Original article

Risk stratification in luminal-type breast cancer: Comparison of Ki-67 with EndoPredict test results

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ABSTRACT

Objectives: Adjuvant chemotherapy decision in patients with hormone receptor positive, HER2 negative breast cancer (BC) is challenging. Ki-67 is widely used for adjuvant therapy decision in BC. The multigene assay EndoPredict (EP) has shown to provide valid and additional information about the risk of recurrence compared to traditional pathological factors. In this study, we compared Ki-67 with EP assay generated risk groups.

Methods: We analyzed the results from prospective EP testing (n = 373) and tumor proliferation assessed by Ki-67 staining in luminal breast cancer. We statistically investigated the association of both parameters and probed for equivalence in risk stratification.

Results: Evaluation of Ki-67 was feasible in 307 (82%) BC specimens with known EP test results. The EPscore (now called 12-gene molecular score) delineated 140 low and 167 high scores. After combining the EPscore with pathological tumor stage and nodal status, we received 203 EPclin low-risk and 104 EPclin high-risk classifications. EPscore and EPclin were significantly associated with Ki-67 indices and tumor grade (p < 0.001). Overall, we observed a moderate correlation between Ki-67 and the EPscore (r = 0.63) as well as the EPclin score (r = 0.59).

Conclusion: Ki-67 values above 25% partly overlap with EP test results and therefore indicate a high-risk profile. In these cases, the additional prognostic information from EP testing might be rather low. However, low and intermediate Ki-67 values (less than 25%) alone were not reliable in predicting a low risk EP profile, indicating that EP testing is useful in this subgroup.

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1. Introduction

Optimal treatment of breast cancer depends on the pathological analysis of expression patterns of hormone receptors, HER2, and the proliferating activity, usually measured by the Ki-67 index. In patients with early hormone receptor positive, HER2 negative carcinomas ("luminal-type"), the decision whether to administer chemotherapy or not is still challenging. Tumor grade, proliferative fraction, tumor size and nodal status are important factors that influence adjuvant therapy decisions. However, the traditional pathological subtyping and staging of breast cancer is not fully precise in predicting patients’ prognosis and response to chemotherapy. Thus, multigene assays have been introduced that may provide additional information for clinical decision making. Some of these tests, such as Oncotype Dx [1], MammaPrint [2,3], Prosigna (derived from the PAM50 (ROR) signature) [4–6] and EndoPredict [7] are established in luminal-type, HER2 negative carcinomas and estimate the risk of tumor recurrence.

Luminal-type breast cancer constitutes the largest subgroup (above 60%) and is categorized into luminal A and B. The luminal B-type is related to a more aggressive course of disease, frequent resistance to systemic therapies and poorer outcomes when compared to the luminal A-type. Endocrine therapy is administered in both subtypes, while chemotherapy is considered for luminal B tumors depending on the risk profile (e.g. tumor size and nodal stage). Experts at the St. Gallen breast cancer consensus conference suggested to differentiate between luminal A-like (high receptor,
low proliferation, low grade), an intermediate group, and luminal B-like (low receptor, high proliferation, high grade) [8]. It was further proposed to interpret the Ki-67 index as a local laboratory value in order to measure proliferation. However, the optimal Ki-67 cut-off to delineate luminal A from luminal B remains controversial, and there is uncertainty about intermediate Ki-67 levels [9–12]. For these cases, a multigene test is valuable [13–15].

Due to the accuracy variation of conventional prognostic and predictive markers, the most precise prediction of patient outcomes can be achieved by multivariate prognostic models (Adjuvant!Online) with inclusion of multigene predictors [16]. One of these multigene tests, EndoPredict (EP), has shown to provide prognostic information regarding distant recurrence that outperforms conventional clinic-pathological risk factors [7]. Moreover, EP was the best overall test in predicting distant recurrence within 10 years and identified the largest group of low-risk patients as compared to other prognostic signatures [17]. The EPscore (now called 12-gene molecular score) reflects the activity of 12 genes and can be subdivided in low- and high-risk. The EPclin score integrates EPscore and clinicopathological information (tumor stage and nodal status) that results in low- and high-risk categories.

