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Correlation of Ki67 Working Group Prognostic Risk Categories with Oncotype DX Recurrence Score in Early Breast Cancer

Rima Patel, MD[1], **Malin Hovstadius, MS**[2], **Melanie W. Kier, MD, MBA**[1], **Erin L. Moshier, MS**[3], **Brittney S. Zimmerman, MD**[4], **Krystal Cascetta, MD**[1], **Shabnam Jaffer, MD**[5], **Joseph A. Sparano, MD**[1], **Amy Tiersten, MD**[1]

[1]Department of Medicine, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

[2]Frank H. Netter School of Medicine at Quinnipiac University, Hamden, Connecticut, United States

[3]Division of Biostatistics, Icahn School of Medicine at Mount Sinai, New York, New York, United States

[4]Northwell Cancer Institute, Riverhead, New York, United States

[5]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York, United States

Abstract

Background: The relationship between Ki67 assessed by immunohistochemistry (IHC) and the Oncotype DX Recurrence Score (RS) is unclear. The objective of this study was to determine the correlation between 21-gene RS and IHC-measured Ki67 using the prognostic classification groups recommended by the International Ki67 Working Group (IKWG).

Methods: We performed a retrospective chart review of women with hormone receptor (HR)-positive, HER2-negative early breast cancer (EBC) with 0–3 positive lymph nodes and both Ki67 and 21-gene RS performed at our institution from 2013–2021. Patients were categorized into Ki67 low (≤ 5%), intermediate (6–29%), and high (≥30%) based on IKWG recommendations. Overall and risk stratified agreement between Ki67 and RS were assessed using the proportion of agreement and Kappa statistic.

Results: The study included 525 patients with HR-positive BC. Among the 49% of patients with intermediate Ki67 of 6–29%, the distribution of low, intermediate, and high RS was 19%, 66%, and 15%, respectively. There was slight agreement (kappa 0.01–0.20) between Ki67 and RS (Kappa= 0.027) in the overall population though this was not significant (p=0.1985). There was

Corresponding author: Rima Patel, 1 Gustave L. Levy Place, New York, NY 10029, 646-819-9850, Rima.patel2@mountsinai.org.
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Conflict of Interest Statement: J.A.S. reports a consulting/advisory role for Genentech/Roche, Novartis, AstraZeneca, Celgene, Lilly, Celldex, Pfizer, Prescient Therapeutics, Juno Therapeutics, Merrimack, Adgero Biopharmaceuticals, Cardinal Health, GlaxoSmithKline, CStone Pharmaceuticals, Epic Sciences, Daiichi Sankyo, BMSi. A.T. reports a consulting/advisory role for Puma Biotechnology, Immunomedics, AstraZeneca, Novartis, eisai and Roche/Genentech. All other authors report no relevant conflicts of interest.

fair agreement (kappa 0.21–0.40) between high Ki67 and RS (Kappa=0.280, p<0.0001). Higher PR% was associated with lower RS (p>0.0001) but not lower Ki67. Positive nodal status and larger tumor size were associated with higher Ki67 (p=0.0059, p<0.0001) but not RS.

Conclusions: In this group of patients selected to have a 21-gene RS, there was no significant correlation between Ki67 and RS in the overall population, and fair agreement between high Ki67 and high RS.

Lay Summary:

In patients with early-stage, hormone receptor-positive breast cancer, decisions on adjuvant chemotherapy are based on certain biologic features of the cancer and genomic assays such as the Oncotype DX Recurrence Score (RS). The goal of this study was to determine the correlation between Ki67, a marker of proliferation, and the Oncotype DX RS, a 21-gene assay demonstrated to be predictive of adjuvant chemotherapy benefit in patients with early-stage breast cancer. In 525 patients, we did not find a significant correlation between Ki67 and RS.

Precis for use in the Table of Contents:

In this retrospective study of 525 patients with early-stage, hormone receptor-positive breast cancer, there was no significant correlation between IHC-measured Ki67 and the 21-gene recurrence score in the overall population and using the International Ki67 Working Group risk categories, only fair agreement between high Ki67 and high RS.

