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Use of artificial intelligence to predict response to neoadjuvant chemotherapy in breast cancer

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ABSTRACT

Introduction: Breast cancer is the object of thousands of studies worldwide. Nevertheless, few tools are available to corroborate prediction of response to neoadjuvant chemotherapy. Artificial intelligence is being researched for its potential utility in several fields of knowledge, including oncology. The development of a standardized Artificial intelligence-based predictive model for patients with breast cancer may help make clinical management more personalized and effective. We aimed to apply Artificial intelligence models to predict the response to neoadjuvant chemotherapy based solely on clinical and pathological data. **Methods:** Medical records of 130 patients treated with neoadjuvant chemotherapy were reviewed and divided into two groups: 90 samples to train the network and 40 samples to perform prospective testing and validate the results obtained by the Artificial intelligence method. **Results:** Using clinicopathologic data alone, the artificial neural network was able to correctly predict pathologic complete response in 83.3% of the cases. It also correctly predicted 95.6% of locoregional recurrence, as well as correctly determined whether patients were alive or dead at a given time point in 90% of the time. To date, no published research has used clinicopathologic data to predict the response to neoadjuvant chemotherapy in patients with breast cancer, thus highlighting the importance of the present study. **Conclusions:** Artificial neural network may become an interesting tool for predicting response to neoadjuvant chemotherapy, locoregional recurrence, systemic disease progression, and survival in patients with breast cancer.

KEYWORDS: artificial intelligence; breast; breast neoplasms; neoadjuvant therapy; neoplasms.

INTRODUCTION

Despite being the object of thousands of studies worldwide and having the largest body of evidence to explain its pathophysiology among all cancer types, breast cancer (BC) continues to claim thousands of lives each year[1]. Many different and customizable treatment options are available for the various types of BC. One treatment strategy widely used in clinical practice is neoadjuvant chemotherapy (NACT)[2].

NACT consists of the preoperative administration of chemotherapeutic drugs with a view to reducing tumor size before surgery. Its use has been associated with improved prognosis. Currently, response to NACT cannot be measured or predicted by the clinician, which restricts decision-making regarding the appropriateness of this treatment option in individual cases. Tools that can predict the response to NACT could be practice-changing by helping define the most appropriate clinical management strategy for each patient[2,3].

Nevertheless, few tools are available to corroborate prediction of response to NACT. Two prediction tools are currently on the market, the 21-gene Oncotype DX® panel and the 70-gene MammaPrint®[4,5] panel, both based on the quantification of the expression of different genes known to be involved in the pathophysiology of BC. Oncotype and MammaPrint are representative and very important on the world stage; however, their applicability is limited by the high cost inherent in the quantitative analysis of gene expression.

Artificial intelligence (AI) is being researched for its potential utility in several fields of knowledge, including oncology.

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The ability of a technology to receive information, process it, and make decisions based on that information can be very relevant in several aspects of the oncology practice, including the prediction of response to NACT. AI systems can currently receive and interpret clinical and pathological information about patients and predict possible outcomes based on cases from past examples, i.e., after learning about the subject[6-8].

The development of a standardized AI-based predictive model for patients with BC may help make clinical management more personalized and effective. In our study, we aimed to apply AI models to predict the response to NACT based solely on clinical and pathological data.

METHODS

a. Patients

All medical records of patients treated with NACT at the High Complexity Unit on Oncology (UNACON) of Hospital Geral de Caxias do Sul (RS), Brazil, and at an affiliated private clinic from March 2012 to June 2020 were reviewed. The records of 130 patients containing all clinicopathologic information of relevance to the study were analyzed and divided into two groups: 90 samples to train the neural network and 40 samples to perform prospective tests and validate the results obtained by the AI method.

b. Clinicopathologic criteria

The study included patients for whom the following information was available: age, body mass index, weight, height, menopausal status, histologic type, histologic grade, expression of estrogen (ER) and progesterone (PR) receptors, human epidermal growth factor receptor 2 (HER-2), expression of Ki-67, tumor size, axillary involvement, molecular subtype, clinical staging, chemotherapy protocol, progression during chemotherapy, targeted therapy, and pathologic staging.

