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ASO PERSPECTIVES

Personal Systemic Therapy Decision-Making has Officially Arrived for Node-Positive Breast Cancer

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Historically, nodal status was deemed to have the most significant prognostic value and played the strongest role in determining need for systemic therapy for patients with breast cancer. Molecular genomic testing, however, has shown tremendous precision in predicting the risk of distant recurrence and shedding light on which patients have a survival benefit from chemotherapy. Following the demonstration of clinical applicability of the Oncotype DX recurrence score (RS) for the node-negative patient in the TAILORx (Trial Assigning Individualized Options for Treatment) trial and subsequent implementation into the American Joint Committee on Cancer (AJCC) 8th edition staging system, RS results were incorporated into our armamentarium—with the understanding that tumor biology tends to trump anatomic staging in prognostication.[1,2] While the initial utility of the Oncotype DX RS was to predict the risk of distant recurrence in the patient with estrogen receptor (ER) positive, node-negative breast cancer, its usefulness in the node-positive patient remained unclear. That is, until the results of the RxPONDER (A Clinical Trial RX for Positive Node, Endocrine Responsive Breast Cancer) trial became available.

Recently published in the *New England Journal of Medicine*, the RxPONDER trial sought to evaluate the role of the Oncotype DX RS in women with ER-positive, Her2-negative, node-positive (1–3 positive nodes) breast cancer.[3] The trial was conducted at 632 sites in 9 countries and hypothesized that the relative benefit of chemotherapy (predictive value) as well as the absolute risk of recurrence (prognostic value) increased with higher RS. In addition to these primary objectives assessing effect of chemotherapy on invasive disease-free survival, the secondary endpoints included distant relapse-free survival and overall survival. Between February 2011 and September 2017, 5,083 women who were at least 18 years of age with T1–T3, ER-positive, Her2-negative breast cancer with 1–3 positive axillary lymph nodes, and a RS of $\leq$25 were randomized to endocrine therapy alone or chemotherapy followed by endocrine therapy. The participants were stratified according to RS (0–13 or 14–25), menopausal status (postmenopausal defined as 12 months since last menstrual cycle, previous bilateral oophorectomy, or older than age 50 years if the other factors were unknown), and type of axillary surgery performed (sentinel lymph node biopsy or axillary lymph node dissection). The most common chemotherapy regimen was an anthracycline and a taxane in 54% of the premenopausal cohort and a taxane plus cyclophosphamide in 57% of the postmenopausal cohort. It is worth noting that within 12 months of randomization, 12.7% of the premenopausal participants received ovarian suppression. The characteristics of the enrolled patients, according to menopausal status, are summarized in Table 1.

After a median follow-up of 5.3 years, overall invasive disease-free survival at 5 years was 91.6%, with no difference detected based on treatment received (92.2% for the chemotherapy plus endocrine therapy group and 91% for the endocrine therapy only group, $p = 0.10$). A significant interaction was seen, however, between chemotherapy benefit and menopausal status. A significant between-group difference was seen among premenopausal women. The 5-year, invasive, disease-free survival rate was 93.9% in the chemotherapy plus endocrine therapy group compared with 89% in the endocrine therapy only

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TABLE 1 Characteristics of RxPONDER study participants

