Perspective

Neoadjuvant therapy for treatment of breast cancer: the way forward, or simply a convenient option for patients?

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Abstract: The complexity of managing early stage breast cancer is well known. Optimal treatment is increasingly multidisciplinary and in the modern era informed by sophisticated molecular tools to help select and guide therapy. Major phase III trials have determined that the order of systemic therapy relative to surgery does not influence important endpoints such as event free survival and overall survival (OS), but questions remain as to how best to utilize these most essential services. For example, there is still uncertainty regarding the ideal timing, intensity, and duration of proposed therapy. For treating physicians, evidence based standardization of these practices is both possible and critically important. Optimization of care will increasingly rely on well-designed studies that have addressed the choice as well as the timing of the steps involved in multidisciplinary breast cancer treatment. Understanding when factors under the oncologist's control will influence outcome, cost and convenience is essential in the era of quality and value-based medical decision making. The timing of surgery before or after chemotherapy for breast cancer is one such factor. Investigators are to be commended for addressing these questions, which may generate additional hypotheses concerning the biology of metastasis and the nature of recurrence.

Keywords: Neoadjuvant chemotherapy; breast cancer; outcomes; time to surgery

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Breast surgery in the context of neoadjuvant chemotherapy

Conceived in the 1970's by forward thinking experts seeking to improve care for women with breast cancer, multidisciplinary breast care has revolutionized the way that breast cancer is treated today (1). Once mainly the province of expert surgeons, breast cancer treatment requires input from many specialties including diagnostic imaging, surgery, radiation oncology, medical oncology, anatomic and molecular pathology, medical genetics, oncoplastic reconstructive surgery and complementary therapy. Decision-making not only involves whether to utilize one or more of these specialty services, but how to use them and in what order. Through two landmark trials, the NSABP demonstrated that systemic chemotherapy could be administered preoperatively in a save and effective manner with one clear clinical benefit: the ability to increase the rate of breast conservation for women seeking that option (2,3). Other benefits, such as improved disease free survival (DFS) and overall survival (OS) were not seen with pre-surgical chemotherapy; however, neither did they suffer. The lessons learned were many, giving clinicians some new options in the

struggle to cure patients diagnosed with breast cancer while improving the quality of survivorship. Better surgical options came with more time for decision making relative to surgical needs and hope that cumulative treatment would one day be risk adapted—that is, defined by the personalized assessment of response of tumors to treatment (4,5).

(Neo)-adjuvant therapy can include combinations of cytotoxic chemotherapy, hormonal therapy and increasingly targeted molecular agents such as trastuzumab and pertuzumab depending upon the breast cancer subtype. Both adjuvant and neoadjuvant therapy have been shown to improve DFS and OS for many if not most women with early stage breast cancer (6,7). In deciding whether to use one or the other, the first question that must be asked is whether either is necessary at all. In the traditional adjuvant model, variables that influence OS and DFS include the patient's age, stage of disease, tumor grade, other biologic factors such as estrogen receptor (ER) and progesterone receptor (PR) expression, and amplification or overexpression of the Her2 oncogene. Increasingly, molecular tools such as Oncotype Dx™, MammaPrint™, and others inform decisions on choice of therapy (8). However, these tools have been most commonly used in combination with rather than in substitution for other clinical parameters. For example, Oncotype Dx™ which quantifies expression of 21 different genes is most rigorously validated to date in node negative, ER+ patients, and its readout (risk of distant recurrence at a time point, or prediction of chemotherapy's effectiveness in reducing the likelihood of distant recurrence) is influenced by the number of involved lymph nodes found at the time of surgery (9). It is important to remember that all of the variables necessary to determine whether chemotherapy will be of value are not always known from an initial core biopsy, and therefore many women may not be ideal candidates for neoadjuvant therapy, now or in the foreseeable future.

Neoadjuvant chemotherapy and the timing of definitive surgery

The timing of the surgical resection of a breast cancer relative to the chemotherapy regimen needed to minimize metastatic recurrence depends upon the disease presentation and input from the patient. A reasonable, clear indication for neoadjuvant chemotherapy is the need to reduce tumor size in an effort to provide breast conservation as an option. A typical patient for this would be a woman with small to medium breast size with a relatively large cancer who would prefer breast conservation as an option. This down staging of tumor size to avoid a mastectomy has been well documented with long-term loco-regional recurrence and survival rates being similar to traditional adjuvant chemotherapy treatment (2,10). Avoiding mastectomy and being able to perform breast conservation surgery provides the benefit of less surgery, quicker recovery and fewer post-operative complications (11). While the benefit of down staging tumor size using neoadjuvant chemotherapy is clear, there may be special considerations in particular circumstances. In the case where breast size is larger and tumor is large (e.g., T2–T3 invasive cancer) breast cancer, neoadjuvant chemotherapy should certainly be in the discussion to reduce tumor size and facilitate breast conservation. However, newer oncoplastic breast conservation techniques now allow very large partial mastectomies followed by the use of mastopexy or breast reduction techniques to rearrange the breast to maintain and possibly improve post-operative breast form (12-14). The need to reduce tumor size pre-operatively in this circumstance may not be as critical as oncoplastic surgical techniques can remove these large tumors while maintaining breast aesthetics. In patients with node negative, ER positive, PR positive, Her2-neu negative invasive breast cancer, this presents an interesting dilemma in that these patients may not need chemotherapy especially if found to have favorable molecular profiling. Neoadjuvant chemotherapy in this population is less likely to achieve pathologic complete response, and neoadjuvant chemotherapy might be overtreatment particularly if oncoplastic surgical options can provide breast conservation even in the setting of larger invasive breast cancers. This underscores the critical need to assess the necessity of (neo)-adjuvant chemotherapy on a case by case basis.