Overall survival was analyzed from the date of diagnosis until the date of the last follow-up (for patients who remained alive) or date of death. Progression-free survival was analyzed from the date of diagnosis to the date of disease progression (for patients who experienced disease progression), date of death (for patients who died), or date of the last follow-up (for patients who remained alive). Pathologic complete response (PCR) was defined as absence of invasive carcinoma and/or carcinoma in situ in the breast, and ipsilateral axilla after NACT.

c. Expression of estrogen, progesterone, Ki-67 and HER-2 receptors

ER, PR, and HER expressions in breast biopsy specimens were evaluated by means of immunohistochemistry, with the following antibodies:

1. anti-ER MAb (Dako, Glostrup, Denmark, 1/100 dilution),
2. anti-PR MAb (Dako, 1/800 dilution), and
3. polyclonal anti-HER2 antibodies (Dako, 1/3200 dilution) for the HER-2-neu gene.

The scoring of ER and PR were based on the staining intensity (weak, moderate, intense). The evaluation criteria of HER2 status were based on immunostaining and the percentage of membrane positive cells, giving a score range of 1+, 2+, 3+. HER2 negative was categorical when no staining was observed or membrane staining was observed in 1–9% of tumor cells. HER2 was classified as score 2+ when there was a weak to moderate complete membrane staining in 10% to 49% of the tumor cells, while HER2 was positive score 3+ when there was a strong complete membrane staining in more than 50% of the tumor cells. In this study, HER2 scores 0 and 1+ were considered negative. HER2 3+ and the Amplified Fluorescence in situ Hybridization (FISH-amplified) tumors were considered positive. All HER2 2+ tumors and tumors for which immunohistochemistry (IHC) was not assessable were also tested for gene amplification by FISH.

Ki-67 labeling index was defined as the percentage of Ki-67 antigen positive cells, giving a score range low (<14%) and high (≥14%).

d. Analysis of tumor-infiltrating lymphocytes

The percentage of tumor-infiltrating lymphocytes (TILs) was assessed in paraffin-embedded tumor sections stained with hematoxylin and eosin (HE) and was defined as the percentage of lymphocytes in direct contact with tumor cells.

e. Artificial intelligence

AI is a growing science. Its core principle is the development of cognitive models that are capable of interpreting and forecasting data. This interpretation is based on the knowledge acquired by the model. Within AI science, "knowledge" is data[7].

Cognitive models are based on so-called artificial neural networks (ANNs), which simulate a biological neuron. Human neurons consist of several specific regions, as:

1. dendrites, which receive nerve impulses;
2. the cell body, or soma, in which information processing takes place; and
3. nerve endings, which are responsible for the output of nerve impulses.

An ANN has very similar regions, as seen in Figure 1 below. Its "dendrites" are represented by the letter *w*, which highlights the presence of more than one "nerve projection" (i.e., allowing receipt of more information), each differentially weighted to ensure a good data interpretation. In the "cell body" of the ANN, designated as *fa*, mathematical functions are applied to the data

obtained through *w*. Finally, "nerve endings" allow communication to take place between ANNs, simulating a neural synapse.

Clinicopathologic criteria were analyzed through the application of four ANNs composed of 200 neurons, each designed specifically for prediction of one of the following outcomes: PCR, locoregional recurrence, systemic disease progression, and death. The variables analyzed by the ANNs are described in Table 1.

Neural networks were created to analyze the outcomes of interest. These networks were trained on 90 samples and afterwards was prospectively tested on 40 additional samples.

f. Ethical aspects

As the present study consists of a retrospective analysis of data from medical records and does not involve direct intervention on human subjects, investigators were asked to sign a data use agreement and confidentiality form. Informed consent was waived.

g. Statistical analysis

After the identification of the core (indispensable) criteria, four supervised-learning ANNs were constructed using a pattern recognition tool. To ensure optimal fit, a backpropagation algorithm with feed-forward network topology was used to identify PCR, systemic disease progression, locoregional recurrence, and survival. To enhance ANN effectiveness, the number of neurons was tested with a variety of different settings. To evaluate whether the proposed system was effective, a prospective study was then carried out using the developed ANNs.