To clarify whether EP tests are necessary for risk stratification or whether the use of Ki-67 enables an equivalent stratification, we compared EP results with proliferation rates assessed by Ki-67 in a cohort of 373 estrogen receptor (ER) positive and HER2 negative primary invasive breast cancer patients. The indication for prospective EP testing was the diagnosis of luminal-type breast cancer in patients with G1-3, pT1a-3 and pN0-1 (1–3 positive lymph nodes) staged tumors. To evaluate an optimal Ki-67 cut-off for risk stratification, we used different statistical methods to probe for convergence to EndoPredict risk scores.

2. Patients and methods

2.1. Patients and tumor samples

Patients with primary ER positive, HER2 negative breast cancer and a prospective EndoPredict analysis (n = 373) between 03/2012–03/2015 were enrolled in this study. The formalin fixed paraffin embedded breast cancer samples were assembled from the archive of the Institute of Pathology, Technical University of Munich (TUM), Munich, Germany to determine Ki-67 proliferation indices. Clinico-pathological and demographic data were drawn from clinical databases and pathological reports. Histological tumor typing and grading were performed according to the WHO classification 2012. All patients had curative surgery at the interdisciplinary breast center of Klinikum rechts der Isar, Technical University of Munich, Munich, Germany. Treatment recommendations were made during case discussions at an interdisciplinary tumor conference for all patients. Endocrine therapy was advised in every case and decision for or against chemotherapy was due to the EndoPredict risk classification with inclusion of clinical parameters and individual comorbidity. The recommended and performed treatment was documented. Follow-up for each patient was documented including compliance to endocrine therapy.

2.2. EndoPredict testing

EndoPredict assays (Myriad Genetics, Salt Lake City, USA) were prospectively performed according to the manufacturer’s instructions in the Institute of Pathology (TUM) as described recently [7,18].

2.3. Ki-67 analysis

Immunohistochemical staining of Ki-67 was carried out on whole slide sections of archival breast cancer resection specimens. In five cases, only biopsy material was available. Briefly, after deparaffinisation and antigen demasking, the slides were incubated with the primary antibody against Ki-67 (clone MIB1, 1:50, DAKO 7240, Denmark) on an automated staining system (BenchMark XT, Ventana Tuscon, AZ). Antibody binding was visualized using DAB as chromogen. Ki-67 scoring was performed according to the recommendations from the International Ki-67 in Breast Cancer Working group [19]. A board-certified pathologist specialized in breast cancer (AN) performed the analysis blinded without knowledge of the EndoPredict test results. In order to preclude inter-observer variability, the Ki-67 evaluation was performed by the same pathologist.

2.4. Statistics

The distribution of quantitative data is described by mean ± standard deviation or median and range. Qualitative data is presented by absolute and relative frequencies. Bivariate associations are tested by t-Tests and Chi-squared Tests. Spearman’s correlation coefficients were computed to quantify the bivariate relation of quantitative variables. Receiver operating characteristics (ROC) curves were used to assess the sensitivity and specificity as well as corresponding cut-off values in continuous variables in relation to a binary outcome. Kaplan-Meier estimates of event-free survival and Cox proportional hazards regression models were used for the analysis of time-to-event outcomes. Optimal cut-off values for stratification into risk groups were determined by maximally selected log-rank statistics in this setting (https://CRAN.R-project.org/package=maxstat). Statistical hypothesis testing was conducted on exploratory, two-sided 5% significance levels. Exact 95% confidence intervals were computed for relative frequencies. All analyses have been performed using R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of the study cohort

EndoPredict assays were prospectively performed on 395 breast cancer samples as previously reported [18]. After exclusion of cases with bilateral breast cancer, 373 cases were enrolled in this study. Mean age at time of diagnosis was 59 years (range 29–88 years). Due to the lack of enough tumor tissue for evaluation in some cases, the determination of Ki-67 was possible in 307 cancer samples. The proliferation index ranged from 3% to 50%, median 17%. Table 1 summarizes the clinic-pathological characteristics of the cohort. The study was approved by the ethics committee of the faculty of medicine at Klinikum rechts der Isar, Technical University of Munich (311/16s).

