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To interview W. Fraser Symmans, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Symmans, click here.

Residual Cancer Burden Can Predict Outcomes for Patients With Any Breast Cancer Type

SAN ANTONIO — A large meta-analysis of breast cancer patients showed that residual cancer burden after neoadjuvant chemotherapy is an accurate long-term predictor of recurrence and survival across all breast cancer subtypes, according to data presented at the 2019 San Antonio Breast Cancer Symposium (SABCS), held Dec. 10–14.

"In recent years, many single-institution studies have shown that residual cancer burden after neoadjuvant chemotherapy can tell us a great deal about a patient's prognosis after surgery," said the study's lead author, W. Fraser Symmans, MD, professor and director of research operations, Department of Pathology, at The University of Texas MD Anderson Cancer Center in Houston. "We undertook this meta-analysis to help determine whether this is true for all subtypes, and how generalizable previous findings might be."

Symmans explained that residual cancer burden is assessed through several factors, including the size of the primary tumor, the percentage of the tumor that is invasive versus in situ, and the involvement of lymph nodes. A calculator hosted by MD Anderson calculates residual cancer burden index and assigns a classification of pathologic complete response, RCB-I (minimal burden), RCB-II (moderate burden), or RCB-III (extensive burden).

In this study, Symmans and colleagues from the I-SPY Clinical Trials Consortium compiled and analyzed data from 12 cancer centers or clinical trials, representing approximately 5,100 patients. Using mixed effect models, they examined associations between the RCB index and event-free survival (EFS) and distant recurrence-free survival (DRFS).

The residual cancer burden index was tightly associated with both EFS and DRFS, and was consistent across 12 clinical sites and all four types of breast cancer. In terms of EFS, the analysis of RCB categories showed:

- For hormone receptor (HR)-positive/HER2-negative, 11 percent of patients were classified as having a pCR, 11 percent as RCB-I, 53 percent as RCB-II, and 25 percent as RCB-III. At the 10-year follow-up, 19 percent of the pCR group had had a recurrence or had died, compared with 14 percent of the RCB-I group, 31 percent of the RCB-II group, and 48 percent of the RCB-III group.

- For HR-positive/HER2-positive, 38 percent of patients were classified as having a pCR, 20 percent as RCB-I, 33 percent as RCB-II, and 8 percent as RCB-III. At the 10-year follow-up, 9 percent of the pCR group had had a recurrence or had died, compared with 17 percent of the RCB-I group, 36 percent of the RCB-II group, and 55 percent of the RCB-III group.

- For HR-negative/HER2-positive, 69 percent of patients were classified as having a pCR, 11 percent as RCB-I, 16 percent as RCB-II, and 4 percent as RCB-III. At the 10-year follow-up, 7 percent of the pCR group had had a recurrence or had died, compared with 15 percent of the RCB-I group, 37 percent of the RCB-II group, and 40 percent of the RCB-III group.

- For HR-negative/HER2-, 43 percent of patients were classified as having a pCR, 12 percent as RCB-I, 33 percent as RCB-II, and 11 percent as RCB-III. At the 10-year follow-up, 14 percent of the pCR group had had a recurrence or had died, compared with 25 percent of the RCB-I group, 39 percent of the RCB-II group, and 75 percent of the RCB-III group.

"The measurement of RCB index is strongly prognostic, allowing us to measure risk of recurrence with confidence," Symmans said. "This meta-analysis of residual cancer burden provides real-world evidence of how patients are responding to neoadjuvant treatments, and calibration of RCB index to prognostic risk enables us to determine the most appropriate next steps for breast cancer patients."

Symmans said that while not all cancer centers routinely collect data on residual cancer burden, this analysis shows that pathologists can implement it with accurate results, adding to its potential as a predictor of recurrence within breast cancer subtypes.

Symmans said one limitation of the study is that it is based on data from multiple institutions, leading to some variation in clinical methods, the handling of specimens, and possible other factors. Some data on residual cancer burden were collected prospectively and some were collected retrospectively.

"Looking ahead, if we can standardize the reporting of residual cancer burden, that will only improve its usefulness in determining long-term prognosis," Symmans said.

This research was funded by the Department of Defense, a National Institutes of Health program grant, the Cancer Prevention Research Institute of Texas, and the Breast Cancer Research Foundation. Symmans co-holds a patent for a mathematical formula used in MD Anderson's RCB index.

