use in early-stage disease is becoming more common. In addition to offering in vivo assessment of breast tumor response and the potential for early control of micrometastatic disease, NCT can significantly improve surgical outcomes. Tumor downsizing can make breast conservation therapy (BCT) possible for patients who were not previously eligible and can allow for smaller resections, potentially improving cosmesis. Furthermore, NCT may eradicate subclinical nodal disease, decreasing the rate of sentinel node positivity and the need for axillary node dissection.¹ However, some have raised concerns that disease progression may make BCT or even mastectomy impossible, although there is no literature delineating the risk of losing surgical options. The goal of this study was to determine the impact of disease progression during NCT on the surgical management of patients with stage I–III breast cancer.

METHODS

Patient Population

Clinicopathological data on patients with stage I–III breast adenocarcinoma treated with NCT at a single comprehensive cancer center from 1994 to 2007 were reviewed. Patients were identified from a prospectively maintained database approved by our institutional review

board. All patients were initially staged based on physical examination, radiological findings, and pathological examination of primary tumor and regional nodal biopsy specimens. Of 3,497 patients identified, we excluded those who were male ($n = 3$), had inflammatory breast cancer ($n = 357$), had distant metastasis at initial diagnosis ($n = 7$), had nodal metastasis without an identifiable primary breast tumor ($n = 36$), or were being treated concurrently for another primary cancer ($n = 8$). Patients who underwent partial or complete excisional biopsies of the breast primary tumor before initiation of chemotherapy ($n = 226$), who discontinued systemic therapy before response could be assessed ($n = 7$), or whose systemic therapy was managed at another institution ($n = 925$) also were excluded. The remaining 1,928 patients were included in the study.

Data were collected from the database and verified through retrospective review of medical records, including clinical and radiological reports, pathology reports, and operative notes. Determination of clinical response was made based on changes in tumor size seen in radiographic assessments or clinical examinations as documented in the medical records. Disease progression was defined as any increase in tumor size or new development of lymphadenopathy or distant metastasis. Determination of response could not be fully defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria retrospectively. However, when radiologic measurements were available, we determined whether the patients had progression based on revised RECIST guidelines (version 1.1), defined as at least a 20% increase in the sum of the target lesions and an absolute increase of at least 5 mm.²

Staging and Treatment

Upon presentation, patients underwent physical examination and routine breast imaging, including bilateral mammogram and ultrasound of the affected breast and regional nodal basins. Magnetic resonance imaging was used selectively. Staging workup for distant metastasis was performed at the discretion of the treating medical oncologist. Chemotherapy consisted of anthracycline- and/or taxane-based regimens as determined by the medical oncology team. Anthracycline-based regimens usually consisted of four cycles given at 3-week intervals. Two different taxane-based regimens were used: the first regimen included four cycles of paclitaxel given at 3-week intervals and later this was changed to weekly paclitaxel for a total of 12 weeks.

Patients were evaluated at regular intervals during chemotherapy using physical examinations as well as radiographic monitoring. Treatment decisions based on this data were made by a multidisciplinary team consisting of

medical oncologists, surgical oncologists, radiation oncologists, plastic surgeons, and radiologists.

RESULTS

Of the 1,928 patients treated with NCT, 1,762 (91%) had a tumor response (minor, partial, or complete), 107 (6%) had stable disease (SD), and 59 (3%) had progressive disease (PD) while receiving at least one regimen. Clinical progression was determined by: radiographic RECIST criteria (51/70, 73%); development of distant metastasis (3/70, 4%); physical examination without radiographic interrogation (11/70, 16%); or concerning clinical changes, such as new skin involvement with radiographic assessment not reaching RECIST criteria (5/70, 7%). We have previously reported the differences in demographic features and pretreatment tumor characteristics between patients with PD and patients with SD or a tumor response finding that pre-NCT T status, AJCC stage, high Ki-67 score, ER negativity, and race correlated with progression in univariate analysis with T status, African American race, and ER status remaining as independent predictors of progression on multivariate analysis.³ In this review, we focused on the 59 patients who had tumor progression during any NCT regimen to assess the impact of PD on surgical management. Their demographic and tumor characteristics are listed in Table 1.

Response to Chemotherapy

Thirty-seven patients received a taxane-based regimen as their first NCT regimen. Eight (8/37, 22%) of these patients had tumor response to the regimen but then progressed on a subsequent anthracycline-based regimen with one developing distant metastasis on the anthracycline-based regimen. The remaining 29 (78%) patients had PD during their initial taxane-based regimen. One patient developed spine and brain metastasis, and another underwent surgery instead of further NCT. Of 27 patients who received an anthracycline-based regimen after progressing on a taxane, 7 (26%) had further PD, 4 (15%) had SD, and 16 (59%) had tumor responses while receiving anthracyclines.