Keywords

breast neoplasms; estrogen receptor; genomics; Ki-67 antigen; tumor biomarkers

Introduction

Adjuvant chemotherapy for patients with early-stage, hormone receptor (HR)-positive, HER2-negative breast cancer was traditionally based on clinicopathologic features such as tumor size, nodal status, histologic grade, and estrogen receptor (ER) and progesterone receptor (PR) status.[1] However, recent advancements have allowed the use of genomic assays to identify patients who may derive the highest benefit from adjuvant chemotherapy.[2,3]

The 21-gene recurrence score (RS) Assay (Oncotype DX) is a validated genomic signature used to guide decisions on adjuvant chemotherapy and predict risk of recurrence in patients with HR-positive, HER2-negative early breast cancer (EBC). The assay results are driven largely by genes reflecting estrogen signaling and tumor cell proliferation, including Ki67.[3,4] There is level 1A and 1B evidence indicating that the 21-gene recurrence score is prognostic of distant recurrence risk, and predictive of adjuvant chemotherapy benefit or lack therefore in women with EBC and up to 3 positive axillary nodes. Patients with low RS have a low rate of distant recurrence that is likely not affected by adjuvant chemotherapy, whereas those with a high RS benefit from adjuvant chemotherapy therapy added to endocrine therapy.[5,6]

Ki67 is a nuclear protein whose expression serves as a proliferation marker that is determined by immunohistochemistry (IHC). Ki67 protein is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), is especially high during cell cycle progression through the S phase, and is absent in quiescent cells during the G_0 phase of the cell cycle.[7] Several studies have suggested that Ki67 may be prognostic in HR-positive EBC.[8–10] However, the use of Ki67 to predict benefit of adjuvant chemotherapy is not recommended in current practice guidelines, and its applicability is limited by variability in methods of measurement and use of different cutoffs.[7,11–16] To date, there is no robust evidence that Ki67 is predictive of response to adjuvant chemotherapy. The International Ki67 Working Group (IKWG) found that there was high concordance among pathologists for specimens with Ki67 ≤ 5% or ≥ 30%.[17] Based on this, the IKWG recommended that the clinical utility of Ki67 may be limited to values ≤ 5% or ≥ 30% and in patients with HR-positive, HER2-negative, T1-T2 and N0-N1 early breast cancer.[17,18]

Recently, the addition of adjuvant abemaciclib to endocrine therapy was demonstrated to improve invasive disease-free survival (DFS) in patients with HR-positive EBC with a high risk of recurrence based on number of positive lymph nodes and tumor grade, size, and Ki67.[19] Based on these results, the US Food and Drug Administration (FDA) approved the use of adjuvant abemaciclib in patients with HR-positive, HER2-negative, node-positive EBC with high risk of recurrence and Ki67 ≥ 20% as determined by an FDA approved test.[20] However, it remains uncertain as to whether Ki67 may be used to predict benefit of adjuvant therapy.

To optimize decisions on adjuvant therapy, it is important to understand the association between genomic assays such as the 21-gene assay which is predictive of chemotherapy benefit and Ki67 which is now approved to guide use of adjuvant abemaciclib. The goals of the current study were to determine the correlation between IHC-measured Ki67 with the 21-gene RS using the IKWG prognostic risk categories and evaluate their association with other anatomic and biologic tumor features in patients with early-stage, HR-positive, HER2-negative breast cancer.

Methods

Patient Population

The study included all female patients with early-stage, HR-positive breast cancer who had both Ki67 and 21-gene RS performed at our institution between 2013 to 2021. All patients in this study were HR-positive as defined by IHC with estimated percentages of staining of ER and/or PR ≥1%. Only patients with 0–3 positive lymph nodes were included. Patients with HER2-positive, triple negative, or metastatic breast cancer were excluded. Patients who had received neoadjuvant endocrine or chemotherapy were also excluded from the study.

Study Design

We performed a retrospective chart review of the electronic medical record to extract information on patient demographics, tumor characteristics including size, histology, lymph node positivity, ER and PR percentage, RS and Ki67. Both the 21-gene RS and

Ki67 were performed on the same surgical specimen. For this analysis, patients were categorized into Ki67 low (≤ 5%), intermediate (6–29%), and high (≥30%) based on IKWG recommendations.[18] All Ki67 testing occurred at our institution's pathology CLIA laboratory. Ki67 was measured through IHC using the MIB-1 antibody. From 2013–2015, the Roche Ventana assay was used but since 2015, the Agilent Dako Omnis test was used to assess Ki67. Pathologists examined the entire glass slide section using low-power magnification (with 4x) to get a general estimate of Ki67 staining. The Ki67 was evaluated only in the invasive carcinoma, excluding carcinoma in-situ and non-tumor tissue such as necrosis and fibrosis. Pathologists performed an unweighted score of Ki67 staining ranging from low to medium and high intensity altogether with no separation of count in these areas. Ki67 positivity was assessed both towards the edge of the tumor, as well as non-proliferating areas of invasive tumor. One hundred cells were counted in both areas, hot and weak spots. These areas were averaged to obtain an overall Ki67 staining percentage. Of note, our method differed from that of the IKWG as the intensity of staining was not incorporated into Ki67 measurement.