Descriptive analysis of clinicopathologic data was performed in SPSS 20.0 software (SPSS Inc. Chicago, IL, United States).

The Figure 1 illustrates the diagram with the methodologies used in this research.

Table 1. Variables used in the neural network.

	Values
Age (years)	Numeric
Body mass index	Numeric
Weight	Numeric
Height	Numeric
Menopausal status	Pre-menopausal or post-menopausal
Histologic type	Invasive lobular, invasive ductal, medullary, or other
Histologic grade	G1, G2, or G3
Estrogen receptor expression	Numeric
Progesterone receptor expression	Numeric
HER-2 expression	1+, 2+, 3+
Ki-67 expression	Low or high
Molecular subtype	Luminal A, luminal B, or HER2-enriched
Clinical staging	IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV
Chemotherapy protocol	Trastuzumab; lapatinib; pertuzumab; trastuzumab + pertuzumab; trastuzumab + lapatinib; other
Progression on chemotherapy	Yes or no
Neoadjuvant targeted therapy	None; trastuzumab; lapatinib; pertuzumab; trastuzumab +pertuzumab; trastuzumab+ lapatinib; other
Tumor size and location	Ductal carcinoma in situ, T1mi, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, T4d
Lymph nodes staging	N0, N1, N2, N3
Number of affected lymph nodes	Numeric

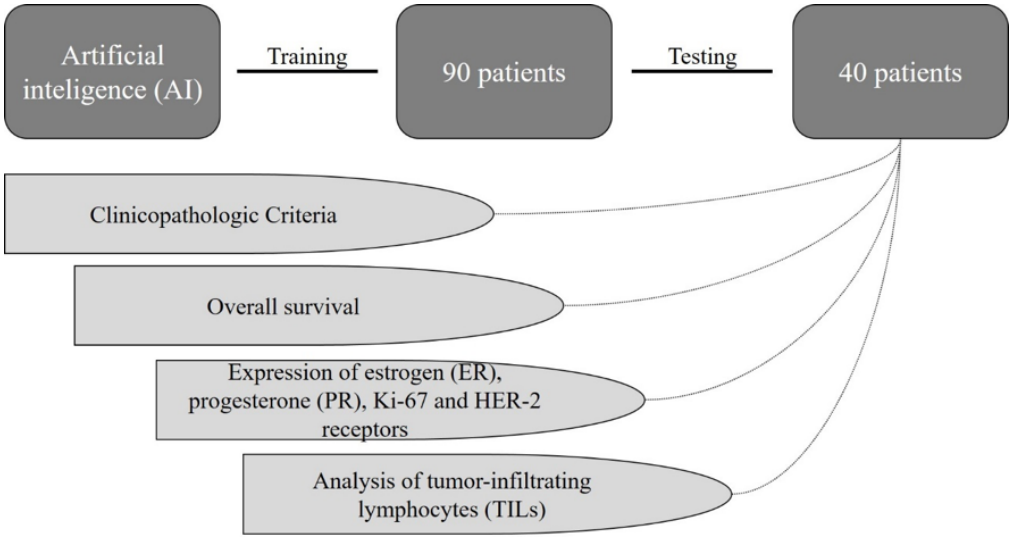


Figure 1. Diagram of methodologies used in this research.