Seventeen patients received an anthracycline-based regimen as their first NCT regimen. Ten (59%) patients had tumor responses to the regimen but progressed after switching to a taxane-based regimen. The remaining seven (41%) patients had progression while receiving the anthracycline-based regimen. Two of these patients did not receive further chemotherapy: one refused all further therapy, whereas the other underwent surgical management with BCT and adjuvant chemotherapy. Of the remaining five patients who were switched to a taxane-based regimen,

TABLE 1 Patient demographics

Median age (range) (years)	49 (27–75)
Menopausal status	
Pre	26 (44%)
Peri/post	33 (56%)
Race	
Caucasian	36 (61%)
African American	17 (29%)
Asian	3 (5%)
Hispanic	2 (3%)
Other	1 (2%)
Tumor characteristics	
Median tumor size (range)	4.3 (1.3–10) cm
T status	
T1	3 (5%)
T2	28 (47%)
T3	18 (31%)
T4	10 (17%)
N status	
N0	21 (36%)
N1	23 (39%)
N2	5 (8%)
N3	10 (17%)
AJCC stage	
I/II/IIA	15 (25%)
IIB/III/IIIA	26 (44%)
IIIB/IIIC	18 (31%)
Histology	
Ductal	50 (85%)
Lobular	4 (7%)
Mixed	2 (3%)
Other	3 (5%)
Nuclear grade	
I/II	16 (27%)
III	43 (73%)
HER-2 positive	9 (15%)
Hormone status	
Estrogen receptor-positive	16 (28%)
Progesterone receptor-positive	15 (27%)

two had tumor responses to taxanes, two had SD, and one had further progression.

Five patients received concurrent anthracycline and taxane chemotherapy as their first NCT regimen. One initially had SD but then had PD while receiving a regimen of paclitaxel, carboplatin, and trastuzumab. The remaining four patients had PD while receiving this combined regimen: one developed distant metastasis, one underwent surgery without receiving further chemotherapy, and two had further PD after switching to a regimen of cyclophosphamide, methotrexate, and fluorouracil (Fig. 1).

In summary, of the 59 patients who had PD at any point while undergoing NCT, 80% (45/57) progressed while receiving taxanes, whereas 44% (25/57) had progression while receiving anthracyclines. In this subset of patients, 22% (13/59) had tumor responses to their first regimen but had PD during their second regimen. Twelve percent (7/59) had SD during their first regimen but PD during their second regimen. The remaining 39 (66%) patients had PD during their first regimen. Among these 39 patients, 1 (3%) developed metastasis during the first regimen and 5 (13%) did not undergo further NCT (4 patients had surgery and 1 refused further therapy). Thirty-three patients received a second NCT regimen, which resulted in tumor responses in 18 (55%) patients, SD in 5 (15%) patients, and further PD in 10 (30%) patients (Fig. 2). Ten patients received a third regimen: eight patients responded and two progressed.

Patients who underwent NCT at our institution had frequent evaluation of tumor response using clinical examinations and radiographic monitoring. Of the 39 study patients who had PD during their first regimens, 26 (67%) were switched to other regimens before completing the planned four cycles. Additionally, in the 30 patients who had PD during their second regimen, chemotherapy was discontinued in 23 (77%) patients before completion of the regimen. Eight (14%) patients of the total study cohort received neoadjuvant radiotherapy for local control.

Among patients who underwent surgery at our institution, 23 patients were considered to have clinical progression during the last chemotherapy regimen before surgery as determined by RECIST criteria radiographically (17/23, 74%), based on physical examination (5/23, 22%), or development of distant metastasis (1/23, 4%). When the tumor size at the beginning of that regimen was compared to the surgical specimen, 65% of the patients (15/23) were found to have a pathologic tumor size larger than pre-regimen measurement.

