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Research Article

Accuracy of Ki-67 with Recurrence Score and Recurrence Score –Pathology – Clinical Assessment in Early Stage Breast Cancer

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Abstract

Background: Ki-67 is a cellular marker of proliferation in breast cancer but varied scoring methods and standardization of the assays have limited its clinical utility. The Recurrence Score Pathology – Clinical (RSPC) value integrates the Recurrence Score (RS) with tumor grade, tumor size, and patient age and has been suggested to provide additional prognostic value and greater accuracy in the assessment of distant recurrence risk than RS. Many patients in El Paso, TX, with breast cancer have limited resources and are unable to receive relatively expensive diagnostic assays. We sought to compare the diagnostic performance of Ki-67 with RS and RSPC to determine the clinical validity of using Ki-67 as a prognostic tool.

Methods: Patients with early stage estrogen receptor or progesterone receptor positive breast cancer were assessed for Ki-67 indices using an immunohistochemical method. Ki-67 was considered as low < 20%, intermediate 20-50%, and high > 50%. RSPC was calculated using a risk assessment tool, with low < 12%, intermediate 18-20%, and high > 20% cutoffs. Raw agreement and weighted Kappa agreement were obtained between Ki-67, RS, and RSPC. McNemar's test was used to compare the proportion of discordant pairs between Ki-67, RS, and RSPC. In addition, sensitivity, specificity, and predictive values of Ki-67 in relation with RSPC and RS were calculated after dichotomizing these measures.

Results: The accuracy of Ki-67 with RS was observed as 51% while with RSPC as 55%. A very good concordance was found between low Ki-67 and low RSPC (80.9%) while a moderate concordance was observed between low Ki-67 and low RS (55%). We also observed a moderate concordance between high Ki-67 and high RS (50%). The concordance between intermediate Ki-67 and RS was found to be moderate (46%) and with intermediate RSPC was observed to be 30%. Specificities of Ki-67 with RS and RSPC (for classifying high or intermediate) were found as 68.3% and 80.5% respectively. The positive predictive values of Ki-67 with RS and RSPC (for classifying high or intermediate) were observed as 63.9% and 72.4% respectively.

Conclusion: Ki-67 provides a very good concordance with RSPC. Ki-67 provides a moderate concordance with RS for low risk (Ki-67 < 20% as cut off) as well as for RSPC and RS for high risk group (Ki-67 > 50%). High specificity of Ki-67 shows that Ki-67 can be used for clinical decision making. Ki-67 can be used reliably for clinical decision making, particularly in low and high risk groups in the absence of RS or RSPC. This has significant clinical and cost implications for many early stage breast cancer patients with limited resources.

Keywords: Pathology; Breast cancer; Reverse transcription polymerase chain reaction; Ki-67

Introduction

Advances in therapeutics and treatment regimens for breast cancer have led to increases in survival in recent decades [1], with prolonged survival achieved in patients with Stage I-III cancer [2]. In this context, prevention of overtreatment with highly toxic chemotherapeutic agents is key in patients with favorable prognoses to avoid complications from long-term sequelae [3]. It is estimated that 85% of patients with early stage breast cancer may not benefit from chemotherapy [4]. Risk stratification has classically focused on clinical and histopathological factors; however, emerging biomarkers and multigene assays are increasingly being used in clinical practice [5,6].