21-gene RS was performed by the laboratory of Genomic Health, Inc. (Redwood City, CA). RS was divided into categories of low (0–10), intermediate (11–25), and high (≥26) based on the TAILORx study and most recent NCCN guidelines.[5,16] These three categories were chosen as they are used in clinical practice to make decisions regarding adjuvant chemotherapy. Collapsing the low and intermediate RS categories into one group (RS 0–25) would not impact the primary analyses. Information on treatment including adjuvant chemotherapy, surgery, radiation therapy and endocrine therapy was also obtained. This study was approved by the Institutional Review Board at the Mount Sinai Health System (STUDY-21–00500) and adhered to ethical standards set forth by the Declaration of Helsinki. Patient consent was not required per the IRB above.

Statistical Analyses

Patient demographic, disease and tumor-related characteristics were summarized for continuous variables as median and interquartile range and for categorical variables as counts and percentages. Group comparisons of continuous variables were performed using Wilcoxon rank sum tests and of categorical variables using the χ^2 test or Fisher's exact test, as appropriate. Overall and risk stratified agreement between Ki67 and RS was evaluated by the Cohen's Kappa (k) statistic. Landis and Koch's guidelines were adopted as benchmark scales of 'k' coefficients (slight: 0.01–0.20; fair: 0.21–0.40; moderate: 0.41–0.60; substantial: 0.61–0.80 and almost perfect: 0.81–1.0). Pearson's correlation coefficients were used to evaluate association between Ki67 and RS using continuous distribution. Linear regression was used to examine associations between tumor features (ER%, PR%, tumor size, nodal status, and tumor differentiation) and Ki67 and RS. Ki67, RS, and tumor size were natural log-transformed because the distributions were right skewed. Geometric means and ratios of geometric means with corresponding 95% confidence intervals were presented for the categorical independent variables: nodal status and tumor differentiation. Slopes and corresponding 95% confidence intervals were presented for the continuous independent variables: ER%, PR% and tumor size. Slopes were interpreted as the percent change in Ki67/RS per 1% increase in tumor size, ER% and PR%. Log-binomial regression

was used to compare the likelihood of receiving adjuvant chemotherapy in patients with high Ki67 and low RS versus low ki67 and high RS. Hypothesis testing was two-sided and conducted at the 5 % level of significance. All statistical analyses were done using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

We identified 959 potentially eligible patients with HR-positive EBC and after excluding patients with HER2-positive or triple negative breast cancer and those without Ki67/RS information, the final dataset included 525 patients who were diagnosed from 2013–2021 (Figure 1). Of note, 98.5% of patients were diagnosed 2016 and after, when the Agilent Dako Omnis assay was being used to assess Ki67. Table 1 presents baseline characteristics of the population. Median age at diagnosis was 59 years; 27% were ≤ 50 years and 30% were pre-menopausal. Eleven percent of patients were node positive. Most (81%) patients had invasive ductal carcinoma while 14% had invasive lobular carcinoma. Overall, 29% of patients had low Ki67 (≤ 5%), 49.5% intermediate (5–29%), and 21.5% high (≥ 30%). Ki67. In terms of RS distribution based on categories from TAILORx, 18.9% had RS 0–10, 66.4% had RS 11–25 and 14.7% had RS 26–100. Using RS categorization from prior studies, 58% had RS 0–18, 38% had RS 19–30, and 4% had RS 31–100.

Correlation between Ki67 and RS

Figure 2 demonstrates the RS distribution based on Ki67 risk group. In the low Ki67 group, 6.6% (n=10) had a high RS. Among patients with intermediate Ki67 of 6–29%, 89% (n=232) had a low or intermediate RS. In patients with high Ki67, only 34.5% (n=39) had a high RS. In the overall population, there was slight agreement (kappa 0.01–0.20) between Ki67 and RS (kappa= 0.027) though this was not statistically significant (p=0.1985). In the high Ki67 group, there was fair agreement (kappa 0.21–0.40) between Ki67 and RS (kappa=0.280, p<0.001). There was no significant agreement between Ki67 and RS in the low Ki67 (kappa=−0.063, p=0.9251) and intermediate Ki67 subgroups (kappa=−0.060, p=0.9136).

