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EDITORIAL – BREAST ONCOLOGY

Axillary Downstaging in ER^+/HER^{2-} Breast Cancer: OncotypeDX As a Tool to Guide Neoadjuvant Approach

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The rates of pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) in both the breast and axilla vary greatly by tumor subtype, with estrogen receptor-positive, HER2-negative (ER^+/HER^{2-}) tumors having notoriously low response rates. Subtype analysis of the American College of Surgeons Oncology Group/Alliance Z1071 trial of patients undergoing contemporary chemotherapy with biopsy-proven clinically node-positive breast cancer found overall pCR rates of 11% in ER^+/HER^{2-} cancers, with axillary pCR rates of 21%.[1] While a neoadjuvant approach is key to axillary downstaging in more responsive tumor subtypes, most patients with clinically node-positive ER^+/HER^{2-} breast cancer will still require axillary dissection. Because axillary dissection carries inherent risks of arm lymphedema and shoulder dysfunction that can negatively impact quality of life, it is important to consider innovative strategies to optimize axillary downstaging for patients with ER^+/HER^{2-} breast cancer.

There is growing evidence to suggest OncotypeDX® Breast Recurrence Score (RS) is useful in guiding chemotherapy decisions in ER^+, node-positive breast cancer. A retrospective analysis of tumor specimens from the randomized Southwest Oncology Group 8814 trial, which randomized postmenopausal women with node-positive, ER^+ breast cancer to adjuvant chemotherapy with tamoxifen or tamoxifen alone, found no difference in disease-specific or overall survival with or without chemotherapy in patients with RS < 18.[2] The ongoing RxPONDER randomized trial of adjuvant chemoendocrine therapy versus endocrine therapy alone in patients with one to three positive nodes and RS < 25 will provide additional high-level evidence to guide postoperative systemic therapy decisions for patients with nodal disease.[3]

Few studies in the neoadjuvant setting have explored the use of RS from the tumor biopsy to predict tumor response to NAC and/or neoadjuvant endocrine therapy (NET). A small multicenter pilot study of 55 ER^+/HER^{2-} cancers assigned patients with RS < 11 to NET, randomized patients with RS 11–25 to either NAC or NET, and assigned patients with an RS > 25 to NAC. Clinical tumor response rates were 83% with RS < 11 and NET, 50% with RS 11–25 in the NET arm, 73% with RS 11–25 in the NAC arm, and 93% with RS > 26 and NAC. However, only 6–8% of patients in the two NET groups achieved pCR in the breast. Of patients with RS > 26 and NAC, 14% achieved pCR in both the breast and nodes; no patients in the other three arms of the study achieved pCR in the nodes.[4] A retrospective analysis of OncotypeDX to predict response to NAC in 81 patients with ER^+/HER^{2-} breast cancer with up to one positive node (from three prospective NAC studies) found pCR to be higher in patients with RS > 18, and highest in the RS > 30 subset (6% RS 18–30, 9% RS > 30 vs. 0% RS < 18, $p < 0.01$).[5] These studies suggest RS can be a useful tool in selecting patients for NAC versus NET, as well as defining expectations of pCR; however, these small studies did not specifically focus on patients with node-positive disease.

In this issue of *Annals of Surgical Oncology*, Fan et al. examined the association of OncotypeDX RS with axillary pCR in 158 patients with cT1-2N1-2 ER^+/HER^{2-} invasive ductal carcinoma treated with NAC from the National

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Cancer Database (NCDB). In patients with RS > 30, the axillary pCR rate was 28%, which was significantly higher than the 10% observed in those with RS < 30 ($p = 0.03$).[6] As downstaging the axilla is often the primary goal with neoadjuvant therapy, this study provides evidence that patients with high RS might benefit most from NAC. Based on the work of Fan et al., consideration of OncotypeDX on the core biopsy specimen of patients with node-positive ER^+/HER^{2-} disease has the potential to stratify patients to the most effective neoadjuvant approach. One caveat is that results may not be applicable to patients with invasive lobular carcinomas as they were excluded from this study.

Some consider tumor grade to be a surrogate for OncotypeDX, when in fact recent studies have shown that the use of OncotypeDX RS has the potential to de-escalate therapy, even in patients with high-grade, node-positive disease. A study of 30,864 women from the NCDB found that 30% of patients with grade 3 node-positive ER^+ tumors had RS < 18, and therefore chemotherapy was not likely to provide additional survival benefit beyond endocrine therapy.[7] Extrapolating the results from the paper by Fan et al., these patients would be expected to have a poor axillary response and unlikely to avoid axillary dissection with NAC.

Alternate treatment approaches such as NET may be considered in these situations. A recent study of 71 patients treated with NET at the Dana-Farber Cancer Institute, supplemented by a cohort of 3902 NET patients from the NCDB, examined the residual nodal burden at the time of axillary surgery, and overall survival implications in cN0 and cN1 patients selected for NET. In the subset of patients with cN1 disease, 30% of the Dana–Farber cohort and 50% of the NCDB cohort had fewer than three positive nodes. Furthermore, overall survival at 5 years was not different in cN1 NET patients treated with sentinel lymph node biopsy or axillary dissection.[8] This suggests that select node-positive patients undergoing NET could be considered for similar axillary treatment strategies as upfront surgical patients and spared axillary dissection in favor of more targeted axillary management.

Taken together, the current literature supports OncotypeDX® Breast RS on the tumor biopsy as a useful tool to help stratify patients with limited node-positive disease to NAC or NET in order to optimize both the systemic therapy regimen and the axillary approach. In patients with a high RS (likely > 25, and definitely > 30), NAC is the favored approach to downstage the axilla and potentially spare up to 28% of patients from axillary dissection. In patients with low or intermediate RS and fewer than three suspicious axillary lymph nodes on preoperative imaging, or those with non-palpable nodal disease, NET is a reasonable strategy if it would be helpful to downstage the breast and/or axilla prior to surgery. Since patients undergoing NET are only having a fraction of their systemic therapy prior to surgery, upfront approaches to omit axillary dissection can most likely safely be adapted from the Z0011 and AMAROS trials[9,10] in the case of low-volume disease (fewer than three positive nodes), understanding that these treatment decisions are complex and best made with input from the multidisciplinary team until prospective study data are available. The concept of a tailored approach to individualizing care and decreasing axillary morbidity in clinically node-positive ER^+/HER^{2-} patients is appealing.

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