A second benefit of neoadjuvant chemotherapy from a surgical perspective is its ability to facilitate complete surgical resection especially when the breast cancer presents in a large, bulky fashion. Breast tumors close to or involving the axilla can be particularly challenging if they are large and abutting critical neurovascular structures such as the thoracodorsal vessels and nerve. Fisher *et al*. (15) noted that after neoadjuvant chemotherapy that involved doxorubicin and cyclophosphamide, breast tumor size was reduced in 80% of patients and completely resolved clinically in 36% of patients. Additionally clinical nodal response occurred in 89% of node positive patients of whom 73% had complete clinical response. The ability for neoadjuvant chemotherapy to decrease tumor burden can aid the surgeon's ability

to safely remove cancer from the breast and axilla region which provides a clear advantage in potential post-operative surgical complications. Pre-operative imaging modalities such as ultrasound and MRI in addition to clinical exam can help evaluate the presence of bulky tumor burden (16) and discussion involving the oncology team and the patient should determine the appropriateness of neoadjuvant chemotherapy in these situations.

Another advantage for using neoadjuvant chemotherapy for invasive breast cancer is the ability to safely delay surgery in certain circumstances. Patients at times are not optimal candidates for surgery based on poor compliance to modifiable behaviors. Common modifiable behaviors include smoking and blood glycemic control for diabetes. Abundant surgical literature exists noting the association of smoking to poor wound healing and post-operative complications (17). In particular, smoking significantly increases post-operative infections in both mastectomy and breast conservation surgery patients (18). Møller *et al*. (17) noted that smoking cessation for even 6 to 8 weeks can result in a significant clinical reduction in overall complications that include cardiopulmonary and wound post-operative complications. Therefore, patients who are willing to stop smoking close to the time of their breast cancer diagnosis should be considered for neoadjuvant chemotherapy given that a surgical treatment delay while they stop smoking minimizes their post-operative complication rate. Association between poor glycemic control and post-operative wound complications also exist in breast surgery (19). Thus, neoajuvant chemotherapy can allow for a purposeful delay in surgery during which time better glycemic control is achieved so that optimal post-operative results can be obtained. Of note, pre-operative chemotherapy is not associated with increased post-operative complications in major breast surgery (20).

Lastly, there may be an advantage to initiating neoadjuvant chemotherapy in the setting of limited breast surgical access or availability. While in ideal circumstances, access to surgery should be present and readily available, some regions of the world may not have immediate access to a surgeon and there may be circumstances where pre-operative chemotherapy can be initiated without compromise as a temporizing treatment until surgery can subsequently be performed with ideal planning.

For those who are candidates for neoadjuvant chemotherapy followed by surgery however, questions remain as to which factors under control of the physician and the health system do influence outcome. It is known for example that the effectiveness of adjuvant chemotherapy can be compromised by undue delay from the time of definitive surgery to cycle 1 day 1 of treatment, with a delay defined as an interval longer than 60–90 days from surgery, particularly for triple negative subtypes (21,22). Many theories have been offered for why this should be so. Recurrence free and OS depend on the eradication of micrometastatic disease, and timing of interventions may variably affect tumor stem cell viability or the immune response to cancer or both, or may impact residual tumor burden in other ways.

In the neoadjuvant paradigm, initiation of systemic therapy is possible at a very early time point following diagnosis, with several additional advantages except where discussed above or for those women seeking to maximize and preserve fertility options after completion of all therapy. In all other respects, adequate time becomes available for women to have genetic counseling, consider more carefully local therapy options such as mastectomy or bilateral mastectomy *vs*. breast conservation therapy, consult with radiation experts, and importantly, consider the most appropriate reconstructive techniques without delaying effective therapy.

It is in this context that Sanford *et al*. in *Annals of Surgical Oncology* (23) have evaluated one important variable that the breast team and the health system can control—the interval between the last dose of neoadjuvant chemotherapy and the day of definitive cancer surgery. The authors chose to summarize the extensive experience of the MD Anderson Cancer Center between April 1995 and June 2007 seeking to measure the correlation if any of the duration of time from the last dose of neoadjuvant chemotherapy to definitive surgery with relapse free survival (RFS) and OS outcomes. While 1,449 candidates for analysis were identified, for 24 the interval could not be determined, 6 had intervals >24 weeks and were not analyzed, and 318 had neoadjuvant therapy at another institution.