Using a continuous distribution of Ki67 and RS, among low risk Ki67 patients, the Pearson correlation coefficient was −0.1057; p=0.1948. Among intermediate risk Ki67 patients, the Pearson correlation coefficient was 0.1005; p=0.1059 while among high risk Ki67 patients, the Pearson correlation coefficient was 0.3177; p=0.0006. Supplementary Figure 1 demonstrates overall association between Ki67 and RS using a continuous distribution and Supplementary Figure 2 depicts boxplots of Ki67 continuous distributions for low, intermediate, and high RS categories. Median [Q1, Q3] Ki67 scores for low, intermediate, and high RS subgroups are 10 [6, 20], 10 [5, 20], and 30 [10, 50] respectively, demonstrating the non-linear association between Ki67 and RS. The analysis thus focused on categorical rather than continuous comparison.

When stratified by racial subgroups, among White patients, there remained a fair agreement between Ki67 and RS in the high Ki67 group (kappa=0.253, p<0.0001), but no significant

agreements were seen in the Hispanic (kappa=0.095, p=0.2236) and Black/African American groups (kappa=0.062, p=0.3427) with high Ki67. Among patients age ≤ 50 years, there was slight agreement between Ki67 and RS in the overall population (kappa=0.111, p=0.0367) and fair agreement in the high Ki67 group (kappa=0.298, p=0.0002). In patients > 50 years, there was fair agreement only in the high Ki67 group (kappa=0.268, p<0.0001).

Association with other Clinicopathologic Factors

The majority (70%) of patients in the high Ki67 group had poorly differentiated tumors, and few (1%) had low grade tumors, indicating that Ki67 may not provide much additional prognostic information beyond grade. High Ki67 was also significantly associated with other adverse prognostic factors, including positive lymph nodes and larger size (Table 1). In age adjusted linear regression estimates (Table 2), poorly differentiated tumors were associated with higher RS and higher Ki67 (p<0.0001). Patients with poorly differentiated tumors had on average Ki67 values that were 3.42 times (27.90/8.16=3.42) that of patients with well differentiated or moderately differentiated tumors and RS values that were 40% higher (19.39/13.84=1.40). With respect to tumor grade, 58% of the 76 patients with high RS had poorly differentiated tumors while only 25% of the 347 patients with intermediate RS and 16% of the 99 patients with low RS had poorly differentiated tumors. In addition, linear correlation between Ki67 and RS was strongest in patients with high grade tumors with Pearson correlation coefficient 0.4103, p<0.0001. In patients with low grade tumors, Pearson correlation coefficient was 0.0368 with p=0.7491 and in those with intermediate grade tumors, Pearson correlation coefficient was 0.0718 with p=0.2168. This is explained by the stronger linear association between Ki67 and RS in patients with higher RS scores, which is also associated with higher tumor grade.

There was an association between positive nodal status and higher Ki67 (p=0.0059) but not with RS (p=0.0686). Patients with positive nodal status had on average a 51% higher Ki67 than patients with negative nodal status (16.59/10.96=1.51). As shown in Figure 3 and Table 2, higher ER% was significantly associated with both lower RS (p<0.0001) and lower Ki67 (p=0.0028) based on multivariable linear regression model estimates. There was an association between high PR% and lower RS (p<0.0001) but not lower Ki67 (p=0.3937). Larger tumor size correlated with higher Ki67 (p<0.0001) but not RS (p=0.6952).

Use of Adjuvant Chemotherapy

Overall, 18.3% (n=96) of patients received adjuvant chemotherapy. Of 77 patients with a high RS (≥ 26), 84.4% received adjuvant chemotherapy. Patients with high Ki67 (≥30%) and high RS were 22% more likely (92% vs. 76%) to receive chemotherapy than patients with an intermediate/low Ki67 (< 30%) and high RS, but this increased likelihood was not statistically significant; p=0.0562. Among 447 patients with an RS ≤ 25, those with a high Ki67 were at least 4 times as likely (19% vs. 4%) to receive chemotherapy compared to patients with an intermediate/low Ki67, p<0.0001.

Discussion

The IKWG reported that Ki67 is prognostic for recurrence in HR-positive, HER2-negative EBC in patients with Ki67 ≤ 5% or ≥ 30% but concluded that its prognostic value and clinical utility is uncertain in patients with intermediate Ki67 of 6–29%.[18] Using these prognostic categories, we found that in this group of 525 patients selected to have a 21-gene RS, 49% had an intermediate Ki67 value of 6–29%, and there was no significant correlation between Ki67 and RS in the overall population and in the low (≤ 5%) and intermediate Ki67 (6–29%) subgroups, and only fair agreement between Ki67 and RS in the high Ki67 (≥ 30%) group. Strengths of this study include the first comparison of RS and Ki67 using the evidence-based, expert-derived IKWG criteria in which the 21-gene RS was used in a real-world practice setting. Limitations include Ki67 assessment by multiple different pathologists at a single laboratory at an academic medical center that may not fully represent a real-world scenario, the retrospective nature of the study including a population selected to have a 21-gene RS performed, and the lack of information regarding clinical outcomes.

