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Comparison between Ki67 Expression and Oncotype Dx® Recurrence Score in Luminal Breast Carcinomas

Ana Helena Willrich Rasera[1]*, Cleverton Spautz[2], Iris Rabinovich[3], Ana Cléa Andrade[4], Cícero Urban[2], Karina Furlan Anselmi[2] and Ana Paula Martins Sebastião[5]

[1]Post Graduation Program in Obstetrics and Gynecology, Clinical Hospital Complex of the Federal University of Paraná, General Carneiro Street, No. 181 Alto da Gloria, Curitiba, Paraná, 80060-900, Brazil

[2]Department of Mastologist. Breast Disease Center (CDM) and Nossa Senhora das Graças Hospital, Curitiba, Paraná, Brazil

[3]Department of Mastologist, Postgraduate Program in Obstetrics and Gynecology Professor, Clinical Hospital, Federal University of Paraná, Curitiba, Paraná, Brazil

[4]Department of Oncologist. Breast Disease Center (Centro de Doenças da Mama – CDM) and Nossa Senhora das Graças Hospital, Curitiba, Paraná, Brazil

[5]Department of Medical Pathology and Post Graduation Program in Obstetrics and Gynecology Professor, Clinical Hospital, Federal University of Paraná, Curitiba, Paraná, Brazil

Abstract

Introduction: In early-stage breast cancer, there is a constant search to identify which patients will benefit from chemotherapy. Among the most widely used genetic tests is Oncotype DX®, a validated prognostic marker. However, its high cost is still a major limitation. As a more financially viable alternative, the cell proliferation index determined by the Ki67 antigen is used.

Objective: To evaluate the percentage of Ki67 expression and its relationship with the Oncotype DX® recurrence score in luminal breast carcinomas.

Methods: 79 Oncotype DX® results available in the last 5 years were analyzed and compared with the respective anatomopathological and immunohistochemical reports.

Results: The mean age was 56 years with tumors ≤ 2 cm (72.2%), with a predominance of carcinomas of no special type (73.4%) and tumor grade 2 (72.2%). Among patients under 50 years of age, intermediate risk was the most common (60.7%). In this group, the cutoff point for Ki67 by ROC curve adjustment was 37% (p=0.032), with sensitivity of 85.7% and specificity of 61.9%. In patients over 50 years of age, low risk was prevalent (70.6%). The cutoff point for Ki67 by ROC curve adjustment was 33% (p=0.040), with sensitivity of 93.3% and specificity of 41.7%. For these cutoff points, the kappa coefficient of agreement was estimated at 0.29.

Conclusions: Ki67 correlated with the Oncotype DX® recurrence score. The kappa index showed low agreement. The results suggest that Ki67 should not be used alone for therapeutic decision-making, but rather associated with clinical factors.

Keywords: Breast cancer • Ki67• Proliferation index • Oncotype DX®

Abreviations: AJCC: American Joint Committee on Cancer; CAP: College of American Pathologists; CM: Centimeter; EGFR: Epidermal Growth Factor Receptor; HER-2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptort; IHC: Immune Histo Chemistry; IKWG: International Ki67 in Breast Cancer Working Group; MM: Mili Miter; NST: No Special Typer; ER: Estrogen Receptor; RP: Receptor Progesterone; RS: Recurrence Score; TNM: Classification of Malignant Tumor.

Introduction

Breast cancer is the most commonly diagnosed type of cancer, accounting for one in eight cancer diagnoses worldwide. In 2022, there were approximately 2.3 million new cases of breast cancer globally and approximately 665,000 deaths from this disease, with large geographic variations observed between countries and regions of the world [1]. The morphological and molecular aspects of breast cancer have been widely explored and, as it is a heterogeneous disease at the morphological, immunohistochemical and molecular levels, therapeutic planning must be individualized for each patient. Several aspects must be taken into consideration, such as age, general health status, tumor stage, Immune Histochemical Evaluation (IHC) of the tumor, axillary lymph node analysis, presence of mutations in important genes in breast cancer such as BRCA1 and BRCA2 and analysis of genomic markers [2].