The authors elected not to include data on this last group of 318 patients, those who completed systemic therapy at another institution. This is unfortunate given that the real world experience is changing where increasingly, patients are required or elect to complete systemic therapy closer to home, while seeking surgical intervention elsewhere. This reality is becoming more and more common and inclusion of this experience would have been informative.

For those who were analyzed, in univariate analysis there was no difference in 5-year recurrence free survival or 5-year loco-regional recurrence free survival. OS did differ somewhat without clear trend among groups. However in multivariate

analysis, whether operated on ≤4, 4–6 or ≥6 weeks from the last dose of chemotherapy, no difference in any outcome was observed. In a sensitivity analysis which included 70 patients who had surgery >8 weeks but less than 24 weeks from completion of chemotherapy, OS appeared to be compromised, but the authors were not able to conclude that OS was influenced by breast cancer related events. The possible effect on survival remains unexplained.

The authors are to be commended for extending the seminal observations of the NSABP studies B18 and B27 and the results of Sanford *et al*. are both practically important and theoretically interesting. Of interest, most of the patients did not have a complete pathologic response (906/1,101) and for those who did, recurrence free survival and OS were significantly improved as expected. Yet whether pCR was achieved or not, the interval to surgery did not appear to affect outcomes. For the former group, if pathologic CR reflects complete eradication of breast and micrometastatic clones, timing of surgery theoretically would be expected to have no effect. For the latter group, all of whom with viable residual tumor, there seemed to be no concerns in waiting for surgery up to 6 weeks. There was a suggestion without statistical certainty that more significant delays past 8 weeks might impact OS adversely, but factors precluded definitive analysis. In particular RFS was adversely affected in univariate but not multivariate analysis and so the influence on survival is of interest for hypothesis generation only.

The combination of unprecedented molecular technology and the identification of exceptional responders that can be assessed ideally through neoadjuvant models of disease management make this a unique time in oncology. It has long been recognized that certain tumors are exquisitely sensitive to even non selective cytotoxic therapies. The analysis of these exceptional responses has been a major catalyst that has propelled a revolution in molecular science. For example, study of the unprecedented durable responses from oral imatinib in chronic myelogenous leukemia patients harboring the known BCR-ABL translocation provided the momentum to believe that all neoplastic disorders will succumb to rational drug design targeting driver mutations or pathways. The ability of investigators to assess these exceptional responders as well as those who develop resistance has led not only to practice changing interventions but also to solutions to acquired resistance as well as to improved understanding of why resistance emerges at all. In combination with trials such as BRE12-158 [Hoosier Cancer Research Network (24)] which seeks to modify treatment in real time by studying those who are not "exceptional responders", clinical investigators are exploring a paradigm shift where many patients will be promptly assessed and ideally treated with systemic therapy while definitive loco-regional treatment is planned. Molecular analysis of residual disease refractory to neoadjuvant treatment (the majority of patients) will allow both research and clinical options to expand for these patients in an attempt to improve the long-term cure rates perhaps to those seen in patients who achieve a pathologic complete response. The recent demonstration of improved DFS for patients who receive adjuvant capecitabine following less than a complete response to neoadjuvant anthracycline, taxane or both suggests that improved results can be achieved with additional treatment; however selection remains a challenge (25).

Perhaps with improved pathologic CR rates as a result of more effective systemic therapy, it may be possible to conceive of a time where surgery (and thus any variable such as time to surgery and/or type and extent of surgery) may be unnecessary to consider for some, should reliable markers such as circulating free DNA or other biomarkers emerge as surrogates for pathologic analysis to assure complete and durable response (26). Relative to radiation therapy, prospective trials such as the RTOG/NSABP B51 trial will begin to answer in a randomized fashion the extent to which regional nodal radiation is needed if pathologic assessment of positive axillary nodes following neoadjuvant chemotherapy shows clearing (27).

Currently guidelines for neoadjuvant therapy include giving all planned therapy prior to surgery to standardize comparison of responses, improve uniformity of practice and reduce morbidity/inconvenience for the patient. Increasingly it will be desirable for investigators to refine the composition of neoadjuvant treatment as well as the post-treatment surgical and radiation variables such as timing, dose and extent. It is reassuring to know that optimal planning of surgery can be done safely within a reasonable time interval (≤8 weeks from completion of chemotherapy) without compromising outcomes.

Thus it appears that the neoadjuvant approach will continue to represent both a way forward and a convenient option for many women diagnosed with early stage breast cancer.

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Footnote

Conflicts of Interest: Dr. Erban is a site investigator for the BRE12-158 trial. Dr. Chatterjee has no conflicts of interest to declare.

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