3.2. Comparison of Ki-67 values with EndoPredict test results

We observed a significant association between Ki-67 with the EPscore and EPclin score. Low Ki-67 levels were more frequent in EP low-risk groups. High Ki-67 levels were more common in EP high-risk groups. The distribution of the Ki-67 levels in the EP risk groups are given in Fig. 1. EPscore high and EPclin score high-risk were found in carcinomas with low Ki-67 levels, and vice versa. Thus, we observed low Ki-67 levels (<10%) in 10% (95% CI: 6.0–15.8%) of the EPscore high group, and in 13.5% (95% CI: 7.5–21.5%) of the EPclin score high-risk group. High Ki-67 (>25%) was found in
5.7% (95% CI: 2.4%–10.9%) of the EPscore low group, and in 10.3% (95% CI: 6.5%–15.3%) of the EPclin low-risk cases.

In addition, we performed a correlation analysis with Ki-67 and the EPscore and EPclin score as continuous variables. In this evaluation, we observed a moderate correlation between Ki-67 and the EPscore (r = 0.63) as well as the EPclin score (r = 0.59) (Pearson’s product-moment correlation, p < 0.0001 respectively) as shown in Fig. 2 (A, B). Boxplots illustrate the distributional characteristics of Ki-67 in low- and high-risk groups of both scores (two sample t-test p < 0.001, respectively) as shown in Fig. 2 (C, D). The medians for the EPscore low- and high-risk group showed Ki-67 levels of 13% (range 3–30%) and 22% (range 5–50%). In the EPclin score low- and high-risk group Ki-67 medians were 15% (range 3–35%) and 22.5% (range 4–50%).

### 3.3. Comparison of tumor grade with Ki-67 and EndoPredict

Next, we evaluated the relation between tumor grade and Ki-67 as well as EP risk groups. We observed a significant association between grading and Ki-67 levels (Pearson’s chi-squared test, p < 0.0001). Well-differentiated carcinomas (G1) exhibited predominantly low Ki-67 levels (median 12%, range 3–25%). Intermediate (G2) and poorly differentiated carcinomas (G3) displayed higher Ki-67 levels with a wider range (G2: median 17%, range 3–35%; G3: median 23%, range 5–40%). We further found a weak correlation between tumor grade and Ki-67 (spearman rank correlation coefficient rho 0.412, p < 0.0001). The distribution of Ki-67 in relation to tumor grade is given in Fig. 3A and B.

Consistent with our recent work [18], we found a significant association between tumor grade and EPscore as well as EPclin score (Pearson’s chi-squared test, p < 0.0001). The majority of G1 carcinomas belong to the low-risk group for both EPscore (77%) and EPclin score (85%), while G3 carcinomas are most common in the high-risk groups (83% and 73%, respectively). In the large subgroup of moderate differentiated carcinomas (G2, n = 240), 55% enter the EPscore high category. However, after combination with tumor stage and nodal status, only 33% are classified as EPclin high-risk.

### 3.4. Prognostic impact of Ki-67 and EndoPredict test results

Follow-up data was available for all patients with EP test results (n = 373). Median follow-up time was 3.47 years. Disease-free survival (DFS) was defined as time between diagnosis and death, local relapse and distant metastasis. The 3-year DFS of the whole study cohort was 96% (95% CI: 93.8%–98.2%). In this time, 22 disease-free events (11 deaths, 3 local recurrences, 8 distant metastases) were observed. We were interested to evaluate the prognostic impact of Ki-67 (cut-off 25%) and EP risk groups on disease-free survival. Kaplan-Meier curves were plotted as shown in Fig. 4 A-C. In univariable analysis, the risk of a DFS event was increased in the Ki-67 ≤ 25% subgroup and EP high-risk groups.