In the early stage of breast cancer, most women diagnosed do not need to undergo chemotherapy [3]. Thus, in order to prevent patients from undergoing chemotherapy unnecessarily, several gene expression profiling assays have been used to identify groups with good and poor prognoses in clinical practice. The analysis of somatic mutation panels helps to understand breast cancer on an individual basis. Some examples are OncotypeDX®, which analyzes 21 genes; Mamma Print®, which analyzes 70 genes; Theros H/I®: I Ratio; Map Quant DXTM/Genomic Grade Index; MammaGene®. Of these, only OncotypeDX®, Theros H/I® and MammaGene® use formalin-fixed, paraffin-

***Address for Correspondence:** Ana Helena Willrich Rasera, Post Graduation Program in Obstetrics and Gynecology, Clinical Hospital Complex of the Federal University of Paraná, General Carneiro Street, No. 181, Alto da Gloria, Curitiba, Paraná, 80060-900, Brazil; E-mail: ahwrasera@gmail.com*

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embedded tissue. Of these, the most widely used is OncotypeDX®. These tests predict the risk of recurrence in addition to indicating whether or not there is a benefit in adopting adjuvant chemotherapy [4]. OncotypeDX® is then recommended for patients with early-stage invasive breast carcinoma, with Hormone Receptor-Positive (HR+) and HER2-negative tumors. The test provides individualized information about the tumor through a recurrence score (Recurrence Score®) with a number between 0 and 100 specific to each patient [5,6]. In developing countries, prognostic evaluation and indication of adjuvant chemotherapy remain, in the vast majority of cases, based exclusively on clinical and pathological criteria. The biggest barriers to access to molecular tests in the supplementary health system refer to the lack of coverage of the test by most Brazilian health insurance plans and its high cost [7].

In this context, there is a growing interest in finding simple and widely accessible tests that can help predict disease recurrence. Among the markers routinely performed in patients with invasive breast carcinomas is the Ki67 cell proliferation index, which is strongly associated with cancer proliferation and a known prognostic indicator. Several researchers have studied its prognostic and predictive value at different stages of breast cancer treatment [8]. High Ki67 expression detected by IHC has been reported as the strongest individual prognostic factor for death or early disease recurrence [9].

Materials and Methods

The study was conducted in an analytical, observational manner, with a retrospective design, at the Pathology Center of Curitiba, at the Nossa Senhora das Graças Hospital, in the city of Curitiba, Paraná state, Brazil country. It was approved by the Human Research Ethics Committee of the Health Sciences Sector of the Federal University of Paraná (UFPR) under number CAAE: 57259022.8.0000.0102 on 04/28/2022.

The information was collected from available Oncotype DX® reports, anatomopathological reports and immunohistochemical reports from the last 5 years, between 2019 and 2024. All collected data were entered into a Table (Excel®) created for later statistical analysis and comparison between the data.

The inclusion criteria were patients with invasive breast carcinoma with positive estrogen receptor evidenced by immunohistochemical study and subsequent Oncotype DX® research. Among the exclusion criteria were patients with incomplete demographic data and absence of immunohistochemical reports in the study laboratory.

Age of patients

The age of patients was recorded according to the date of birth recorded in the anatomopathological report. Patients were stratified into age groups less than or equal to 50 years and greater than 50 years.

Tumor size

The TNM classification published by the American Joint Committee on Cancer (AJCC), 8th edition, published in 2017, was used to classify tumor size. It divides breast tumors according to size into: T1 (Tumor measuring 2 cm or less in its greatest dimension), T1a (1-5 mm), T1b (5-10 mm), T1c (11-20 mm), T2 (Tumor measuring more than 2 cm, but no more than 5 cm in its greatest dimension), T3 (Tumor measuring more than 5 cm in its greatest dimension) and T4 (Tumor of any size with direct extension to the chest wall and/or skin, or inflammatory carcinoma). Tumor size was assessed according to the macroscopic description described in the anatomopathological report of the surgical resection specimen.

Histological type of the tumor

The identification of the histological type of the tumor was performed following the criteria adopted by the World Health Organization - WHO (WHO CLASSIFICATION OF TUMOURS EDITORIAL BOARD) published in 2019. In this study, the histological types found were: invasive carcinoma of No Special Type (NST), lobular carcinoma, mixed carcinoma and mucinous carcinoma.

Histological grade of the tumor

The histological grade was determined according to the Scarff-Bloom-Richardson Grading System modified by Elston and Ellis, which has been endorsed by the College of American Pathologists, which is divided into: low grade/well differentiated (G1), Grade 1; intermediate grade/moderately differentiated (G2), Grade 2 and high grade/poorly differentiated (G3), Grade 3.

Lymph node metastasis

Lymph node involvement was assessed in a binary manner as: presence of micrometastasis (>0.2mm and <2mm) or metastasis in one or more regional lymph nodes and absent as no metastasis identified in regional lymph nodes, or only presence of isolated tumor cells.