The 21 gene recurrence assay is a genomic assay that utilizes Reverse Transcription Polymerase Chain Reaction (RT-PCR) analysis of a gene panel and an algorithm to estimate a Recurrence Score (RS), indicating rate of distant recurrence at 10 years. Among the 21 genes

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in this assay, expression of the 16 genes selected based on their cancer related functions are normalized to the 5 reference genes in the panel. Initial development of this assay was designed to determine the risk of recurrence in patients with node-negative, Estrogen Receptor (ER) positive breast cancers treated with tamoxifen. In the NSABP B-14 trial, distant recurrence at 10 years was estimated to be 6.8%, 14.3%, and 30.5% for low (RS<18), intermediate (RS = 18 – 31), and high-risk (RS>31) groups, respectively [4]. RS was found to be predictive of overall survival and its use in guiding treatment of early stage cancers was validated by independent studies, which extended the utility of RS to patients treated with anastrozole or chemotherapy in node-negative and node-positive cancers [7-9]. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial further demonstrated a linear increase in distant recurrence with increasing RS, as well as higher risks consistently observed in patients with node-positive in comparison to node-negative cancers [8]. It has been suggested that RS analysis may be beneficial in the HER2 negative subpopulation [10] and not relevant in HER2 positive cancers as they will clearly benefit from chemotherapy treatment. Although, concerns have been raised regarding the validity of RS in highly ER positive, HER2 negative tumors [11]. A separate group assessing quality control in RS reporting of HER2 demonstrated a high false negative rate greater than 50%, leading to a potential under estimation of RS [12]. A more accurate RS-Pathology-Clinical (RSPC) score has been developed from integration of the RS with patient age, tumor size, and tumor grade. While this refined score does not appear to affect chemotherapy benefit, it has been shown to be of most value in defining intermediate risk groups [13].

Despite the implementation of RSin the management of ER positive, HER2 negative, early stage breast cancer, the test remains a relatively expensive tool for patients who are underinsured or in low-resource settings. Therefore, many centers continue to routinely rely on immunohistochemical and molecular studies, namely to evaluate hormone receptor status and proliferation indices. Ki-67 is an antigen with a short half-life predominantly accumulated in the S phase of proliferating cells, and is an especially useful marker of cancer cells considering its relatively selective cell cycle phase expression pattern and response to hormonal therapy [14-18]. Higher Ki-67 indices are generally considered to indicate a poor prognosis [19], associated with higher rates of disease relapse [20,21] and overall decreased survival [22]. Congruently, it has been reported that invasive breast cancers with increased proliferation rates have a poor prognosis regardless of assay used [23]. Though prognosis is unfavorable, higher baseline levels of Ki-67 are predictive of response to chemotherapy, specifically in the absence of hormone receptor expression [24,25]. Results of the IMPACT (Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen) trial performed in patients with estrogen positive primary breast cancers suggest that Ki-67 levels post hormonal treatment is more predictive compared to baseline levels [26]. HighKi-67expression post tamoxifen or anastrozole treatment has been correlated with lower recurrence-free survival, inferring a lack of decrease in Ki-67 levels in non-responsive tumors [27].

With the abundance of methodologies available, it becomes imperative to achieve concordance between systems in the interest of accurate risk stratification. Limited data is available correlating the value of RS to Ki-67 indices. A study of 32 estrogen positive, HER2 negative, invasive carcinomas revealed specimens with high Ki-67 proliferation rates (mean of 32.1%) corresponding to a higher mean of RS (mean of 23) [28]. A portion of their tumors with low RS unexpectedly displayed high Ki-67 values, and they further reported a strong association of RS with the Nottingham histologic grade [28]. Within the parameters of the Nottingham grade and score, mitotic count was independently found to correlate to RS by others [29]. In a sample of 53 tumors with a similar profile to the previous study, low Ki-67 specimens had RS values of low or intermediate risk, with high Ki-67 specimens grouping to high or intermediate risk categories [30]. This trend has been validated in disseminated tumor cells in the bone marrow, as well as circulating tumor cells [31]. A lack of correlation has been noted, however, between RS and Nottingham grade when controlling for Ki-67, indicating its contributing effect [30]. More variable results have been obtained in low-grade breast cancers. The presence of proliferative stromal tissue or inflammatory cells in the specimen has been associated with higher than expected RS values in low-grade tumors [32,33].