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**Table 1**

| Clinic-pathological parameter of the breast cancer cohort (n = 307) |
|---------------------------------------------------------------|
| **Characteristics**                                           | **n (%)** |
| Sex                                                          |           |
| female                                                       | 301 (98)  |
| male                                                         | 6 (2)     |
| Menopausal status (n = 301)                                   |           |
| pre-menopausal                                               | 96 (31.9) |
| post-menopausal                                              | 205 (68.1)|
| pT stage                                                     |           |
| pT1a                                                         | 17 (5.5)  |
| pT1b                                                         | 50 (16.3) |
| pT1c                                                         | 120 (39.1)|
| pT2                                                          | 110 (35.8)|
| pT3                                                          | 10 (3.3)  |
| Nodal status                                                 |           |
| nodal negative                                               | 232 (75.6)|
| nodal positive (1–3 positive nodes)                          | 75 (24.4) |
| Histologic subtype                                           |           |
| invasive ductal (NST)                                        | 212 (69.1)|
| invasive lobular                                             | 59 (19.2) |
| others                                                       | 36 (11.7) |
| Grading                                                      |           |
| G1                                                           | 62 (20.2) |
| G2                                                           | 193 (62.9)|
| G3                                                           | 52 (16.9) |
| ER positive (>1%)                                            | 307 (100) |
| negative                                                     | 0 (0)     |
| PR positive (>1%)                                            | 284 (92.5)|
| negative                                                     | 23 (7.5)  |
| Proliferation index (Ki-67)                                  |           |
| ≤ 10%                                                        | 73 (23.8) |
| 11–15%                                                       | 62 (20.2) |
| 16–20%                                                       | 75 (24.4) |
| 21–24%                                                       | 34 (11.1) |
| >25%                                                         | 63 (20.5) |
| EPscore (12-gene molecular score)                            |           |
| ≤ 5 (low)                                                    | 140 (45.6)|
| >5 (high)                                                    | 167 (54.4)|
| EPclin score                                                 |           |
| ≤ 3.3 (low risk)                                             | 203 (66.1)|
| >3.3 (high risk)                                             | 104 (33.9)|

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**Fig. 1.** Association of Ki-67 with EPscore (A) and EPclin score (B).
3.5. Determination of the Ki-67 cut-off for risk stratification

Finally, we statistically investigated the optimal Ki-67 cut-off to achieve the highest possible equivalence to the EndoPredict risk stratification. We used the receiver operating characteristic (ROC) curve to assess sensitivity and specificity of different Ki-67 cut-off values for the EP risk stratification. The result for Ki-67 and the EPscore dichotomized into risk groups revealed an area under the curve (AUC) value of 0.797 (95% CI: 0.748–0.846, \( p < 0.0001 \)). The sensitivity of the Ki-67 index with the cut-off value of 20% was 68%, and the specificity was 80% (Fig. 5 A). For Ki-67 and EPclin score dichotomized into risk groups, the AUC value was 0.7454 (95% CI 0.684–0.806, \( p < 0.0001 \)). The sensitivity of the Ki-67 index with the cut-off value of 20% was 67%, and the specificity was 78% (Fig. 5 B).

In a totally different approach, we explored two other optimal Ki-67 cut-off values for disease-free and overall survival by LogRank statistics. The estimated optimal cut point for OS was 18% and for DFS was 24%.

4. Discussion

The pathological analysis of the Ki-67 index in primary invasive breast cancer helps to differentiate between luminal A- and B-type tumors, and thereby to estimate patients’ prognosis and treatment strategy. In the last decade, the analytical reliability and identification of the optimal cut-off for Ki-67 was a matter of great debate. Despite several standardization processes, the use of the Ki-67 proliferation marker is still controversial [12,19–22].
In this study, we evaluated whether the risk stratification with the immunohistochemical investigation of Ki-67 is equivalent to the multigene EndoPredict (EP) assay in a large prospective breast cancer cohort. We observed a significant association and correlation between Ki-67 and EP score (now called 12-gene molecular score) as well as EP clin score. The latter combines EP score with the pathological parameter's tumor stage and nodal status which makes a direct comparison to Ki-67 data alone difficult. We further observed a relevant number of discordant cases where low Ki-67 levels matched to high-risk EP scores, and vice versa.