In our cohort, among the approximately one-half of patients with an intermediate Ki67 of 6–29%, 89% would be spared chemotherapy based on a low-intermediate RS. Even in patients with high Ki67, 68% might not benefit from chemotherapy based on the RS. Within the low Ki67 group, 6% of patients had a high RS. Our findings suggest that across all prognostic risk categories, and especially in the low and intermediate Ki67 subgroups, Ki67 has limited utility in identifying patients with high or low RS. This is the first study to our knowledge evaluating the relationship between RS and Ki67 based on the Ki67 prognostic risk categories set forth by the IKWG and using a real-world dataset.

Prior studies have demonstrated that Ki67 does provide prognostic value for recurrence, supporting the recommendations of the IKWG for use of Ki67 as a prognostic biomarker in this population with HR-positive, HER2-negative EBC. In a meta-analysis of 12,155 patients with early breast cancer, Ki67 positivity was associated with increased risk of recurrence as well as worse overall and DFS in both node-positive and node-negative patients.[21] However, Ki67 has not demonstrated to predict response to adjuvant chemoendocrine therapy versus endocrine therapy alone. Ki67 assessment of tumor tissue from the International Breast Cancer Study Group (IBCSG) Trials VIII and IX found that among 1521 patients with endocrine-sensitive tumors, high Ki67 (≥ 19%) did not predict efficacy of adjuvant chemoendocrine therapy compared with endocrine therapy alone though Ki67 was prognostic.[22] Studies evaluating the predictive role of Ki67 are scarce and variable cutoffs and methods of measurement limit their interpretation. Data from adjuvant trials suggest that high Ki67 may predict benefit for a taxane-based regimen compared with a non-taxane regimen.[11,12,23]

Although use of Ki67 to guide decisions on adjuvant chemotherapy is uncertain, it may have a role in guiding the use of adjuvant CDK 4/6 inhibitor therapy in high-risk HR-positive, HER2-negative localized breast cancer. Results from the monarchE trial indicated that a high Ki67 (≥ 20%) was associated with a higher recurrence risk and greater absolute benefit from adjuvant abemaciclib.[19]

The use of Ki67 is challenging due to its lack of standardization, inter-observer variability, and arbitrary cutoffs.[18,24] For these reasons, the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline recommends that in terms of guiding adjuvant chemotherapy and endocrine therapy, Ki67 should only be used in conjunction with other parameters and in patients without access to genomic assays.[14] Our results support these recommendations as we found that Ki67 cannot be reliably used to identify patients with low or high RS who ultimately benefit from chemotherapy. Interestingly, retrospective analyses from our study indicated that at our institution, higher Ki67 was associated with increased use of chemotherapy in patients with intermediate/low RS. This may reflect Ki67's association with other adverse prognostic factors such as larger tumor size and positive axillary nodes.

Our results on the association between Ki67 and RS are consistent with previously reported data from prospective trials. Prospective analyses of patients from the West German Study Group Phase III PlanB trial showed a weak to moderate correlation between RS and Ki67 in patients with early HR-positive breast cancer. Among patients with low Ki67 (0–9%), less than 10% of patients had high RS. In patients with high Ki67 of greater than 39%, nearly 10% had RS 0–25.[25] These distributions support the lack of a strong overall correlation between Ki67 and RS.

The results of our study provide additional information by evaluating the correlation between RS and Ki67 using the IKWG classification.