Hormone receptors (Estrogen and Progesterone)

The cases in the study were evaluated by the pathologist according to the ASCO and CAP recommendations for reporting the results of immunohistochemical assays for ER and PR. The guidelines recommend classifying all cases with at least 1% of positive cells as receptor-positive, including the percentage and intensity of stained nuclei.

Ki67 cell proliferation index

The evaluation method used by the service was in accordance with those established by the CAP, with a count of 100 cells in at least four areas of the tumor. All Ki67 data found were recorded, both those obtained in the needle biopsy and those from the surgical specimen. For the statistical evaluation, the value from the surgical specimen was chosen, whenever available. The IHC technique used by the study laboratory was the EnVision FLEX/HPR detection method (Dako - Code K8000), performed on an immunohistochemistry automation platform - Dako Autostainer Link 48, with 3-micron paraffin sections on silanized slides. Antigen retrieval in PT Link tanks at 97°C with EnVision FLEX Target Retrieval Solution solutions with primary antibody incubation method at room temperature for 20-30 minutes according to a specific protocol. EnVision FLEX DAB development system + chromogen. The Ki67 antibody clone used was MIB-1.

Recurrence Score (RS) in oncotype DX®

The Recurrence Score (RS) result was recorded according to its variation between 0 and 100. In patients younger than or equal to 50 years: <10 as Low score, 11-15 as low intermediate score, 16-25 as high intermediate score and >25 as high score. In patients older than 50 years: ≤25 as low score and >25 as high score.

Absolute benefit of chemotherapy

The assessment of the benefit of chemotherapy was recorded according to the variation and data from the Oncotype DX® report: patients over 50 years old as <1% or >15% an patients under 50 years old as <1% if RS 0-15, 1.6% if RS 16-20, 6.5% if RS 21-25 and >15% if RS 26-100.

Statistical analysis

The data were analyzed using the IBM SPSS Statistics v.29.0.0 software program. The results obtained in the study were described by mean, standard deviation, median, minimum and maximum values (quantitative variables) or by absolute frequency and percentage (categorical variables). The comparison of two groups defined by demographic and clinical variables, in relation to Ki67 expression, was performed using the Student's t-test for independent samples. More than two groups were compared using the one-way analysis of variance (ANOVA) model and the Bonferroni post-hoc test. Regarding categorical variables, the groups were compared using Fisher's exact test. To analyze the correlation of Ki67% with other quantitative variables, Pearson's linear correlation coefficients were estimated. To determine cutoff points for Ki67 considering the risk classifications by RS (low/intermediate or high), ROC curves were adjusted.

Sensitivity and specificity were calculated for the cutoff points thus defined. The positive and negative predictive values calculated considering

the prevalence estimated by the study sample were also presented. To analyze possible associations between clinical variables and the Ki67 value, univariate and multivariate linear regression models were adjusted. A 95% confidence interval was presented for each estimated coefficient. After adjusting the multivariate models, multicollinearity, homoscedasticity and distribution of residuals were evaluated. The performance of the model was evaluated by estimating the coefficient of determination R2, which indicated the proportion of the variability of the dependent variable explained by the independent variables. The statistical significance of each coefficient was tested by the Student's t-test. The normality condition of quantitative variables was assessed by the Kolmogorov-Smirnov test. Values of $p<0.05$ indicated statistical significance.

Results

Data from 105 patients with Oncotype DX® reports available from the last 5 years were recorded and after applying the inclusion and exclusion criteria, a total of 79 patients were included in the study. The analysis presented below was performed based on data from 79 patients diagnosed with Luminal A or Luminal B breast cancer. Classifications were made according to the two cutoff levels for Ki67, 20% and 30%. Table 1 shows the clinicopathological characteristics of the patients, such as age and mean age, tumor histological type, tumor size, tumor grade and lymph node metastasis.

Table 2 shows the biological characteristics of the tumor, such as the proliferative index, molecular subtype, and chemotherapy benefit and hormone receptors. Table 3 shows the distribution of the recurrence score in patients aged 50 years or younger.

A ROC curve was adjusted for Ki67 to assess whether, for age ≤ 50 years, this variable predicts RS risk as being (low/intermediate) or (high). Low-risk patients were grouped with intermediate-risk patients due to the small sample size.

The ROC curve makes it possible to monitor the variation in sensitivity and specificity. The Area under the Curve (AUC) is used as a measure of performance and discriminator and was equal to 0.78 (p=0.032), shown in Graph 1.