RESULTS

Clinicopathologic data

A retrospective analysis of the medical records of 90 patients was carried out. The mean age at diagnosis was 46.3 years, and the mean body mass index was 27.0. Overall, 59 (65.6%) patients were pre-menopausal and 31 (34.4%) were post-menopausal. On histologic analysis, only 1 patient (1.1%) had invasive lobular BC, 73 patients (81.1%) had invasive ductal carcinoma, 5 (5.6%) had medullary carcinoma, and 11 (12.2%) had BC of other histological types. Most of the patients had histologic grade G3 tumors, totaling 48 (53.3%), 36 (40.0%) had grade G2, and only 6 (6.7%) had grade G1 (Table 2).

Regarding gene expression in biopsy specimens, 50 of 90 (55.6%) had biopsies strongly positive for ER, followed by 30 (33.3%) which were ER-negative. The rest of the biopsies showed low ER expression (2; 2.2%) and positive ER expression (8; 8.9%). As for PR expression, most biopsies were negative, being 39 (43.3%), followed by strongly positive expression in 31 (34.4%), positive expression in 18 (20.0%), and low expression in only 2 cases (2.3%) (Table 2).

Once HER2 expression was evaluated, 54 biopsies (60%) showed no expression and 36 (40.0%) showed 1+ expression. Furthermore, 87 biopsies (96.7%) showed high Ki67 expression. The molecular subtypes observed were: luminal B in 32 cases (35.6%), HER2-enriched in 24 (26.7%), triple-negative in 19 (21.1%), pure HER2 in 12 (13.3%), and luminal A in 3 (3.3%) (Table 2).

Of the 90 patients who received treatment, only 32 (35.6%) achieved PCR, while 58 (64.4%) did not. Fifteen patients (16.7%) experienced systemic disease progression, while 75 (83.3%) were progression-free (Table 2). This same analysis was performed in the prospective study (Table 2).

Artificial neural network performance evaluation

Clinicopathologic criteria were analyzed through application of an ANN composed of 200 neurons to predict the response to NACT. To assess predictive capacity, confusion matrices were generated. Sensitivity, specificity, false-positive rate, and false-negative rate were then derived.

With clinicopathologic data alone, the ANN was able to correctly predict PCR in 83.3% of cases, with 84.4% sensitivity, 82.8% specificity, a positive predictive value (PPV) of 73%, and a negative predictive value (NPV) of 90.6%. Tested prospectively, the ANN achieved an accuracy of 80.0%, sensitivity of 81.8%, specificity of 79.3%, and negative and positive predictive values of 92 and 60% respectively (Table 3).

When predictive capacity for systemic progression was assessed, the ANN exhibited 82.2% accuracy, with 0% sensitivity, and 98.7% specificity. The PPV was 0%, and the NPV, 83.1%. When prospectively tested, an accuracy of 77.5% was achieved, with sensitivity and specificity of 100% and 76.9%, respectively, and NPV of 100% and PPV of 10% (Table 3).

Table 2. Clinicopathologic data.

	n (%) retrospective	n (%) prospective
Age (years)	46.3	47.5
Body mass index	27.0	27.9
Weight	70.5	71.3
Height	1.6	1.6
Menopausal status		
Pre-menopausal	59 (65.6)	27 (67.5)
Post-menopausal	31 (34.4)	13 (32.5)
Histologic type		
Invasive lobular	1 (1.1)	0 (0)
Invasive ductal	73 (81.1)	37 (92.5)
Medullary	5 (5.6)	2 (5)
Other	11 (12.2)	1 (2.5)
Histological grade		
G1	6 (6.7)	5 (12.5)
G2	36 (40)	19 (47.5)
G3	48 (53.3)	16 (40)
Estrogen receptor expression		
None	30 (33.3)	17 (42.5)
Low	2 (2.2)	0 (0)
Positive	8 (8.9)	3 (7.5)
Strongly positive	50 (55.6)	20 (50)
Progesterone receptor expression		
None	39 (43.3)	19 (47.5)
Low	2 (2.3)	0 (0)
Positive	18 (20)	7 (17.5)
Strongly positive	31 (34.4)	14 (35)
HER2 expression		
0	54 (60)	33 (82.5)
1+	36 (40)	7 (17.5)
2+	0 (0)	0 (0)
Ki67 expression		
Low	3 (3.3)	7 (17.5)
High	87 (96.7)	33 (82.5)
Molecular subtype		
Luminal A	3 (3.3)	5 (12.5)
Luminal B / HER2-negative	32 (35.6)	15 (37.5)
Luminal B / HER2-enriched	24 (26.7)	3 (7.5)
Pure HER2	12 (13.3)	4 (10)
Triple negative	19 (21.1)	13 (32.5)
Pathologic complete response	32 (35.6)	15 (37.5)
No pathologic complete response	58 (64.4)	25 (62.5)
Systemic progression	15 (16.7)	10 (25)
No systemic progression	75 (83.3)	30 (75)

