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Genomic signatures in breast cancer in a real-world setting: Experience in a Brazilian Northeastern Center

Sabas Carlos Vieira[a], Cristiane Amaral dos Reis[a], Mariana Elvas Feitosa Holanda[b], Danilo Rafael da Silva Fontinele[c,*], Alessandro Igor Cavalcanti Leal[d] and Fernanda Teresa de Lima[d]
[a]*Oncocenter - Teresina, Piauí, Brazil*
[b]*UniFacid Wyden - Teresina, Piauí, Brazil*
[c]*University State of Piauí – UESPI - Teresina, Piauí, Brazil*
[d]*Albert Einstein Israeli Hospital, São Paulo, Brazil*

Abstract.
OBJECTIVE: We aim to evaluate the indication and use of genomic signatures in breast cancer patients and outcomes who in patients undergoing adjuvant chemotherapy or not.
METHODS: This is a retrospective study of breast cancer patients managed in a private oncology clinic in Teresina, from November 2014 to February 2021. All patients with an indication of genomic signature were included. Clinical and pathological variables, use of genomic signatures, treatment and follow-up were obtained. The nomogram to predict Oncotype DX results (University of Tennessee Medical Center) was also calculated. Clinical risk calculation was based on MINDACT, using the modified version of Adjuvant Online. The genetic signatures performed were: the Oncotype, MammaPrint and EndoPredict.
RESULTS: Fifty (50) female patients were included in the study. The mean age of the participants was 57.1 years. Among the patients receiving a genomic signature (26–52.0%), there was a change in treatment in 8 (30.7%) cases. Chemotherapy was indicated in four patients, It was contraindicated in another four patients. Treatment changed in 30.7% of the tested patients. Chemotherapy was indicated for those who would not receive it before. It was contraindicated in patients who would previously undergo chemotherapy.

Keywords: Breast neoplasms, chemotherapy, adjuvant, precision medicine, genomics, gene signatures

1. Introduction

Breast cancer is the most common cancer in women worldwide. It was estimated that 2,261,419 new breast cancer cases occurred in 2020, accounting for 24.5% of all female cancers [1].

In Brazil, the National Cancer Institute estimated that 66,280 new breast cancer cases occurred in 2020, representing 29.7% of all cancers in women. In 2019, 18,068 deaths from the disease were recorded [2].

Breast cancer treatment is dependent upon tumor biology which can be determined by genomic signatures. Unnecessary treatment can be avoided in patients at low risk for distant recurrence. Nevertheless, the use of these signatures is still infrequent in developing countries, due to the high cost of the tests. In Brazil, for instance, these tests are neither covered by the Unified Health System, that manages the majority of breast cancer patients, nor by supplemental health and insurance plans [3,4].

The indication of neoadjuvant or adjuvant systemic treatment may also be based on the expression of hormone receptors and HER-2, determined by immunohistochemistry. Usually, patients with triple-negative

*Corresponding author: Danilo Rafael da Silva Fontinele, University State of Piauí – UESPI - Teresina, Piauí, Street Olavo Bilac, 2335, Brazil. Tel.: +55 86 981284744; E-mail: drsilvafontinele@gmail.com. ORCID: https://orcid.org/0000-0001-8754-6871.

and HER-2 positive tumors are treated with systemic chemotherapy. In patients with HER-2 positive tumors, anti-HER-2 monoclonal antibodies are added. On the other hand, luminal tumors which represent 70% of breast cancer cases, standard practice is to omit chemotherapy in patients at low risk, Chemotherapy is generally indicated for high-risk patients. However, in intermediate-risk patients, the benefit of chemotherapy is questionable. For this patient profile, genomic signatures enable the selection of patients who may benefit or not from chemotherapy. Unnecessary chemotherapy is thus avoided in patients with low-risk genomic signatures and offered to those who are at high genomic risk [5–7].

The first genomic signature validated for breast cancer was the Oncotype DX. The test included 21 genes, three of which are reference genes. It was initially approved for patients with estrogen receptor-positive, HER-2 negative and node-negative tumors, providing prognostic and predictive information about the benefit of adjuvant chemotherapy [8,9]. Subsequent studies have also validated the Oncotype DX in node-positive patients [10,11].