The cutoff point for Ki67% indicated by the ROC curve adjustment is 37. For women aged ≤ 50 years, values below 37 correspond to low/intermediate risk and values above 37 correspond to high risk.

The sensitivity of this point is 85.7% and the specificity is 61.9%. In Table 4, we can see the recurrence score found if we consider the value of 37% as the cutoff point for low and high risk, in the population aged 50 years or less.

Table 5 shows the distribution of the recurrence score in patients over 50 years old.

In the evaluation of Ki67 as a biomarker to predict the risk of recurrence in patients over 50 years of age, a ROC curve was adjusted for the percentage of Ki67, which provides a quantitative measure of its discriminative capacity between classes and the higher the AUC (area under the curve), the better the model's ability to make this distinction. Therefore, this variable predicts the RS risk as being low or high. The Area Under the Curve (AUC) is equal to 0.68 with statistical significance (p=0.040), shown in Graph 2.

The cutoff point for Ki67% indicated by the ROC curve adjustment is 33. For women aged > 50 years, values below 33 correspond to low risk and values above 33 correspond to high risk. The sensitivity of this point is 93.3% and the specificity is 41.7%. In Table 6, we can see the recurrence score found if we consider the value of 33% as the cutoff point for low and high risk, in the population aged over 50 years.

KAPPA coefficient analysis between RS and Ki67

For this analysis, the cutoff point recommended by the St Gallen Consensus for Ki67 of 30% was used. The cutoff point <30% was compared with Low/Intermediate RS and the cutoff point ≥ 30% with High-Risk RS. And for age, the values found in the study for patients younger than or equal to 50 years of 37% and for patients older than 50 years of 33% were considered.

Data for kappa when Ki67 cut-off point 30%

Agreement between RS and Ki67 occurred in 39 (49.4%) cases and disagreement occurred in 40 (50.6%) cases. The Kappa coefficient of agreement is estimated at 0.16 with a confidence interval given by: 0.03 to 0.29. This result indicates a weak agreement between RS and Ki67 considering the cutoff point of 30 for Ki67.

Data for kappa when Ki67 cut-off point 33% and 37%

Agreement between RS and Ki67 occurred in 48 (60.7%) cases and disagreement occurred in 31 (39.3%) cases. The Kappa coefficient of agreement is estimated at 0.29 with a confidence interval given by: 0.13 to 0.45. This result indicates a weak agreement between RS and Ki67 considering the cutoff points of 37% (age ≤ 50) and 33% (age >50).

Table 1. Clinical-pathological characteristics of the study population.

Variable	Classification	Total	Results*
Age (years)	-	79	56.1 ± 12.3 (28-78)
Age (years)	≤ 50	79	28 (35.4%)
	>50	-	51 (64.6%)
Histological Type	Carcinoma NST	79	58 (73.4%)
	Mixed	-	11 (13.9%)
	Lobular	-	9 (11.4%)
	Mucinous	-	1 (1.3%)
Tumor Size (cm)	-	79	1.9 ± 0.9 (0.7-6.5)
Tumor Size (cm)	≤ 2	79	57 (72.2%)
	>2 e ≤5	-	21 (26.6%)
	>5	-	1 (1.3%)
Tumor Grade	1	79	4 (5.1%)
	2	-	57 (72.2%)
	3	-	18 (22.8%)
Lymph node	Negative	79	72 (91.1%)
	Positive	-	7 (8.9%)

Results described by mean ± standard deviation (minimum–maximum) (quantitative variables) or by absolute frequency (percentage) (categorical variables)

Table 2. Biological characteristics of the tumors under study.

Variable	Classification	Total	Result*
Ki67 %	-	79	40.3 ± 18.6 (5-85)
KI67%-Core	-	49	38.1 ± 19.4 (5-78)
KI67%-Surgical specimen	-	67	41.0 ± 18.9 (5-85)
Luminal (cut off 20%)	A (Ki67 <20%)	79	9 (11.4%)
	B (Ki67 ≥ 20%)	-	70 (88.6%)
Luminal (cut off 30%)	A (Ki67 <30%)	79	21 (26.6%)
	B (Ki67 ≥ 30%)	-	58 (73.4%)
RS** (risk classification according to the range age)	Low	79	40 (50.6%)
	Intermediate	-	17 (21.5%)
	High	-	22 (27.8%)
Chemo Benefit	<1%	79	55 (69.6%)
	≥15%	-	24 (30.4%)
ER–IHC %	Positive	79	79 (100%)
ER–Oncotype	Positive	79	79 (100%)
PR–IHC %	Positive	77	77 (97.5%)
	Negative	2	2 (2.5%)
PR–Oncotype	Positive	79	64 (81%)
	Negative	-	15 (19%)