Surgical Management

Of the 59 patients who had PD at any point during NCT, 40 (68%) underwent mastectomy, 12 (20%) underwent BCT, and 7 (12%) did not undergo surgery. Surgery was not performed in these seven patients because of development of metastasis ($n = 3$), patient refusal ($n = 1$), or inoperable disease ($n = 3$). Although it is difficult to assess operability before NCT retrospectively, one of these three patients was noted in the medical record to have inoperable disease before chemotherapy, whereas the other two were considered resectable. We evaluated pretreatment documentation for the 40 patients who underwent mastectomy to determine whether tumor progression affected the ability to offer BCT to these patients. Thirty (75%) patients were

FIG. 1 a Patients who received a taxane-based regimen as their first chemotherapy regimen. **b** Patients who received an anthracycline-based regimen as their first chemotherapy regimen

not BCT candidates before NCT, four (10%) patients remained BCT candidates after NCT but chose mastectomy, two (5%) patients were not evaluable from available data, one (3%) required mastectomy for technical reasons,

leaving three (8%) patients who were BCT candidates before NCT but were not candidates after disease progression. The patient who was converted to mastectomy for technical reasons had PD during the first regimen but had a

FIG. 2 Timing of progression on NCT

complete clinical response to the second regimen. Mastectomy was performed because the marker clip and primary tumor site could not be located at the time of attempted BCT.

Overall, disease progression changed the surgical plan in 11 of the 1,928 patients who received NCT (0.5%): 3 developed distant metastasis, 2 developed clinical lymphadenopathy, 2 required mastectomies instead of BCT, 2 became inoperable, and 1 required rotational flap for chest wall closure (Table 2).

DISCUSSION

The goal of this study was to determine the effect of disease progression during NCT on surgical management of patients with breast cancer. In this study population, PD during NCT was rare and was discovered rapidly secondary to frequent evaluation of patients. This early detection of progression allowed for discontinuation of ineffective regimens and conversion to other potentially beneficial treatments. For instance, many patients had a tumor response to the second chemotherapy regimen even after progression of the first. Also, early surgical referral preserved surgical options for patients despite local progression with <1% of the total group requiring a change in planned surgical management.

The optimal sequencing of local and systemic therapies in the multimodality care of patients with breast cancer has been examined by several groups. Multidisciplinary trials, such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial and European Organisation for Research and Treatment of Cancer Trial (EORTC) Trial 10902, established that patients who undergo NCT for

TABLE 2 Surgical management

Type of surgery	<i>N</i> = 59
Mastectomy	40 (68%)
BCT	12 (20%)
No surgery	7 (12%)
Patients who underwent mastectomy	<i>N</i> = 40
Not a BCT candidate pretherapy	30 (75%)
BCT candidate post-therapy but chose mastectomy	4 (10%)
BCT candidate before tumor progression	3 (8%)
Converted to mastectomy for technical issues	1 (3%)
Not evaluable	2 (5%)
Patients who did not undergo surgery	<i>N</i> = 7
Developed distant metastasis	3
Refused surgery	1
Became unresectable because of progression	2
Was not resectable pretreatment	1
Progression changed operative plan	<i>N</i> = 11
Developed distant metastasis	3
Developed clinical lymphadenopathy	2
Required mastectomy instead of BCT	3
Became inoperable	2
Required flap closure secondary to locally advanced disease	1

breast cancer have disease-free and overall survival rates similar to those of patients who undergo surgery first followed by adjuvant systemic therapy.⁴⁻⁷ NCT has many potential advantages, such as allowing in vivo assessment of tumor response to therapy. This has led to greater utilization of NCT as a research platform for testing the efficacy of novel therapies and discovering predictors and

pharmacodynamic markers of response. One of the greatest benefits of NCT is an increased rate of BCT, shown in multiple studies, including the NSABP B-18 trial. Whereas the rate of breast conservation was significantly higher in patients who received NCT than in those who received adjuvant therapy (67 vs. 60%; $p = 0.002$), this effect was even more dramatic in patients who presented with tumors >5.1 cm: the BCT rate was 22% in the NCT group versus only 8% in the adjuvant therapy group.⁴

Likewise, multiple groups have shown that women with locally advanced tumors receive additional benefits from NCT in addition to increased BCT rates. For instance, in one study of patients who underwent BCT, those with tumors >2 cm who received NCT had smaller resection specimens than did those who did not receive NCT (113 vs. 213 cm³; $p = 0.004$).⁸ Although the investigators in that study did not assess cosmesis, the known association between breast excision volume and cosmesis raises the possibility that NCT can positively impact cosmetic outcomes in patients with T2 breast tumors.⁹ In some studies, NCT also reduced re-excision rates with BCT.^{8,10} Furthermore, BCT can be safely performed in carefully selected patients who initially present with T4a-c disease but have tumor response to NCT.¹¹

