

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Predicting Locoregional Recurrence After Neoadjuvant Chemotherapy in Patients With Breast Cancer



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H&O How common is locoregional recurrence after neoadjuvant chemotherapy in patients with breast cancer?

TM Nowadays, prevalence is mostly in the single digits, particularly among patients with large operable breast cancer, who are the majority of candidates for neoadjuvant chemotherapy. Through the years, there has been a reduction in the rate of locoregional recurrence due to a combination of more effective chemotherapy regimens, better surgical and radiotherapy techniques, and improved management of patients who had received prior neoadjuvant chemotherapy.

H&O What is known about the causes of locoregional recurrence after neoadjuvant chemotherapy?

TM The causes of locoregional recurrence after neoadjuvant chemotherapy are, to some extent, similar to the causes reported after upfront surgery. Factors that predict risk of locoregional recurrence in these patients include larger tumor size; younger patient age; the number of positive nodes; the presence of lymphovascular invasion; and aggressive biology, such as triple-negative breast cancer and human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Some of these factors also predict risk of distant recurrence. Among patients who have received neoadjuvant chemotherapy, it has been found that response to chemotherapy is also a significant predictor of locoregional recurrence.

H&O What have previous data suggested about predictors of locoregional recurrence after neoadjuvant chemotherapy in patients with breast cancer?

TM Prior data have suggested that significant predictors included the initial stage of the patient and response to chemotherapy. These data were somewhat limited because they were generated from retrospective studies, in which treatment selection was based on predetermined criteria. For example, locoregional radiotherapy is recommended after surgery in patients who are at high risk for locoregional recurrence. After neoadjuvant chemotherapy, locoregional radiotherapy is also used according to the clinician's discretion. Some patients receive it and others do not, depending on the original stage at presentation and how much disease is left. An important aspect of our recent study published in the *Journal of Clinical Oncology* is that it was an analysis of 2 National Surgical Adjuvant Breast and Bowel Project (NSABP) trials that, according to protocol, did not permit postmastectomy radiotherapy after neoadjuvant chemotherapy and surgery or anything more than breast radiotherapy if patients had undergone lumpectomy. Therefore, the patient population represented a group of cases that were treated uniformly, without the selective addition of radiotherapy per investigator's discretion. This protocol permitted a good understanding of the baseline rate of locoregional recurrence and the factors that predict it, as opposed to some previous studies,

in which radiotherapy had been used inconsistently, leading to a bias in terms of the true assessment of risk.

H&O What was the design of your study?

TM It was a retrospective review of outcomes of locoregional recurrence among close to 3,000 patients who had participated in 2 NSABP prospective, randomized clinical trials examining neoadjuvant chemotherapy. One trial compared preoperative chemotherapy to postoperative chemotherapy with 4 cycles of doxorubicin/cyclophosphamide (AC). The other trial compared 4 cycles of preoperative AC to 4 cycles of preoperative AC followed by 4 cycles of preoperative docetaxel (Taxotere, Sanofi Oncology); a third arm consisted of 4 cycles of AC preoperatively followed by 4 cycles of docetaxel postoperatively. All patients in the analysis had received neoadjuvant chemotherapy. After mastectomy, patients were not allowed to receive radiotherapy. After lumpectomy, they were supposed to receive breast radiotherapy, but regional nodal radiotherapy was not allowed. The goal of the study was to examine the patterns of locoregional recurrence, as well as the factors that contribute to its development.

H&O What were the findings?

TM The findings were not surprising. Predictors of locoregional recurrence included baseline factors, such as how the tumor presented, as well as factors related to response of the tumor to chemotherapy. Interestingly, for lumpectomy patients who received breast radiotherapy, independent predictors included the patient's age before chemotherapy, her clinical nodal status (whether the nodes were palpable or not), and also a combination of the pathologic responses of the tumor in the breast and the nodes. The best category was no disease in the breast, with negative nodes. The second best category was disease in the breast but with negative nodes. The third best category was positive nodes after chemotherapy irrespective of what happened in the breast. In essence, the rate of locoregional recurrence was associated with the age of the patient and the clinical nodal status before chemotherapy, as well as the pathologic response of the tumor in the breast and pathologic status of the nodes to neoadjuvant chemotherapy. For mastectomy patients, the findings were similar. Clinical tumor size and clinical nodal status before chemotherapy, along with pathologic response of the primary breast tumor to chemotherapy and pathologic status of the axillary nodes, were independent predictors. In other words, some of the same factors that were found for lumpectomy were also found for mastectomy in terms of predicting locoregional recurrence after chemotherapy (clinical nodal status before chemotherapy and pathologic response in the breast/pathologic status of

the axillary nodes). On the other hand, age predicted risk for locoregional recurrence only in lumpectomy patients, and clinical tumor size predicted risk of locoregional recurrence only in mastectomy patients.