In the studies herein, we sought to assess the concordance between Ki-67indiceswith RS and RSPC in ER positive, early stage breast cancer (Stage 1 and 2) in a predominantly Hispanic population.

Materials and Methods

After obtaining Institutional Review Board approval, consecutive patients with early stage ER positive breast cancer who underwent RS testing at the Texas Tech Garbar Breast Care Center in El Paso, TX, from January 2011 – January 2013 were included. Ki-67 was performed using a consistent immunohistochemical method revised by a pathologist (O. P.). Ki-67 results are reported for the nuclear staining as the percentage of positively stained cells among the total number of malignant cells scored. The immunohistochemical antibody clone for Ki-67 used is a rabbit monoclonal (30-9) from Ventana (Tucson, AZ.). Deparaffinization, antigen retrieval method, and antibody incubation (40 minutes) are performed as recommended by the manufacturer. A comparison of a positive and negative control is also performed for quality assurance.

Each Ki-67 slide was evaluated through 10 random high power fields (40X), which included counting the number of positive and negative nuclei. Based on the average number of nuclei evaluated in each microscopic field, we estimated that at least 2000 invasive tumor nuclei were counted for each case. The estimated number of positive nuclei was divided by the total estimated number of negative nuclei, which resulted in the proliferative or Ki-67 index for each case. This index was then categorized as low (<20%), intermediate (20-50%), or high (>50%) [34].

Statistical analysis

Our primary objective was to assess the diagnostic performance of Ki-67 with RS and the RSPC which determines disease recurrence risk at 10 years. For this we have considered two forms of RS: low <18%, intermediate 18-30%, and High ≥ 31%; and low <18%, intermediate/High ≥18%. For Ki-67 we considered: low <20%, intermediate 20-50%, and High > 50%; and low <20%, intermediate/High ≥20%. Similarly, we have considered two forms of RSPC: low <12%, intermediate 18-20%, and High > 20%; and low <20%, intermediate/High > 20% [13]. Data was described using appropriate summary

Table 1: Descriptive statistics of continuous variables.

Variable	N	Mean	Standard Deviation
Age (years)	88	59.5	10.84
Diagnosis age (years)	88	56.51	10.78
Tumor size (cm)	74	2.16	2.09
Ki-67 (%)	88	23.51	18.26
RS (%)	88	18.31	10.19
RSPC (%)	88	11.95	11.57

measured for categorical and continuous data. Raw agreement and weighted Kappa agreement along with 95% Confidence Interval (CI) were obtained between Ki-67, RS, and RSPC. A weight of 1 was assigned for agreement and 50% for responses that differed by 1 category and 0 for responses that differed by 2 categories in weighted Kappa analysis. McNemar's test was used to compare the proportion of discordant pairs between Ki-67, RS, and RSPC. In addition, for binary responses of Ki-67 and RS, the diagnostic performance of Ki-67 was summarized using sensitivity, specificity, and predictive values by considering RS as a reference test. We also determined the diagnostic accuracy of Ki-67 with RSPC by considering RSPCS as a reference test. Similarly, sensitivity, specificity, and predictive values of dichotomized RSPC was also computed by considering RS as a reference test. The agreement may be considered as very good (>0.80), good (0.61-0.80), moderate (0.41-0.60), fair (0.21-.40), and poor (<0.20) [35]. P-values less than 5% were considered as significant results. Stata 12.1 was used for data analysis.

Results

Table 1 and 2 show the summary of the study population. A total of 88patients were included with a mean age of 59. Of total, 88 were females, 84% Hispanic, 4% White Caucasian, 4% African-American; 3% Asian, and 3% Native American. 60% had Stage I and 40% had stage II breast cancer. Of total, 83% were PR positive, and 86% were HER2 negative. Types of invasive cancer were ductal (84.09%), lobular (6.82%), and mixed or nonspecific (9.1%). Ki-67 score stratified our study population as: low 46.59% of patients; intermediate 42.05%; and high 11.36%.