The EP assay provides prognostic information about the risk of developing distant recurrence within 10 years after surgery. Patients with an estimated risk of recurrence of more than 10% at 10 years are considered to benefit from adjuvant chemotherapy [7,17,23,24]. In the validation cohorts (ABCSG 6 and 8 trials), the EP clin score outperformed all conventional clinic-pathological risk factors [7]. The study also demonstrated a significant association between EP score and Ki-67 cut-off of 11% as well as tumor grade. In most of the cases of the overall cohort, low Ki-67 levels (≤11%) were observed (78%, 1271 out of 1638). 58% of cases with Ki-67 ≤11% had a low EP score and 83% of cases with Ki-67 ≥11% had a high EP score. In the EP score low group, 92% showed low Ki-67 levels (p < 0.001), but in the EP score high group, only 36% had high levels of Ki-67.

In our cohort, Ki-67 levels ≤10% showed a low EP score category in 40% of tumors and with Ki-67 levels ≤15% in nearly 68% of tumors. Ki-67 values > 20% displayed an EP score high category in 51.5% of tumors. When we closer looked at EP clin categories, a cut-off of Ki-67 ≤10% resulted in low-risk cases in only 29.1% of tumors and 13.5% belonged to the EP clin high-risk category, risking undertreatment. Using a cut-off of Ki-67 ≥25%, 40% were classified as EP clin high-risk, showing the strongest overlap. This finding is supported by our analysis of the prognostic impact on DFS, where both Ki-67 (cut-off 25%) and EP clin display a good ability to distinguish risk of recurrence. However, 10% of the EP clin low-risk cases remain in the Ki-67 high-group which would probably result in overtreatment, when using Ki-67 alone. In another study of 34 breast carcinomas, a significant correlation between continuous Ki-67 and EP score (Pearson coefficient 0.55, p < 0.0001) but not with EP clin score (Pearson coefficient 0.24, p = 0.16) was observed [25].

Recently, the Ki-67 index was compared to the PAM50/Prosigna ROR (risk of relapse) assay (NanoString Technologies, Seattle, WA, USA) [26]. Most luminal A tumors (65%) with ROR low (71%) had low Ki-67 values (0–10%). The distribution of ROR medium/high within the Ki-67 0–10% group was 42.7% in patients with tumor size less than 2 cm and 33.9% with tumor size greater than 2 cm.
The authors concluded that the Ki-67 cut-off of 14% is suitable to identify luminal A-type and ROR low and therefore to select low-risk outcome patients who can be spared of adjuvant chemotherapy. They further proposed that gene tests are not needed in luminal-type BC with Ki-67 levels <10% and >20%. In a previous work, the comparison of Ki-67 and qRT-PCR based PAM 50 version revealed a comparable cut-off of 13.25% for Ki-67 to distinguishing between luminal A and B [11]. The Ki-67 cut-off of 14% was also recommended by previous breast cancer consensus panels [9,10], but later revised to a cut-off of 20% [12].

In addition, Ki-67 levels have been compared to the 21-gene Recurrence Score (RS) assay (OncotypeDx, Genomic Health, USA). In the PlanB trial, a moderate positive correlation between Ki-67 and RS was found [27]. Less than 5% of the patients with Ki-67 levels <20% had RS > 25. All patients with Ki-67 ≥ 40% had RS > 25. A significant correlation between Ki-67 and RS was also observed in another report suggesting the use of cost sparing immunohistochemistry in some clinical scenarios [28].

In summary, Ki-67 correlates in part but not completely with prognostic signatures. There are also differences across several multigene and molecular subtyping tests [17,29,30].

In our analysis, we observed that a low EPscore was more common in G1 cancers while a high EPscore was more prevalent in G3 cancers. In the large group of G2 tumors, the EPscore was equally distributed between both risk categories. In our study cohort, different pathologists performed the histopathologic grading within the routine diagnostic process. We used these results from the pathological reports without reevaluation. The distribution of the different tumor differentiation levels, however, is in line with the literature showing a moderate differentiation (G2) in most of the breast carcinomas (64%). Accurate grading is essential since the tumor grade is also recommended for the classification of luminal A and B categories (St. Gallen 2017) [13]. We observed some G1 carcinomas showing high EPscores and EPclin score high-risk, and vice versa. In addition, a significant association between grading and Ki-67 was found.