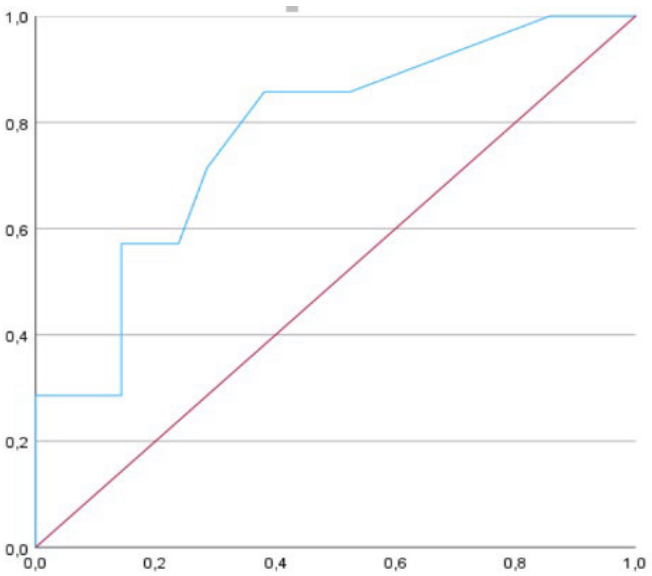
Results described by mean ± standard deviation (minimum–maximum) (quantitative variables) or by absolute frequency (percentage) (categorical variables)

**Age≤50 years: <11 low risk; 11 to 25 intermediate risk; >25 high risk

Age ≥ 50 years: ≤ 25 low risk; >25 high risk

Table 3. Recurrence score in patients ≤ 50 years old (n=28).

Risk Classification	n	%
<11 (low)	4	14.3%
11–25 (intermediate)	17	60.7%
>25 (high)	7	25.0%
Total	28	100%



Graph 1. Roc curve (ki67 and oncotype in patients ≤ 50 years old).

Table 4. Recurrence score and ki67 in patients≤50 years old (n=28).

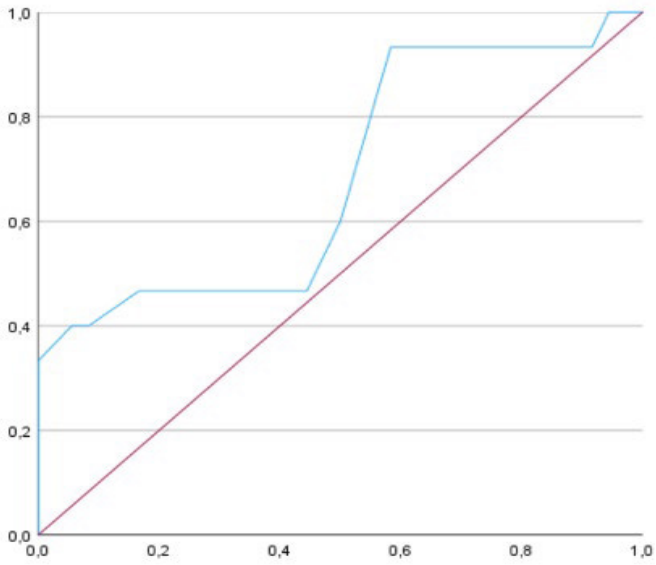
Ki67%	RS	
	Low/Intermediate	High
≤ 37%	13	1
	61.9% (Specificity)	14.3%
≤ 37%	8	6
	38.1%	85.7% (Sensibility)
Total	21	7

Table 5. Recurrence score in patients >50 years old (n=51).

Risk classification	n	%
≤ 25 (low)	36	70.6%
>25 (high)	15	29.4%
Total	51	100%

Table 6. Recurrence score and ki67 in patients>50 years old (n=51).

Ki67%	RS	
	Low	**High**
≤ 33%	15	1
	41.7% (specificity)	6.7%
>33%	21	14
	58.3%	93.3% (sensibility)
Total	36	15



Graph 2. Roc curve (ki67 and oncotype In patients >50 years old).

Discussion

The clinical indication for performing the Oncotype DX® test is for greater safety in not performing chemotherapy on patients in the early stages. In countries where there is no easy access to Oncotype DX®, other information is needed that can contribute to a better choice and also justify it. The study sought to verify and prove the value of Ki67 as an ally in this choice for oncologists and mastologists.