The concordance of Ki-67 and RSPC with RSandKi-67 with RSPC is shown in Table 3. The raw agreement and Kappa agreement between Ki-67 and RS were found as 51% and 25%, respectively; while raw agreement and Kappa agreement between RSPC and RS were found as 66% and 49%, respectively. The raw and Kappa agreement between Ki-67 and RSPC were found as 55% and 25% respectively. There were no significant differences in the discordant pairs between Ki-67 and RS (p=0.282) and between RS and RSPC (p=0.204). However, the discordant pairs between RSPC and Ki-67 were found statistically significant (p=0.0016).The highest concordance was found for low RSPC and low RS(86.7%), followed by low Ki-67 and low RSPC (81%). Moderate concordance was observed between high Ki-67 and high RS (50%), as well as between high RS and high RSPC (60%). We also observed a moderate concordance between intermediate RS and intermediateKi-67 (46%), and between low RS and low Ki-67 (55%). Fair concordance was noted with the intermediate group (27% for RS, and 30% forKi-67, in relation with RSPC) as well in the high group for Ki-67 and RSPC (40%).

Table 2: Descriptive statistics of categorical variables.

Variable	Frequency	Percent
Race		
African American	4	4.55
Asian	3	3.41
Hispanic	74	84.09
Native American	3	3.41
White	4	4.55
Diagnosis		
Ductal	74	84.09
Ductal and Lobular	4	4.55
Lobular	6	6.82
Other	4	4.55
Types of surgery		
Lumpectomy	60	68.18
Mastectomy	28	31.82
Cancer stage		
1	28	31.82
1a	24	27.27
2	10	11.36
2a	20	22.73
2b	6	6.82
PR receptor		
Negative	15	17.05
Positive	73	82.95
HER2 receptor		
Negative	76	86.36
Positive	11	12.5
Unknown	1	1.14
RS		
Low <18	52	59.09
Intermediate:18-30%	26	29.55
High ≥31%	10	11.36
Ki-67		
Low <20%	41	46.59
Intermediate: 20-50%	37	42.05
High >50%	10	11.36
RSPC		
Low <12%	59	67.05
Intermediate: 12-20%	17	19.32
High >20%	12	13.64

The prevalence of high and intermediate risk was 41% according to RS and RSPC. The sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Ki-67 for classifying high and intermediate RS were determined to be 48.9%, 68.3%, 63.9%, and 53.8%; while 61.1%, 86.5%, 75.9%, and 76.3% were observed respectively for RSPC. In relation with high and intermediate RSPC, the sensitivity, specificity, PPV and NPV of Ki-67 were observed as 44.7%, 80.5%, 72.4%, and 55.9% respectively. The specificity of Ki-67 was found more than or equal to 68% in relation with RS and RSPC (Table 4).

Discussion

In this study, we report high concordance between Ki-67 indices and RS, as well as between Ki-67 indices and an integrated RS Pathological-Clinical Score (RSPC) in ER positive, early stage breast cancers in a predominantly Hispanic population. Our results are in

Table 3: Agreement between Ki-67, RSPC, and RS.

	Ki-67 and RS	RSPC and RS	Ki-67 and RSPC
Agreement	**Value (95 % CI)**	**Value (95 % CI)**	**Value (95 % CI)**
Accuracy	0.511 (0.402, 0.619)	0.659 (0.55, 0.756)	0.545 (0.435, 0.652)
Kappa Agreement	0.245 (0.192, 0.286)	0.488 (0.398, 0.637)	0.253 (0.179, 0.257)
Concordance for low	0.547	0.867	0.809
Concordance for intermediate	0.461	0.269	0.297
Concordance for high	0.500	0.600	0.400

Table 4: Diagnostic accuracy of Ki-67 and RSPC according to RS and diagnostic accuracy of Ki-67 according to RSPC.