Overall, the cumulative data from our study and others confirm that Ki-67 is helpful for BC subtyping and treatment decisions and that it is highly correlated with various multigene assays. However, the reproducibility and variability of Ki-67 assessment is a matter of debate. Many efforts of the pathologist’s community having been made to standardize the staining procedure and assessment as published by the Ki-67 international working group and other studies like e.g. round robin tests [19,31,32]. The lack of a standardized cut-off criteria is one of the reasons why Ki-67 is not recommended in the actual Clinical Practice Guideline of the American Society of Clinical Oncology. Also, the interpretation and comparison of previously published data is considered difficult, as various studies used different cut-offs for Ki-67 (ranging from 10 to 30%). In contrast, the St. Gallen panel recommended an interpretation of the Ki-67 scores in combination with local laboratory values [33]. The median Ki-67 expression should be used to define high and low Ki-67 levels. In our analysis, the median of Ki-67 scoring was 17%. This is in the range of previously reported values [27,34].

The current German Clinical Practice Guideline (Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms 2017 AWMF-Registernr: 032-0450L) states that in primary invasive, hormone receptor positive, HER2-negative breast cancer, Ki-67 can define low, intermediate and high-risk groups. Ki-67 levels of ≤10% define low-risk carcinomas while Ki-67 levels of >25% should be classified as high-risk based on the meta-analysis of Petrelli and colleagues [35]. They also state that in the range between 10 and 25%, Ki-67 is not able to accurately differentiate risk groups.

A limitation of our study is that it is a retrospective analysis of Ki-67. At the time of diagnosis and therapy planning, Ki-67 staining was not routinely performed. Treatment decisions were based on EP test results. On the other hand, the advantage of our retrospective Ki-67 evaluation is that it was performed in all cases by one experienced breast cancer pathologist, which excludes interobserver variability. In addition, the monocentric design of our study is a limitation, but the prospective EP testing and the large number of patients increase the novelty and value of our report.

5. Conclusion

To our knowledge, this is one of the largest primary invasive ER positive, HER2 negative breast cancer cohorts that compares EndoPredict risk scores with Ki-67 and grading in clinical routine. We found that levels of Ki-67 above 25% showed a strong overlap with high-risk EP test results. This indicates a uniform ability of both approaches to identify unfavorable tumor biology and the need for chemotherapy recommendations. In contrast, low and intermediate Ki-67 values alone were not reliable enough to predict a low-risk EP profile. Taking these results into account, Ki-67 is a useful additional parameter in risk stratification in context with other traditional pathological factors and can be used to preselect patients for additional EP testing. Still, therapy recommendations solely relying on Ki-67 test results as the decisive factor, seems risky and might lead to over- and undertreatment of patients. The EP test with the combination of assessing gene expression levels and clinical parameters of the individual tumor might be able to give clinicians a more accurate method for risk stratification in luminal breast cancer. In order to substantiate our conclusion, long-term outcome data for the EndoPredict stratification for our patient collective are needed and will be available in the future.

Ethical Approval

The work has been approved by the ethics committee of the faculty of medicine at Klinikum rechts der Isar, Technical University of Munich (311/16s).

Declaration of competing interest

JE received honoraria from Astra Zeneca, Roche, Celgene, Novartis, Lilly, Pfizer, Pierre Fabre, TEVA and travel support from Celgene, Pfizer, TEVA and Pierre Fabre. WW received research funding (Roche) and had consulting or advisory role (AZ, Roche, Takeda, Novartis, BMS, MSD). MK received remuneration from Springer Press, Biermann Press, Celgene, AstraZeneca, Myriad Genetics, and Teva, received consultancy or advisory fees from Myriad Genetics, KVB, DKMS LIFE, BLAK, and TEVA, holds stock in Theravis Diagnostics GmbH and Busenfreundin GmbH, and received funding from Sphingotec, Deutsche Krebshilfe, DFG, Senator Roesner Foundation, and Dr. Pommer-Jung Foundation. The remaining authors (AN, SIA, AH, KS, KS, EK) have no competing interest to declare.

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