Opponents of NCT argue that whereas some patients with breast cancer have tumor responses, tumor progression during NCT may make BCT or even operability impossible. However, there is little reported evidence regarding this issue, as the rate of tumor progression during NCT is low, limiting relevant sample sizes. In the present series, disease progression changed the surgical plan in only 11 of the 1,928 patients who received NCT, a very small proportion. However, a closer look at this small group revealed that NCT was not disadvantageous for all 11 patients. For instance, distant metastasis developed in three patients while they were receiving NCT. The neo-adjuvant approach at least had allowed these patients to receive systemic therapy at the earliest possible time point, without delays attributable to surgery. Assessing the impact of disease progression in the two patients who developed clinical lymphadenopathy is difficult. Whereas our group aggressively stages the axilla clinically using physical examinations as well as ultrasound, occult lymph node involvement is discovered through the use of sentinel lymph node evaluation requiring subsequent lymph node dissection in some patients. Determining whether disease progression affected the surgical options in the patients in our study whose disease became inoperable or required flap closure in a retrospective manner was not possible. Thus, the three patients who required mastectomy instead of BCT after disease progression are the only patients who would have been best served by first-line surgical management from a local management standpoint.

This study is limited by its retrospective nature. This represents a heterogeneous group of patients who received treatment over many years, reflecting changes in treatment algorithms that occurred during the study period. Also, determination of pretreatment BCT candidacy or even operability is difficult in a retrospective manner. Certainly, prospective studies documenting pretreatment surgical options as well as standardized chemotherapy regimens would better address this question. In addition, clinical evaluation of tumor response has limitations. Radiologic assessment of tumor size often is not precise, which may be accentuated after NCT. A previous study from our institution reported that size estimates after NCT by physical examination, ultrasonography, and mammography only moderately correlated with residual pathologic tumor size (correlation coefficients: 0.42, 0.42, and 0.41, respectively).¹² In this study, among the patients who had progression on their second regimen, only 65% were found to have a pathologic size larger than size by imaging at the beginning of the regimen. Given the limitations of radiographic-pathologic correlation, it not possible to determine whether some of these patients were inaccurately assessed to have PD.

Use of NCT for breast cancer requires thoughtful evaluation of patients, tumor characteristics, and delineation of the goals of therapy. For instance, if the goal is to increase the likelihood of successful BCT, tumor histology should be considered, because the use of NCT does not increase rates of breast conservation in patients with lobular cancers.¹³ We recently reported on predictors of progression in patients who received NCT for breast cancer.³ Some of the factors that were predictive of progression, such as high Ki-67 score, high nuclear grade, and hormone receptor negativity, also have been shown to be predictors of a complete pathological response.^{14,15} Additionally, we found that patients who were African American or presented with larger tumors were more likely to have disease progression.³ Thus, there remains a need to identify novel molecular markers predictive of disease response and, more importantly, progression during NCT that can guide clinical decisions regarding systemic therapy regimens as well as sequencing of surgery and chemotherapy. These factors, as well as patient compliance, the patient's surgical preferences, and the ability to offer close monitoring should be considered when determining a treatment plan.

Frequent evaluation of patients receiving NCT is of paramount importance. Evidence of tumor progression should prompt a change in chemotherapy regimen or expeditious referral to a surgeon. In a previous study of this same population of patients, we observed that tumor progression occurred during the first two cycles in 56% of the patients and the last two cycles in 44%.³ This is why the majority of the patients did not complete a regimen when

they started showing signs of progression. Most of the patients who had PD during the first regimen were switched to another regimen: 55% had tumor responses to the second regimen, some of whom had a dramatic, even complete, clinical response. At our institution, in the absence of an indication for surgical intervention, the NCT regimen is changed if a patient experiences tumor progression during the first regimen. However, in the present study, 30% of the patients with PD during the first regimen also had PD during the second regimen. Thus, patients who are switched to another therapy regimen should be monitored very carefully. In addition, 77% of the patients who had PD during the second regimen were switched to another therapeutic modality, usually surgery, before completion of the regimen. If tumor progression puts BCT candidacy or operability in jeopardy, patients should be immediately referred for surgical management. This requires a multidisciplinary team in constant communication with each other and the flexibility to change the modality of therapy quickly.

In summary, NCT offers many potential benefits to patients with breast cancer. Although the vast majority of patients have a response to therapy, a very small proportion experience tumor progression. With careful evaluation and the ability to change quickly the therapeutic modality, tumor progression rarely affects the surgical management of these patients. In patients in whom progression seems to put BCT or operability in jeopardy, early surgical referral is warranted.

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CONFLICT OF INTEREST None.

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