In conclusion, the current study suggests that Ki67 does not significantly correlate with RS, especially in patients with low-intermediate Ki67, and should not be used to guide decisions on adjuvant chemotherapy. Additional studies are needed to determine the predictive value of Ki67 for adjuvant endocrine therapy and biologic agents such as CDK 4/6 inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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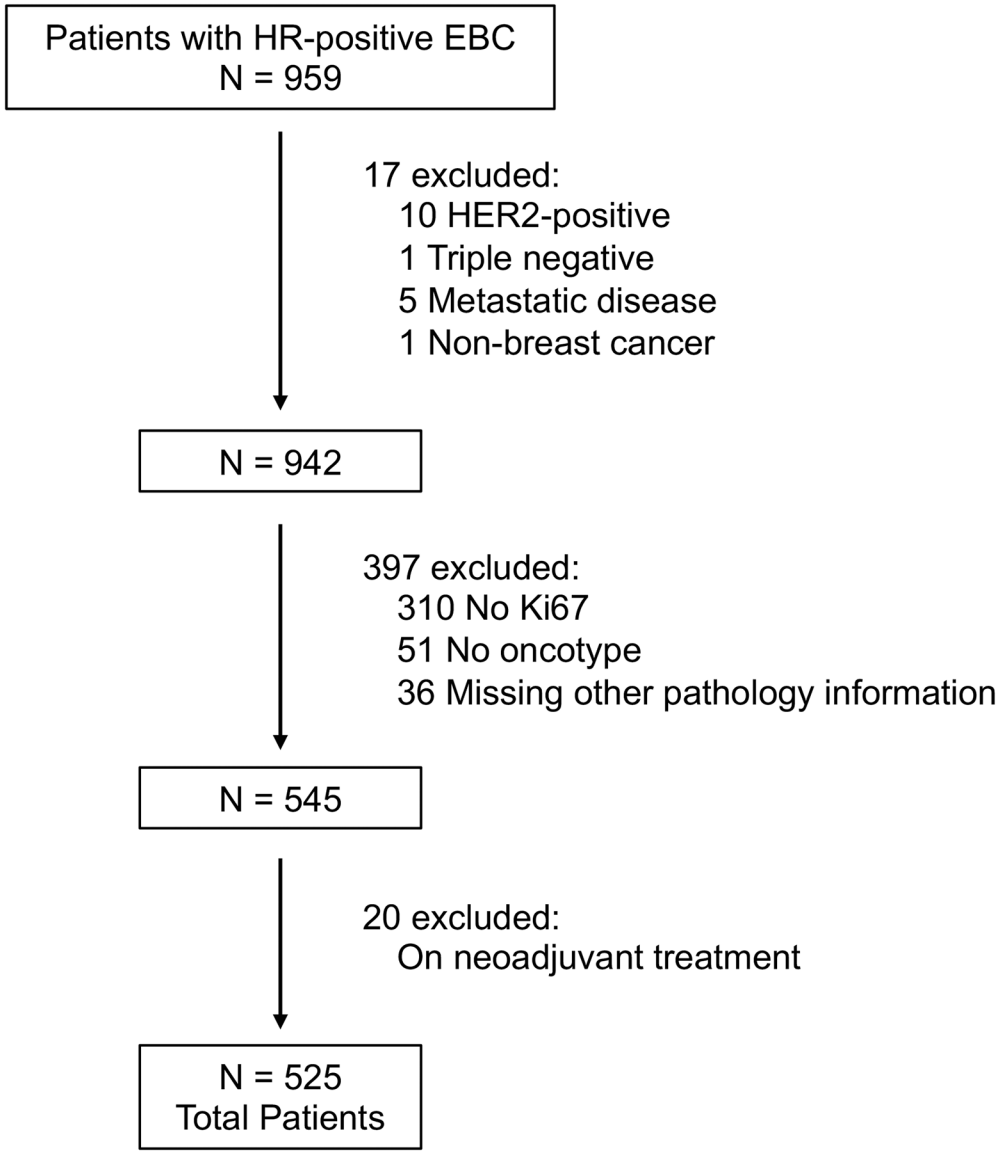