Characteristic (total n = 5,018)	Premenopausal (n = 1,665; 33.2%)	Postmenopausal (n = 3,353; 66.8%)
Treatment arm		
Chemotherapy + endocrine therapy	834 (33.2%)	1677 (66.8%)
Endocrine therapy only	831 (33.1%)	1676 (66.9%)
Chemotherapy administered		
Anthracycline, no Taxane	35 (5%)	35 (3%)
Anthracycline + Taxane	387 (54%)	522 (39%)
Taxane + Cyclophosphamide	298 (41%)	758 (57%)
Race		
White	981 (58.9%)	2314 (69.0%)
Black	57 (3.4%)	194 (5.8%)
Asian	188 (11.3%)	136 (4.1%)
Other/unknown	439 (26.4%)	709 (21.1%)
Ethnicity		
Hispanic	231 (13.4%)	391 (11.7%)
Non-Hispanic	1071 (64.3%)	2355 (70.2%)
Unknown		
Median age (yr)		
< 40	142 (8.5%)	5 (0.2%)
40–49	1012 (60.8%)	65 (1.9%)
50–59	507 (30.5%)	1168 (34.8%)
60–69	4 (0.2%)	1534 (45.8%)
≥ 70	0 (0%)	581 (17.3%)
Recurrence score		
0–13	645 (38.7%)	1502 (44.8%)
14–25	1020 (61.3%)	1851 (55.2%)
Axillary surgery		
Axillary lymph node dissection	1105 (66.4%)	2035 (60.7%)
Sentinel node biopsy alone	560 (33.6%)	1318 (39.3%)
Hormone receptor status		
ER+ and PR+	1620 (97.8%)	3081 (92.5%)
ER+ and PR−	37 (2.2%)	249 (7.5%)
Positive lymph nodes		
1 node	1084 (65.3%)	2191 (65.6%)
2 nodes	427 (25.7%)	839 (25.1%)
3 nodes	149 (9%)	311 (9.3%)
Tumor size		
T1	938 (56.3%)	1985 (59.2%)
T2	621 (37.3%)	1222 (36.4%)
T3	106 (6.4%)	146 (4.4%)
Histologic grade		
Low	361 (21.7%)	857 (25.6%)
Intermediate	1122 (67.6%)	2093 (62.6%)
High	159 (9.6%)	348 (10.4%)
Unknown	18 (1.1%)	45 (1.4%)
Histology		
Invasive ductal carcinoma	1199 (73.2%)	2474 (75.3%)
Invasive lobular carcinoma	243 (14.8%)	431 (13.1%)
Invasive mixed ductal/lobular	95 (5.8%)	183 (5.6%)
Other	100 (6.1%)	199 (6.1%)
Extranodal extension		
No/unknown	1330 (81.2%)	2544 (77.4%)
Yes	307 (14.3%)	598 (17.8%)

group (hazard ratio 0.60, 95% confidence interval [CI] 0.43–0.83, $p < 0.001$), indicating a benefit from chemotherapy for node-positive, premenopausal women, regardless of recurrence score. The premenopausal cohort who received chemotherapy plus endocrine therapy showed a significant increase in distant relapse-free survival compared with endocrine therapy alone (hazard ratio 0.58, 95% CI 0.39–0.87). The authors also compared the invasive disease-free survival rates in premenopausal women by age: ≥ 50 years, 45–49 years, and ≤ 45 years. There was no significant benefit to chemotherapy in the premenopausal women aged ≥ 50 years (hazard ratio 0.98, 95% CI 0.54–1.78). Invasive disease-free survival at 5 years was investigated in a post-hoc analysis among premenopausal women according to treatment group by four RS categories. Absolute increases were seen, most notably in the patients ≤ 50 years of age: 6.9 percentage points with a RS of 10 or less, 2.3 percentage points with a RS of 11–15, 7.1 percentage points with a RS of 16–20, 10 percentage points with a RS of 21–25.

No significant difference between treatment groups was found in postmenopausal women. The 5-year, invasive, disease-free survival rate was 91.3% in the chemotherapy plus endocrine therapy group and 91.9% in the endocrine therapy only group ($p = 0.89$). Additionally, no significant difference between groups was seen in disease relapse-free survival ($p = 0.70$), indicating no benefit from chemotherapy in the postmenopausal cohort.

A plethora of information can also be obtained from the supplemental appendices associated with this manuscript. Although the RS was found to be independently prognostic for chemotherapy and menopausal status, the other variables had no impact. No difference in invasive disease-free survival was seen in any subgroup of either cohort—all subgroups in the premenopausal cohort had a benefit from chemotherapy, while none of the subgroups in the postmenopausal cohort derived a benefit. The histologic grade, tumor size, recurrence score category, type of axillary surgery performed, and number of involved lymph nodes

were not independent predictive factors for chemotherapy benefit. It is important to note that nodal micrometastases (0.2–2 mm) were not included in this analysis. The data from RxPONDER cannot be generalized to patients with axillary micrometastases.

