Breast Cancer Biology: Implications for Local-Regional Therapy

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I-SPY 1 was an important multicenter trial conducted to identify indicators of response to neoadjuvant chemotherapy, recurrence-free survival, and the relationship between the two. The study enrolled patients with clinical and biologic high-risk features; all tumors measured ≥ 3 cm, 41 % were hormone receptor (HR) negative, 90 % were intermediate or high grade, and 91 % were characterized as high risk by the 70-gene profile.¹ Pathologic complete response (pCR) rates varied by constructed molecular subtypes, with the highest rates seen in patients with HR-negative/HER2-positive tumors and the lowest rates in patients with HR-positive/HER2-negative tumors. Achieving a pCR predicted for favorable recurrence-free survival. The investigators concluded that outcomes were dictated by tumor biology. In the current article from Cureton et al., they extend this observation to local recurrence. Specifically, they report that local recurrence is associated with aggressive biological features, including higher clinical stage and the presence of lymphovascular invasion. This article therefore adds to a growing body of literature demonstrating the importance of tumor biology in local-regional outcomes for breast cancer patients.

One question that Cureton and colleagues sought to address with their study was whether breast conserving therapy (BCT) provides adequate local control after neoadjuvant chemotherapy. In the NSABP B-18 trial, the in-breast recurrence rate was 16 % for patients downsized to BCT versus 10 % in patients initially planned for breast conservation, a difference that was not significant when controlling for age and clinical tumor size.² Similarly, in the EORTC 10902 trial, 23 % of patients were downsized and underwent BCT, and there was no significant difference in local-

regional recurrence (LRR) rates when compared with patients who were BCT candidates at presentation.³ In a meta-analysis of studies comparing neoadjuvant with adjuvant chemotherapy, Mieog et al. found that when patients were analyzed by type of surgery, LRR rates in patients undergoing BCT were not affected by the timing of chemotherapy.⁴ These older studies demonstrated that tumors in a significant number of patients will decrease in size after neoadjuvant chemotherapy, facilitating breast preservation and overall providing good local control. The question remained, however, whether factors such as adverse biologic characteristics could be used to identify the subset of patients with higher rates of local regional failure and who may be better served by mastectomy.

These data from the I-SPY 1 trial, which evaluated local recurrence rates according to clinical and pathologic factors in the context of BCT versus mastectomy, suggest that more aggressive surgery, i.e., mastectomy, will not overcome aggressive biology. As an example, for patients presenting with node-positive disease, the 5-year local recurrence risks were 36 and 29 %, respectively, for patients undergoing mastectomy and BCT. In contrast, for patients presenting with node-negative disease, the 5-year local recurrence risks were 11 and 6 %, respectively. It is also notable that very few patients experienced a local recurrence without also experiencing distant disease. This impact of “bad biology” is consistent with data recently published from our own institution evaluating local-regional control in patients undergoing BCT to include segmental mastectomy with whole-breast irradiation (WBI).⁵ This study included 652 patients who received neoadjuvant chemotherapy, whom we compared with 2331 patients who underwent surgery as a first intervention. As would be anticipated, patients receiving neoadjuvant chemotherapy had more adverse clinicopathologic characteristics. The 10-year LRR-free survival rates were 94 % for surgery-first patients and 90 % for those receiving neoadjuvant chemotherapy. It is important to note that, when compared by presenting clinical stage, there were

no differences between the two groups. In addition, whether chemotherapy was administered in the neoadjuvant or adjuvant setting was not associated with LRR. Thus, these studies together suggest that LRR is driven by tumor biology and disease stage and not by the timing of chemotherapy or the type of surgery.

Although the timing of chemotherapy may not impact local regional outcomes, important prognostic information can be gleaned by assessing the response to treatment if it is administered before surgery. Multiple studies have shown that response to neoadjuvant chemotherapy predicts for disease-free and overall survival, with patients achieving a complete or near-complete pathologic response having improved outcomes.⁶ In a study of triple-negative breast cancer patients administered neoadjuvant chemotherapy, those who achieved a pCR had a 3-year overall survival rate of 94 versus 68 % in those who had residual disease.⁷ Although it is not a significant focus of their study and they are limited by small numbers, Cureton et al. note that local recurrence risk also correlates with response to therapy.⁸ In another report from our group in which we investigated local-regional control according to surrogates of molecular subtype and response to neoadjuvant chemotherapy, we found that the importance of the response to therapy varied by subtype.⁹ For patients with HR-positive/HER2-negative tumors, the 5-year LRR-free survival rate was 96 % for patients achieving a pCR and 97 % for those who did not. In contrast, for patients with HR-negative/HER2-negative tumors, the 5-year LRR-free survival rate was 99 % for patients achieving a pCR versus 84 % in those who did not achieve a pCR. These data reflect the overall favorable biology of HR-positive breast cancer and the effectiveness of endocrine therapy and radiation therapy, as well as the unfavorable outcomes experienced by patients with HR-negative/HER2-negative tumors that do not respond well to neoadjuvant chemotherapy.

Given the prognostic information derived from response to chemotherapy, the question remains as to whether such information can be used to tailor local-regional treatments; for good responders, can we do less, and for poor responders, should we do more? One ongoing study that is evaluating the question of whether we can do less in the good responders is the NSABP B-51/RTOG 1304.¹⁰ This is a randomized phase III clinical trial evaluating the addition of regional nodal radiation (RNI) in patients with positive axillary nodal disease who convert to pathologically negative nodes after neoadjuvant chemotherapy. Briefly, the trial is enrolling patients with clinical T1–3N1 breast cancer who receive neoadjuvant chemotherapy and then are found to have negative axillary nodes documented in their surgical specimen. Patients will be randomized to one of two arms. In arm 1, segmental mastectomy patients will be treated with WBI without RNI, and mastectomy patients

will get no radiation at all (chest wall or RNI). In arm 2, segmental mastectomy patients will have RNI added to WBI, and mastectomy patients will receive chest wall radiation and RNI. Stratification factors include type of surgery, HR receptor status, HER2 status, and whether a patient achieves a pCR in the breast. Therefore this trial will provide additional insight regarding the effects of biology on local-regional outcomes.

The poor responders represent a population of patients in whom novel strategies need to be evaluated. As the I-SPY data show, it does not appear that more aggressive surgery will improve outcomes of these poor responders. Data from the Danish Breast Cancer Cooperative Group highlight the limits of radiation therapy in HR-negative subtypes of breast cancer, and, thus, additional radiation to patients poorly responsive to systemic therapy may not offer substantive improvements in local-regional control.¹¹ Therefore, an opportunity exists for novel strategies to include radiosensitizers to enhance radiation effects in either BCT or mastectomy patients.

It is clear that biology plays an important role in local-regional outcomes for breast cancer patients. We would encourage clinicians to consider enrolling patients on the NSABP B-51/RTOG 1304 trial, the ongoing I-SPY trials evaluating new agents in the neoadjuvant setting, and other novel studies that will continue advancing our knowledge regarding the importance of biology in breast cancer and optimizing the outcomes of breast cancer patients.

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