ABSTRACT
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Residual cancer burden after neoadjuvant therapy and long-term survival outcomes in breast cancer: A multi-center pooled analysis

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Background: Recent studies have demonstrated independent validation of the prognostic relevance of residual cancer burden (RCB) after neoadjuvant chemotherapy. However, a pooled subject-level analysis of multiple cohorts is needed to determine estimates of long-term prognosis for each class of RCB in each phenotypic subtype of breast cancer (BC) to better inform on patient outcomes. Also, a pooled subject-level analysis allows more detailed analyses of generalizability of the prognostic meaning of RCB assessments in a broader experience of practice settings. **Method:** Subject-level RCB results, with relevant clinical and pathologic stage, tumor subtype and grade, demographic, treatment and follow-up data from 11 institutes/trials are being collected for combined analysis. The association between the continuous RCB index and event-free survival (EFS), and distant recurrence free survival (DRFS) were assessed using mixed effect Cox models with the incorporation of random RCB coefficients to account for between-study heterogeneity. We will also allow for differences in baseline hazard across biological BC subtypes and, if needed, across studies as well. In addition to this stratified mixed effect model, a multivariate analysis adjusting for age, T-category, nodal status and grade was performed within each subtype. In addition, mixed effect Cox models will be employed to evaluate association between RCB index with EFS and DRFS within each HR/HER2 subtype. Kaplan Meier estimates of EFS and DRFS at 5 and 10 years were computed for each RCB class within subtype. **Results:** We analyzed subject-level data from 9 institutes/trials representing 4077 patients currently available from an anticipated final total of 4,800 patients (to be presented at the meeting). There were 950 EFS and 876 DRFS events during follow up (median 65 months, IQR: 70 months). RCB index (continuous) was independently prognostic within each subtype: HR+/HER2- (EFS HR (per unit increase in RCB index) =1.64, 95%CI 1.48-1.82; DRFS HR=1.68, 1.51-1.87), HR+/HER2+ (EFS HR=1.80, 1.57-2.05; DRFS HR=1.93, 1.67-2.24), HR-/HER2+ (EFS HR=2.15, 1.76-2.62; DRFS HR=2.10, 1.77-2.50), and HR-/HER2- (EFS HR=2.05, 1.89-2.22; DRFS HR=2.16, 1.90-2.46); and remained prognostic in multivariate models adjusting for age, grade, and clinical T and N stage at diagnosis. Table 1 contains the response rate and estimated EFS at 5 years and 10 years for each RCB class within each HR/HER2 phenotype (DRFS results were similar). **Conclusions:** Long-term prognosis after pCR was similarly excellent in all phenotypic subtypes. RCB index and classification was independently and strongly prognostic in all subtypes, and generalizable to multiple practice settings. Prognostic differences by RCB class occurred within 5 years in HR- BC, but extended to 10 years in HR+ BC. RCB-I had slightly worse EFS than pCR in HR- BC and HR+/HER2+ BC (after 5 years), but the same EFS as pCR in HR+/HER2- BC. Complete analysis of all subjects, including neoadjuvant treatments, will be presented at the meeting.

Phenotype	Outcome	pCR	RCB-I	RCB-II	RCB-III
HR+/HER2-	Frequency (%)	11%	10%	52%	27%
(N=1467)	5 yr EFS (95% CI)	91% (86-96)	93% (89-98)	82% (79-85)	70% (65-75)
	10 yr EFS (95% CI)	84% (75-93)	88% (82-95)	71% (67-75)	52% (46-58)
HR+/HER2+	Frequency (%)	38%	18%	35%	9%
(N=762)	5 yr EFS (95% CI)	94% (91-97)	93% (88-98)	78% (73-84)	49% (37-65)
	10 yr EFS (95% CI)	91% (86-96)	79% (70-90)	65% (59-73)	42% (29-60)
HR-/HER2+	Frequency (%)	66%	11%	18%	5%
(N=550)	5 yr EFS (95% CI)	93% (90-96)	88% (79-97)	60% (50-71)	45% (30-69)
	10 yr EFS (95% CI)	90% (86-94)	84% (74-95)	56% (46-68)	45% (30-69)
HR-/HER2-	Frequency (%)	41%	13%	33%	13%
(N=1293)	5 yr EFS (95% CI)	92% (90-94)	85% (79-91)	68% (63-72)	28% (21-36)
	10 yr EFS (95% CI)	87% (82-91)	80% (72-88)	63% (58-68)	24% (18-33)

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