By using this combination of factors that can be obtained before and after neoadjuvant chemotherapy, we were able to divide the patient population into groups with low, intermediate, or high risk for locoregional recurrence. Among patients with pathologically negative axillary nodes after preoperative chemotherapy, with or without a pathologic complete response (pCR) in the breast, the rates of recurrence were fairly low, even if patients had presented with clinically positive nodes. Patients who remained pathologically node-positive after neoadjuvant chemotherapy had higher rates of recurrence, which rose even higher if the tumor was clinically node positive before neoadjuvant chemotherapy. In other words, if clinically involved nodes before preoperative chemotherapy remained pathologically involved after preoperative chemotherapy—indicating that they did not respond to chemotherapy very well—then the rate of recurrence was the highest.

Based on these findings, we proposed that response to chemotherapy could be used to assess risk of locoregional recurrence after chemotherapy and to potentially tailor the use of radiotherapy for these patients. Radiotherapy can be reserved for patients who have high residual risk for recurrence and potentially avoided in patients who have low residual risk of recurrence. To prospectively validate this hypothesis, the NSABP and the Radiation Therapy Oncology Group (RTOG) have designed a randomized clinical trial for patients who present with histologically confirmed positive axillary nodes (by fine needle aspiration or core needle biopsy) that become histologically negative after chemotherapy (at surgery) (NSABP B-51/RTOG 1304). These patients will be randomized to either undergo or not undergo postmastectomy comprehensive chest wall and regional nodal radiotherapy or to receive postlumpectomy breast plus regional nodal radiotherapy versus breast radiotherapy only. The main goal of the trial is to prospectively address whether patients who convert their axillary nodes with preoperative chemotherapy from positive to negative do or do not benefit from comprehensive radiotherapy.

H&O Could you please describe the nomogram that was created?

TM The nomogram is a model that takes into account all of the independent predictors—clinical tumor size, clinical nodal status, response to chemotherapy, and patient age—to estimate the risk of locoregional recurrence in a particular patient. This nomogram has not yet been validated in another dataset, but we are in the process of attempting to do so. It is a helpful tool, at least to obtain

an estimate of risk of recurrence and to initiate a conversation with the patient regarding her risk of recurrence and need for postoperative radiotherapy.

H&O How can physicians use the study findings in clinical care?

TM In clinical care, it is a challenge to identify those patients who, after neoadjuvant chemotherapy, do or do not need postmastectomy comprehensive radiotherapy or post-lumpectomy regional nodal radiotherapy. Previously, most of the data used to make these decisions came from studies that employed surgery first, and then evaluated the risk of recurrence based on factors such as number of positive nodes at surgery. There were limited data regarding locoregional recurrence outcomes in patients receiving neoadjuvant chemotherapy and whether the risk was modified by response. The data from our study are helpful because they allow physicians and patients to better assess the risk of locoregional recurrence and make more educated decisions regarding the need for postoperative radiotherapy.

However, as mentioned above, before this approach becomes adopted in clinical practice, we would like to validate it prospectively in a randomized clinical trial. Currently, however, our data provide reassurance that it is possible to avoid postmastectomy radiotherapy in patients who present with clinically negative nodes before neoadjuvant chemotherapy and have pathologically

negative nodes afterwards because the risk of recurrence appears to be fairly low. We know that radiotherapy in this setting will probably reduce the rates of locoregional recurrence, but whether it will reduce breast cancer recurrence rates and improve survival is a different question. If the baseline rate of recurrence is low, a significant benefit in survival may not be seen.

H&O Are there any limitations to your study?

TM Because these patients were treated in the neoadjuvant setting, and many were diagnosed by fine needle aspiration, one limitation of our data is that we do not have information on other factors, such as estrogen or progesterone receptors and lymphovascular invasion, which are known to affect rates of locoregional recurrence. Certainly, there is more room for research to continue to explore whether factors such as estrogen/progesterone receptors, HER2-neu status, or lymphovascular invasion will modify risk of locoregional recurrence or whether response to chemotherapy may render some of these other factors irrelevant. Hopefully, other data will be generated in the future to address these questions.

Suggested Reading

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*. 2012;30:3960-3966.

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