Other genomic signatures emerged and were also validated by clinical studies, such as the MammaPrint, EndoPrint, PAM 50 and BCI [12].

Similar to genomic signatures, Oncotype predicts recurrence risk and chemotherapy benefit in breast cancer treatment. Due to limited access to genomic assays in Brazil, treatment decisions largely rely on traditional clinicopathological risk factors. Oncotype has been reported as cost-effective in various healthcare systems, but data are limited regarding the context of middle-income countries like Brazil [13].

The present study evaluated the implementation of genomic signature testing for breast cancer following medical recommendation and its impacts on patient outcomes when recommending or discouraging adjuvant chemotherapy.

2. Methodology

This is a retrospective study in breast cancer patients treated in a private oncology clinic in Teresina, capital of the state of Piauí, Northeastern Brazil, from November 2014 to February 2021. Included in the study were all patients given an indication of genomic signature to define whether or not they should undergo adjuvant chemotherapy. The study is part of a project approved by the Research Ethics Committee of UESPI, protocol number: 30154720.0.0000.5209.

Clinical and pathological variables, genomic signature (whether or not it was used), treatment and follow-up were obtained from patient medical records. In all cases, the nomogram predicting Oncotype DX results, developed at the University of Tennessee Medical Center, was also calculated [14]. The nomogram was applied to female patients over age 50, with estrogen receptor-positive, HER-2-negative tumors, and tumor size ranging from 6–50 mm. Estrogen receptor status was considered positive when ≥1%. For patients aged 50 years or younger, the nomogram estimates only the probability of a high risk of recurrence by the Oncotype DX (RS 26-100). This nomogram was based on data from 65,754 patients who received the Oncotype DX, obtained from the National Cancer Database of 2010–2014 [15]. Clinical risk calculation was based on the MINDACT trial, using the modified version of Adjuvant! Online. MINDACT was a multicentre, randomised, phase 3 trial done in 112 academic and community hospitals in nine European countries and their genomic risk (using the MammaPrint 70-gene signature) and clinical risk (using a modified version of Adjuvant! Online) were determined. Patients with low clinical and low genomic risk results did not receive chemotherapy, and patients with high clinical and high genomic risk did receive chemotherapy [16]. The genetic signatures performed were: the Oncotype, MammaPrint and EndoPredict. The choice of the test performed was solely up to the patients, primarily based on financial cost.

For chemotherapy indication, the standard practice of the Breast Unit of Cambridge University was adopted. As a result, chemotherapy was indicated when the benefit was higher than 5%. When the benefit of chemotherapy was lower than 3%, it was not indicated. When its benefit ranges from 3–5%, the standard of care is to discuss the risks and benefits of treatment with each patient [17].

3. Results

Fifty (50) female patients were included in the study. The mean age of the participants was 57.1 years. Invasive Carcinoma of No Special Type (NST) was the most common histologic type (94.0%) of tumor, and the most common molecular subtype was Luminal B (68.0%) (Table 1). Genomic signatures were used in 26

Table 1
Clinical and pathological characterization of breast cancer cases-Teresina - Brasil, 2021

Variables	Category	*n*	%
Age at diagnosis (years)		57.1 (10.9)*	
Histology	NST	47.0	94.0
	ILC	1.0	2.0
	Mucinous	1.0	2.0
	NST and ILC	1.0	2.0
Grade	1	9.0	18.0
	2	35.0	70.0
	3	5.0	10.0
Tumor size	Up to 20 mm	29.0	58.0
	>20 mm	21	42.0
Negative axilla	-	32.0	64.0
Positive axilla	1 lymph node	8.0	16.0
	2 lymph nodes	3.0	6.0
	≥4 lymph nodes	1.0	2.0
ER- positive		49.0	98.0
PR- positive		44.0	88.0
Molecular subtype	Luminal A	16.0	32.0
	Luminal B	34.0	68.0
Clinical staging	IA	23.0	46.0
	IB	16.0	32.0
	IIA	9.0	18.0
	IIB	2.0	4.0
Pathological staging	IA	42.0	84.0
	IB	4.0	8.0
	IIA	3.0	6.0
	IIIA	1.0	2.0
Total		50.0	100.0

Source: Direct research; *mean (standard deviation); NS: Invasive Carcinoma of No Special Type (NST); ILC: Invasive Lobular Carcinoma.