Figure 1. Consort Diagram of Patient Population
EBC: early breast cancer

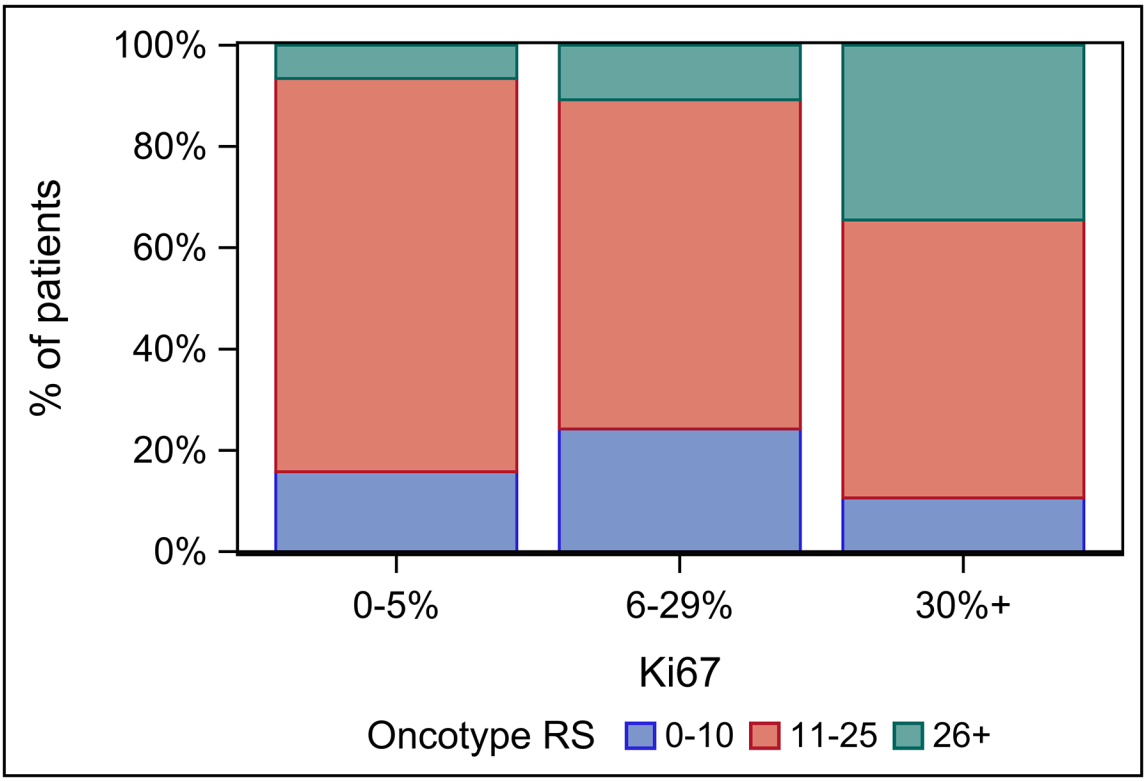

Figure 2. Oncotype RS Distribution by Ki67 Risk Group

Stacked bar chart showing the percent of patients among low, intermediate, and high Ki67 risk subgroups with low, intermediate, or high RS.

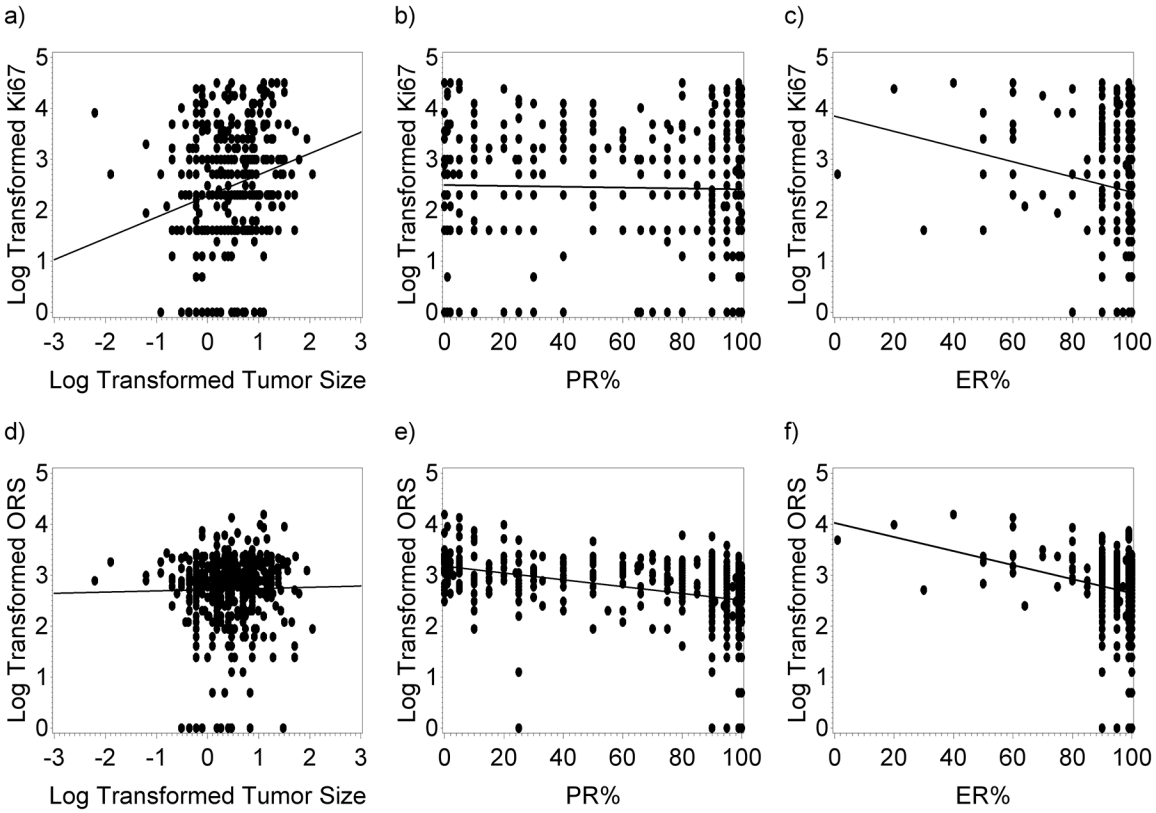

Figure 3. Associations between Ki67/RS and Biologic and Anatomic Tumor Features

Scatter plots and linear regression lines of natural log transformed Ki67 versus a) natural log transformed tumor size, b) PR%, c) ER% and natural log transformed Oncotype recurrence score (ORS) vs. d) natural log transformed tumor size, e) PR%, and f) ER%.