	Ki-67 and RS	RSPC and RS	Ki-67 and RSPC
Diagnostic measures	**Value (95 % CI)**	**Value (95 % CI)**	**Value (95 % CI)**
Sensitivity	48.9% (34.1 – 63.9)	61.1% (43.5 – 76.9)	44.7% (30.2 – 59.9)
Specificity	68.3% (51.9 – 81.9)	86.5% (74.2 – 94.4)	80.5% (65.1 – 91.2)
Positive predictive value	63.9% (46.2 – 79.2)	75.9% (56.5 – 89.7)	72.4% (52.8 – 87.3)
Negative predictive value	53.8% (39.5 – 67.8)	76.3% (63.4 – 86.4)	55.9% (42.4 – 68.8)

agreement with previous reports indicating stronger associations in low and high categories in comparison to intermediate risk samples.

Accurate risk stratification in early stage breast cancers is imperative to ensure the appropriate management of patients with regards to the initiation of chemotherapy to avoid unnecessary exposure. A number of clinical and pathological parameters are routinely considered in guiding the physician, with the Ki-67 biomarker being of notable value due to its widespread availability and cost effectiveness. Furthermore, immune-histochemical analysis of Ki-67 is the current assay of choice agreed upon by the International Ki-67 in Breast Cancer Working group for assessment of tumor proliferation, although the lack of definitive guidelines for result interpretation is acknowledged (36 – 38). Discrepancy in standardization of procedures and scoring has prevented the American Society of Clinical Oncology (ASCO) Tumor Marker Guidelines Committee from recommending routine use of the Ki-67 marker for prognosis in patients with newly diagnosed breast cancer [39]. Variability in Ki-67 results is attributed in part to pre-analytical components including antigen retrieval, fixations, storage, and staining techniques, with additional concerns of epitope loss [40-42]. Despite these apprehensions, the St Gallen International Expert Consensus held in 2009 strongly endorsed reporting of percentage of Ki-67 stained cells, although they recommended supplemental use of a multigene-profiling assay if available [43].

Multigene-profiling assays have enhanced our ability to determine the need for aggressive vs. conservative treatment specifically in low risk patient categories, with reports indicating a change in clinical decision in up to 33.4% of cases upon assessment with RS results [44]. Such advanced methodologies are not always accessible to patients limited by socioeconomic circumstances, as is the case with a substantial patient population in El Paso, TX. Routine analyses available to these patients include Ki-67 indices, and can be performed with more confidence given establishment of concordance with validated multigene models.

The evidence is clear on the benefit of chemotherapy in patients in high risk categories, emphasizing the importance in determining a correlation between RS and Ki-67 levels in low and intermediate risk groups. A very good concordance was displayed in our low risk category for RSPC with Ki-67 (0.809) while a moderate concordance was displayed in our low risk category for RS with Ki-67 (0.547), supporting use of Ki-67 as a relatively reliable tool in clinical decision making in this group. We were unable to establish high concordance between Ki-67 with either RS or RSPC in the intermediate risk group, and this group continues to pose inherent challenges with regards to clinical management. Further, specificity of Ki-67 in relation with RS and RSPC were found in between 68%-80.5%. This shows that it has more utility in classifying patients who need initiation of chemotherapy. Further studies are necessary to refine the parameters and recurrence risks of the intermediate group. The TAILORx (Trial Assigning Individualized Options for Treatment) trial is currently in progress and aims to elucidate the benefit of treatment in this risk category, with projected results anticipated in 2015 [45]. At our institution, diagnostic measures of Ki-67 were found to be considerably high for our study population, specifically in patients with breast tumors falling in either the high risk or low risk categories. Therefore, the Ki-67 index can be used reliably for clinical decision making in the absence of RS in these patients. Our study utilized a standard and consistent method for Ki-67 assessment. We recommend that each institution might attempt to standardize the use of its Ki-67 techniques to limit variability and lead to more clinically reliable results.

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