In both age groups studied, the high sensitivity of Ki67 was demonstrated in identifying high-risk patients (patients under 50 years of age, 85.7% and in patients over 50 years of age, 93.3%). However, patients with high Ki67 but who presented low risk to Oncotype DX® was still identified. These may have had an overestimation of the percentage of Ki67 in the pathological analysis. Therefore, patients over 50 years old exhibiting high percentage of Ki67 expression should be assessed in conjunction with additional clinicopathological parameters to accurately identify those most likely to benefit from chemotherapy.

When the data were compared and a ROC curve was adjusted, the Ki67 values found for low and high risk stratification were close to the 30% recommended by the St Gallen Consensus. The curve cutoff point suggested 37% for patients under or equal to 50 years old and 33% for patients over 50 years old.

The correlation found was similar to most data in the literature, with statistical significance between the association of Ki67 with Oncotype DX® for both patients under 50 years old (p=0.032) and for patients over 50 years old (p=0.040). As in a recent systematic review from 2024 with 18 studies included, 16 indicated a positive or weakly positive correlation between Oncotype DX® and the Ki67 index. The combined p-value of the included studies was <0.05 (p=0.0001). However, among the difficulties encountered, most studies still have small sample sizes and different cutoff values for Ki67 levels, which may limit the generalization of their findings. Larger prospective studies with diverse populations could provide more robust evidence. In addition, some studies reported interobserver variability and interlaboratory variation. This variability may impact the consistency and reliability of Ki67 as a prognostic marker in place of Oncotype DX®. Therefore, it is still premature to propose that Ki67 be used as a substitute for Oncotype DX® [10]. When assessing the agreement between Ki67 and RS using the Kappa index, both using the 30% cutoff, according to the St Gallen Consensus and for the values suggested in the study of 37% for patients under 50 years of age and 33% for those over 50 years of age, agreement was found, although weak (Kappa 0.16 and 0.29, respectively).

As for the association of Ki67, RS, grade and tumor size, although a positive correlation was observed between the variables, since among the patients with high Grade (G3) there was a predominance of a high Ki67, greater than 50% and also of a high-risk RS, no statistical significance was found due to the small number of cases of low and intermediate risk. Regarding tumor size, for tumors smaller than 2 cm there was a predominance of a low-risk RS. However, for tumors larger than 2 cm there was no relationship with RS, since low risk was still prevalent, without statistical significance. Unlike some

publications that found clinicopathological variables significantly associated with high-risk Oncotype DX®, such as age ≤ 50 years, absence of RP expression, histological grade 2 or 3, Ki67 >20% and tumor necrosis [11].

Among the limitations of the study are the still limited number of patients and the lack of follow-up and evolution information of these patients to verify whether or not there was a recurrence of the disease.

Oncotype DX® analyzes 5 genes associated with the regulation and activity of cell proliferation in different biological and pathological contexts (Ki67, STK15, Cyclin B1, Survivin and MYBL2), which may indicate that an exclusive comparison of the Ki67 assessment would be a limited possibility of estimating the cell proliferation of a tumor.

Ki67 is a valuable marker because it provides prognostic and predictive information. However, its main problem is its limited reproducibility due to the lack of standardization in both its performance and quantification, as well as its great interobserver variability in interpretation. Studies have shown a great search for the standardization of Ki67 evaluation methods, such as the use of automated methods and artificial intelligence. Comparing an institution's Ki67 values together with the proportion of Luminal A-like *vs.* Luminal B-like subtypes, in a clinicopathological dataset, can help define the institution's cutoff value. Due to the low cost of the tests and their wide availability, Ki67, when properly evaluated, maintains an important position in the daily practice of breast cancer centers [12].

There is still a constant search for ways to predict the outcome of the Oncotype DX® recurrence score. Models for comparing clinical/epidemiological and histological data such as OncoDHNet [13], Artificial Intelligence Algorithms [14] and Magee Equations [15-26]. Although there are limitations, a favorable association between Oncotype DX® and the Ki67 index has been established, implying that Ki67 can offer important predictive details, especially regarding the probability of recurrence. This is particularly significant in low- and middle-income countries, where financial constraints often hinder the availability of expensive genetic tests.