(52.0%) patients, and the most widely used test in study participants was the Oncotype DX (Table 2).

Among the patients receiving a genomic signature (26–52.0%), there was a change in treatment in 8 (30.7%) cases. Chemotherapy was indicated in four patients, It was contraindicated in another four patients, i.e., 4 were at low risk according to the Mindact criteria and high risk according to the Oncotype RS (chemotherapy was recommended). Of the 4 patients that had been regarded as having a high clinical risk by the Mindact criteria, 3 patients were found to be at low risk after the test, according to the Oncotype RS and 1 was at low risk according to the MammaPrint test, thus characterizing changes in patient treatment (Table 3).

Table 2
The use of genomic signatures in breast cancer patients - Teresina - Brazil, 2021

Variables	*n*	%
Oncotype	20.0	40.0
MammaPrint	5.0	10.0
EndoPredict	1.0	2.0
Not applied	24.0	48.0
Total	50.0	100.0

Source: Direct research.

Participants received follow-up care for 33.2 months, and loss to follow-up was 14%. Disease-free survival was 86%.

4. Discussion

In the current study, 52% of the patients with an indication of genomic signature were tested. The authors pondered that it was a high testing rate. It was probably due to the higher purchasing power of the patients, since the study was conducted in a private institute. In Brazil, the genomic signatures are neither covered by the Unified Health System nor by Supplemental Medicine, which involves health plans and health insurance.

In the United States, a publication involving data from the SEER (National Cancer Institute's Surveillance Epidemiology and End Results) registry showed increased use of the Oncotype DX from 2005 to 2010 in breast cancer patients. During this time period, testing in patients with estrogen receptor-positive breast cancer, increased from 8 to 27% and 2 to 15.7%, in node-negative or node-positive tumors, respectively. In the above-mentioned study, among the patients classified as low-risk (*Recurrent Score* – RS < 18) and high-risk (RS > 30), 3.23% and 95.9% received chemotherapy, respectively. In the intermediate-risk group of patients, 12.8% (RS 18–19), 35% (RS 20–23) and 84% (RS 24–30) underwent chemotherapy [18].

British study of 201 women with ER-positive and HER-2-negative breast cancer, showed that the benefits of chemotherapy in 10-year survival rate was >3% based on EndoPredict scores and these women were considered for adjuvant chemotherapy. In this study, the use of Oncotype DX avoided chemotherapy in 60.3% and 69.2% of the patients with (axillary) node-negative and node-positive breast cancer,

Table 3
Correlation between clinical risk and genomic signatures in breast cancer patients-Teresina - Brazil, 2021

	Mindact		*n* (%)	% Low Risk - Nomogram (Mean)	Chemo
Oncotype RS	Low-Risk	High-Risk			
Up to 15	2.0	3.0	5.0 (25.0)	88–93 (90.2)	0.0
15–26	6.0	2.0	8.0 (40.0)	86–98 (92.5)	2.0
>26	4.0	3.0	7.0 (35.0)	52–96 (77.1)	6.0
Total			20.0 (100.0)	-	
MammaPrint				-	
Low Risk	1.0	1.0	2.0 (40.0)	-	1.0
High Risk	-	2.0	2.0 (40.0)	-	2.0
Inconclusive	-	1.0	1.0 (20.0)	-	1.0
Total			5.0 (100.0)	-	
EndoPredict				-	
Low Risk	-	-		-	-
High risk	-	1.0	1.0 (100.0)	-	0.0
Total			1.0 (100.0)	-	

Source: Direct research.

respectively. In addition, treatment costs and morbidity also decreased [20]. In our study Genomic signatures guided changes in treatment plans in 30.7% of the cases.

In the current study, the mean EndoPredict score was 2.5 in the group receiving chemotherapy and 1.8 in the group that was not given chemotherapy. The probability of a high-risk Oncotype score by the nomogram of the University of Tennessee was 21.8% in the group that underwent chemotherapy, and 14.2% in the group that did not receive this treatment modality.