Combining the information obtained through the TAILORx trial for the node-negative patient and the RxPONDER trial for the node-positive patient, we can now give evidence-based guidance to our patients regarding the possibility of chemotherapy.

Take Home Points:

- Postmenopausal, T1–T3, any grade, ER-positive, Her2-negative, 1–3 positive lymph nodes, RS $\leq$ 25: no added benefit from chemotherapy; endocrine therapy only recommended
- Postmenopausal, T1–T3, any grade, ER-positive, Her2-negative, 1–3 positive lymph nodes, RS $>$ 25: chemotherapy plus endocrine therapy recommended
- Premenopausal, age $<$ 50 years, T1–T3, any grade, ER-positive, Her2-negative, 0 positive lymph nodes, RS $\geq$ 16: chemotherapy plus endocrine therapy recommended (in general: 1–2% benefit if RS 16–20, 6–7% benefit if RS 21–25)
- Premenopausal, age $<$ 50 years, T1–T3, any grade, ER-positive, Her2-negative, 0 positive lymph nodes, RS $<$ 16: no added benefit from chemotherapy; endocrine therapy only recommended
- Premenopausal, age $<$ 50 years, T1–T3, any grade, ER-positive, Her2-negative, at least 1 positive lymph node: no indication for Oncotype testing; chemotherapy plus endocrine therapy recommended

Given the data from RxPONDER, a few questions come to mind:

- With only 5% of the study participants being African American and 6.5% being Asian, can these results be safely generalized to all non-white patients with breast cancer?
- With 34% of the node-positive patients in this trial only having a sentinel lymph node biopsy, there is a strong possibility that the number of involved lymph nodes were underestimated. Because chemotherapy will be recommended for all premenopausal, node-positive patients regardless of RS, will axillary surgery beyond SLNB ever be needed? Are we at the point where we just need to know lymph node positive and not necessarily determine "how" positive?
- The RxPONDER authors point out that the effect of ovarian suppression in the premenopausal patient remains unclear. Is the chemotherapy benefit noted in this trial strictly from its cytotoxic effects? How substantial of a role does treatment-induced menopause play? Are there patients in whom ovarian suppression can replace chemotherapy?
- Should RS be used to guide chemotherapy regimen decision making? Can the RS be used to determine which premenopausal patients could avoid an anthracycline-based regimen?
- In the postmenopausal, clinically node-positive patient at presentation, is there a role for preoperative Oncotype DX testing? While there are many benefits to it, including in-breast and axillary down-staging, as well as the ability to assess treatment response for prognostic purposes, would it be more appropriate in node-positive patients with more indolent tumor biology to proceed with preoperative Oncotype DX testing and reserve neoadjuvant chemotherapy for those with high RS only? In those patients with RS $\leq$ 25, proceed with the recommended breast operation and targeted SLNB followed by endocrine therapy?
- If lymph node positivity is determined by image-guided core biopsy and the patient is clinically node negative on exam, is surgical nodal staging even necessary? If so, when? Why? Does the RxPONDER data allow us to forego any axillary surgery and treat systemically based on RS? What would the results of any axillary surgery offer?

As surgeons, we are almost always the first encounter for a patient with newly diagnosed breast cancer. Defining the details of the disease, outlining the expected course of treatment and describing the risks and benefits of all options fall under our purview. We have the opportunity to establish a personal relationship with these patients immediately and are routinely tasked to help them with subsequent decisions regarding treatment. Whether or not chemotherapy is needed tends to be at the top of their concerns. The algorithms are becoming increasingly multifactorial, and very few care plans are straight-forward at the time of diagnosis. It is our responsibility to have a solid grasp on the latest data and a comprehensive understanding of the prognostic tools at our disposal to ensure that multidisciplinary treatment recommendations can be implemented in a timely fashion. The results of the RxPONDER trial give us the ammunition to have an evidence-based discussion with the node-positive patient regarding effective treatments based on tumor biology. As expected, the RxPONDER trial is a game-changer.

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