Conclusion

The percentage of Ki67 expression correlates with the Oncotype DX® recurrence score in luminal breast carcinomas, especially in high-risk patients. High Ki67 values, greater than 37% for patients younger than or equal to 50 years and greater than 33% for patients older than 50 years, may indicate patients with a high recurrence score, while values lower than these may indicate low-risk patients. The Kappa coefficient of agreement resulted in weak agreement. The univariate analysis of the RS is significantly associated with the Ki67 value. It is estimated that high-risk patients have 16.4 more Ki67 units than those at low/intermediate risk. Assessment of age is of fundamental importance for a better assessment of the Oncotype DX® recurrence rate, although in isolation it does not suggest low or high risk of recurrence. For women over 50 years of age, the Ki67 percentage suggested for low- and high-risk stratification was 33% (AUC of 0.68 and p=0.040) and for women under 50 years of age, it was 37% (AUC of 0.78 and p=0.032). The histological type is significantly associated with the Ki67 value. The non-special type (ductal) has on average 14.1 units more Ki67 than the lobular type. No correlation was found between the Oncotype DX® recurrence score and the percentage of Ki67 expression with the histological tumor grade (p=0.903). Patients with tumor grade 3 have an average of 23.5 more Ki67 units than patients with grade 1 or 2. A correlation was found between the Oncotype DX® recurrence score and the percentage of Ki67 expression with tumor size when smaller than 2 cm (p=0.001).

Ki67 is a prognostic marker to be used routinely for better stratification of patients. A low Ki67 may indicate a low-risk patient and a high Ki67 may indicate a high-risk patient, although she may present a low risk on Oncotype DX®. These patients should be further evaluated due to a possible higher risk of recurrence.

The method of Ki67 assessment should also be established by protocol and consensus, as studies have shown that digital assessment is superior to manual counting.

Although there are consensuses and recommended values for the Ki67 cutoff point for low- or high-risk patients, each service should establish its own value for the cutoff point, as this can minimize underestimated or overestimated values.

The importance of individual assessment of each patient is fundamental for a better classification, as clinical factors such as age, tumor size and lymph node metastasis are decisive for the best therapeutic decision.

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Authorship Contribution Statement

Ana Helena Willrich Rasera: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization.

Ana Paula Martins Sebastião: Supervision, Methodology, Conceptualization, Writing – review & editing.

Cleverton Spautz: Resources.

Iris Rabinovich: Resources, Writing – review & editing.

Ana Cléa Andrade: Resources.

Cícero Urban: Resources.

Karina Furlan Anselmi: Resources.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Bray, Freddie, Mathieu Laversanne, Hyuna Sung and Jacques Ferlay, et al. "Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA Cancer J Clin* 74 (2024): 229–263.
2. Loibl, Sibylle, Fabrice André, Thomas Bachelot and C. H. Barrios, et al. "Early breast cancer: Esmo clinical practice guideline for diagnosis, treatment and follow-up." *Ann Oncol* 35 (2024): 159–182.
3. Sparano, Joseph A., Robert J. Gray, Della F. Makower and Kathleen I. Pritchard, et al. "Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer." *N Engl J Med* 379 (2018): 111–12
4. Van De Vijver, Marc J., Yudong D. He, Laura J. Van't Veer and Hongyue Dai, et al. "A gene-expression signature as a predictor of survival in breast cancer." *N Engl J Med* 347 (2002): 1999–2009.
5. Albain, Kathy S., William E. Barlow, Steven Shak and Gabriel N. Hortobagyi, et al. "Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial." *Lancet Oncol* 11 (2010): 55–65.
6. Baehner, Frederick L. "The analytical validation of the Oncotype DX recurrence score assay." *Ecancermedicalscience* 10 (2016): 675
7. Oliveira, Leandro Jonata Carvalho, Thais Baccili Cury Megid, Daniela Dornelles Rosa and Carlos Alberto da Silva Magliano, et al. "Cost-effectiveness analysis of Oncotype DX from a Brazilian private medicine perspective: A GBECAM multicenter retrospective study." *Ther Adv Med Oncol* 14 (2022): 17588359221141760.
8. Davey, Matthew G., Sean O. Hynes, Michael J. Kerin and Nicola Miller, et al. "Ki-67 as a prognostic biomarker in invasive breast cancer." *Cancers* 13 (2021): 4455.