In contrast, in patients who did not receive genomic signatures, the mean EndoPredict score was 2.8 in the group receiving chemotherapy and 1.5 in the group that was not given chemotherapy. The probability of a high-risk Oncotype score by the nomogram of the University of Tennessee was 22.0% in the group undergoing chemotherapy, and 11.9% in the group that did not receive chemotherapy.

A study including patients from 14 British oncology centers evaluated the role of the Oncotype test in 713 patients with breast carcinoma. The RS was low (<18), intermediate (18–30) and high (>30) in 49.8%, 36.2% and 14% of the patients, respectively. Patients with an RS > 30 and >25 received chemotherapy in 49.2% and 93.3%, respectively. There was also a decrease in the use of adjuvant chemotherapy in this series [20].

The cost of breast cancer treatment in patients receiving the Oncotype DX test was assessed, using data from the SEER registry. After the publication of the TAILORx study, which proposed changes in clinical practice reduce in costs in the first 12 months of breast cancer treatment. The cost of treatment before the study was $2.816 billion and the projected cost with the Oncotype DX test, after the study was $115 to 231 million. The indication and cost of chemotherapy decreased from 25–17% and by $49 million, respectively. There was a small decrease in costs (1.8%) and the authors pondered that further studies are warranted to evaluate long-term costs [21].

A study in two Brazilian public hospitals including 179 women with breast cancer also assessed the role of Oncotype DX in reducing chemotherapy indications. In 40 (22%) patients, the RS was 0–10, 91 (51%) had an RS between 11–25 and 48 (27%) had an RS between 26–100. Before receiving the Oncotype DX test, chemotherapy had been indicated for 91% of the patients. After testing, chemotherapy recommendation changed in 117 (65%) of the cases. Hormonal therapy alone was indicated in one hundred and twelve (112; 63%) patients when chemotherapy had been initially indicated, and 5 (3%) underwent chemotherapy when the initial approach had been hormonal therapy alone [22]. In our study, genomic signature testing also aided in better chemotherapy recommendations for patients, reducing its utilization in 30.7% of cases.

The role of Oncotype DX in node-positive patients was evaluated in a study with 347 ER-positive and HER-negative breast cancer patients with axillary node metastasis. Of these patients, 272 (78.4%) received

the genomic test. The RS was <18 in 164 (61.4%), ranged from 18–30 in 89 (32.7%) and was ≥31 in 16 (5.9%) patients. On multivariate analysis, an RS < 18 was associated with a lower likelihood of undergoing chemotherapy in 53% of cases. Lymphovascular invasion and lobular subtype were associated with a higher likelihood of receiving chemotherapy. There was no difference in disease-free survival and overall survival at three years, between patients undergoing chemotherapy or those maintained under observation only [23]. In this case study, 12 patients had positive lymph nodes, 1 received the Oncotype test, 2 received the MammaPrint test and 8 underwent chemotherapy. Of the 3 receiving the signature, only 2 underwent chemotherapy.

Our study has some major limitations. The number of cases is small. The quality of life and treatment costs were not assessed, with or without a genomic signature.

5. Conclusion

In the current study, 52.0% of the patients who were given an indication of genomic signature, were tested. Genomic signatures guided changes in treatment plans in 30.7% of the cases. Chemotherapy was indicated for those who would not receive it before. It was contraindicated in patients who would previously undergo chemotherapy. Disease-free survival was 86%.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Interpretation or analysis of data: Sabas Carlos Vieira, Cristiane Amaral dos Reis, Mariana Elvas Feitosa Holanda, Danilo Rafael da Silva Fontinele, Alessandro Igor Cavalcanti Leal, Fernanda Teresa de Lima. *Preparation of the manuscript*: Sabas Carlos Vieira, Cristiane Amaral dos Reis, Mariana Elvas Feitosa Holanda, Danilo Rafael da Silva Fontinele. *Revision for important intellectual content*: Sabas Carlos Vieira, Cristiane Amaral dos Reis, Alessandro Igor Cavalcanti Leal, Fernanda Teresa de Lima. *Supervision*: Alessandro Igor Cavalcanti Leal and Fernanda Teresa de Lima.

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