Table 1.

Patient Baseline Characteristics

	All Patients N=525	Ki67 Low N=152	Ki67 Intermediate N=260	Ki67 High N=113	P-value
Age at Diagnosis[a] (years)					
	59 [50, 68]	60 [51.5, 69]	59 [50, 68]	56.5 [47.5, 65]	0.0921
Race/Ethnicity [b]					
White	296 (58%)	100 (67%)	135 (53%)	61 (55%)	0.0143 *
Hispanic/Latino	43 (8%)	16 (11%)	19 (8%)	8 (7%)	
Black/African American	64 (13%)	9 (6%)	43 (17%)	12 (11%)	
Asian/Pacific Islander	53 (10%)	13 (9%)	29 (11%)	11 (10%)	
Other	58 (11%)	11 (7%)	29 (11%)	18 (16%)	
Unknown	11 (2%)	3 (2%)	5 (2%)	3 (3%)	
Menopausal Status [b]					
Pre-Menopausal	153 (30%)	35 (24%)	79 (31%)	39 (37%)	0.0085 *
Post-Menopausal	345 (68%)	110 (74%)	173 (68%)	62 (58%)	
Peri-Menopausal	9 (2%)	3 (2%)	1 (1%)	5 (5%)	
Unknown	18 (3%)	4 (3%)	7 (3%)	7 (6%)	
Largest Tumor Size[a] (cm)					
	1.5 [0.9, 2.2]	1.2 [0.8, 1.6]	1.6 [1.2, 2.3]	1.6 [1.2, 2.4]	<0.0001 *
Tumor Grade [b]					
Well Differentiated	78 (15%)	56 (37%)	21 (8%)	1 (1%)	<0.0001 *
Intermediate	298 (57%)	89 (59%)	177 (68%)	32 (29%)	
Poorly Differentiated	146 (28%)	6 (4%)	61 (24%)	79 (70%)	
Unknown	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	
Nodal Status [b]					
Positive	58 (11%)	6 (4%)	36 (14%)	16 (14%)	0.0040 *
Negative	466 (89%)	146 (96%)	224 (86%)	96 (86%)	
Unknown	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	

[a] Median [1st Quartile (Q1), 3rd Quartile (Q3)];

[b] N(%);

* P <0.05

Table 2.

Age Adjusted Linear Regression Estimates for Ki67 and Oncotype RS regressed on tumor characteristics

Tumor Characteristics	Ki67			Oncotype RS		
	Geometric Mean[a]	Ratio of Geometric Means[a]/Slope[b,c] [95% CI]	P-value	Geometric Mean[a]	Ratio of Geometric Means[a]/Slope[b,c] [95% CI]	P-value
Poorly Differentiated Tumor [a]						
No	8.16	Reference		13.84	Reference	
Yes	27.90	3.42 [2.86, 4.08]	<0.0001*	19.39	1.40 [1.24, 1.58]	<0.0001*
Nodal Status [a]						
Negative	10.96	Reference		14.95	Reference	
Positive	16.59	1.51 [1.13, 2.03]	0.0059*	17.58	1.18 [0.99, 1.40]	0.0686
Tumor Size [b]		0.42% [0.26%, 0.58%]	<0.0001*		0.02% [−0.08%, 0.12%]	0.6952
PR% [c]		−0.11% [−0.37%, 0.14%]	0.3937		−0.71% [−0.85%, −0.58%]	<0.0001*
ER% [c]		−1.40% [−2.31%, −0.49%]	0.0028*		−1.31% [1.84%, −0.78%]	<0.0001*

[a]Geometric Mean presented within each level of categorical variables with Ratios of Geometric Means.

[b]Slope presented for continuous variables; percent change (negative-reduction; positive-increase) in risk score per 1% increase in tumor size.

[c]Slope presented for continuous variables; percent change (negative-reduction; positive-increase) in risk score per 1 unit increase in PR%, ER%.

*P<0.05; CI: Confidence Interval