9. Ma, Qin, Yao-Bang Liu, Tong She and Xin-Lan Liu. "The role of Ki-67 in HR+/HER2- breast cancer: A real-world study of 956 patients." *Breast Cancer: Targets Ther* (2024): 117–126.
10. Mooghal, Mehwish, Muhammad Ali Akbar Khan, Mirza Rameez Samar and Hafsa Shaikh, et al. "Association between Ki-67 proliferative index and Oncotype DX recurrence score in hormone receptor-positive, HER2-negative early breast cancers: A systematic review of the literature." *Breast Cancer: Basic Clin Res* 18 (2024): 11782234241255211.
11. Ji, Jung-Hwan, Sung Gwe Ahn, Youngbum Yoo and Shin-Young Park, et al. "Prediction of a multi-gene assay (Oncotype DX and Mammaprint) recurrence risk group using machine learning in estrogen receptor-positive, HER2-negative breast cancer—the BRAIN study." *Cancers* 16 (2024): 774.
12. Maranta, Angela Fischer, Simon Broder, Constanze Fritzsche and Michael Knauer, et al. "Do YOU know the Ki-67 index of your breast cancer patients? Knowledge of your institution's Ki-67 index distribution and its robustness is essential for decision-making in early breast cancer." *Breast* 51 (2020): 120–126.
13. Goyal, Manu, Jonathan D. Marotti, Adrienne A. Workman and Graham M. Tooker, et al. "A multi-model approach integrating whole-slide imaging and clinicopathologic features to predict breast cancer recurrence risk." *NPJ Breast Cancer* 10 (2024): 93.
14. Harowicz, Michael R., Timothy J. Robinson, Michaela A. Dinan and Ashirbani Saha, et al. "Algorithms for prediction of the Oncotype DX recurrence score using clinicopathologic data: A review and comparison using an independent dataset." *Breast Cancer Res Treat* 162 (2017): 1–10.
15. Bhargava, Rohit and David J. Dabbs. "The story of the Magee equations: The ultimate in applied immunohistochemistry." *Appl Immunohistochem Mol Morphol* 31 (2023): 490–499.
16. Al-Zawi, Abdalla Saad Abdalla, Marina Barron, Wayne Chicken and Zina Aladili, et al. "The correlation between the Oncotype DX recurrence score and Ki-67 proliferation index in ER-positive, HER2-negative, node-negative breast cancer." *Eur J Surg Oncol* 48 (2022): e82.
17. Albain, Kathy S., William E. Barlow, Steven Shak and Gabriel N. Hortobagyi, et al. "Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial." *Lancet Oncol* 11 (2010): 55–65.
18. Augustovski, Federico, Natalie Soto, Joaquin Caporale and Lucas Gonzalez, et al. "Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with a 21-gene assay: Systematic review and meta-analysis." *Breast Cancer Res Treat* 152 (2015): 611–625.
19. Burstein, H. J., G. Curigliano, Beat Thürlimann and W. P. Weber, et al. "Customizing local and systemic therapies for women with early breast cancer: The St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021." *Ann Oncol* 32 (2021): 1216–1235.
20. Carlson, Josh J. and Joshua A. Roth. "The impact of the Oncotype DX breast cancer assay in clinical practice: A systematic review and meta-analysis." *Breast Cancer Res Treat* 141 (2013): 13–22.
21. Cattoretti, Giorgio, Michael H. G. Becker, Göran Key and Michael Duchrow, et al. "Monoclonal antibodies against recombinant parts of the Ki-67 antigen (MIB 1 and MIB 3) detect proliferating cells in microwave-processed formalin-fixed paraffin sections." *J Pathol* 168 (1992): 357–363.
22. Cazzaniga, M. E., Giorgio Mustacchi, P. Pronzato and A. De Matteis, et al. "Adjuvant treatment of early breast cancer: Do the St Gallen recommendations influence clinical practice? Results from the NORA study." *Ann Oncol* 18 (2007): 1976–1980.
23. Crager, Michael, Sameera R. Wijayawardana, Aaron M. Gruver and Andrea Blacklock, et al. "Population-based estimate for the correlation of the Oncotype DX breast recurrence score® result and Ki-67 IHC MIB-1 pharmDx in HR+, HER2–, node-positive early breast cancer." *Breast Cancer Res* 24 (2022): 74.
24. De Azambuja, Evandro, Fatima Cardoso, Gilberto de Castro and Mariantonietta Colozza, et al. "Ki-67 as prognostic marker in early breast cancer: A meta-analysis of published studies involving 12,155 patients." *Br J Cancer* 96 (2007): 1504–1513.
25. Dowsett, Mitch, Torsten O. Nielsen, Roger A'Hern and John Bartlett, et al. "Assessment of Ki67 in breast cancer: Recommendations from the International Ki67 in Breast Cancer Working Group." *J Natl Cancer Inst* 103 (2011): 1656–1664.
26. Fallah, Parvaneh, N. Mulla, A. A. N. Rose and L. Panasci. "Can high Ki67 predict distant recurrence in early stage breast cancer with low Oncotype DX score?." *Ann Oncol* 32 (2021): S425–S426.

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