The same analysis was performed for locoregional recurrence. The ANN had 95.6% accuracy, with a sensitivity of 0% and specificity of 100%. Positive and negative predictive values were 0% and 95.6%, respectively. In the prospective test, the network accuracy was 95%, with sensitivity and specificity of 0% and 95%, respectively. The PPV was 0% and the NPV was 100% (Table 3). The sensitivity and PPV were 0% because no patient had disease progression or recurrence in the retrospective dataset.

When the ANN was used to predict whether patients would be alive or dead, it achieved 90% accuracy, with a sensitivity of 95.1%, and specificity of 44.4%. Positive and negative predictive values in this analysis were 93.9 and 50%, respectively. Tested prospectively, the ANN achieved an accuracy of 87.5%, sensitivity of 94.3%, specificity of 40%, NPV of 50%, and PPV of 91.7% (Table 3).

DISCUSSION

NACT is associated with PCR as well as with locoregional or systemic recurrence, and the response to NACT is the main determinant of each of these events. The present study demonstrated, for the first time, how the response to NACT can be predicted with AI methods. AI is a growing area of study, with an ever-increasing body of evidence demonstrating its applicability in various fields[6-8]. The possibility of using an AI tool to guide clinical management of BC, a life-threatening condition, is extremely relevant.

Neoadjuvant Chemotherapy and Pathologic complete response

PCR is associated with several factors. Understanding which are these factors and the relative importance of each one is essential. In this study, clinicopathologic data were used to train an ANN to predict response to NACT. Corroborating the present study, prior researches have described various clinical and pathologic factors that may be related to the response to NACT. Díaz-Casas et al.[9], in a study of 414 patients with BC, found that PCR was associated with tumor molecular type, observing higher rates of PCR in pure-HER2 and triple-negative tumors. They also found that larger tumors are associated with nonresponse to NACT.

When analyzing clinicopathologic predictors of recurrence in patients with BC who achieved PCR to NACT, advanced clinical staging, tumor size, presence of lymph node metastases, and HER2 positivity before NACT were identified as significantly predictive of disease recurrence. Conversely, residual ductal and nodal disease in situ after NACT were not significant predictors[10].

In a study of 117 patients, PCR was significantly associated with expression of ER and absence of HER2 expression (p=0.0006), as well as with stages T2 (p=0.043) and T3 (p=0.018)[11]. The same factors were assessed in our study and, corroborated as predictive of PCR. We used data to construct an ANN and predict the same outcome previously described in the literature, Thus, our results corroborate the data published in the literature, but with a significant difference: the use of AI to obtain them.

Neoadjuvant chemotherapy and locoregional recurrence

In our study, the ANN correctly predicted locoregional recurrence 95.6% of the time, with a NPV of 95.6%. These data were obtained through the use of an AI model based on clinicopathologic data only. This same correlation was described in a large study involving 3,088 patients over a 10-year follow-up period, which found that the clinical characteristics of a tumor can be used to predict the risk of locoregional recurrence[12]. The same association was observed by Gillon et al. in 1,553 patients; the authors reported that BC classification and PCR are important predictors of locoregional recurrence[13].

To date, there are no reports of the use of AI to predict locoregional recurrence in patients with BC after NACT. Therefore, this is the first study to demonstrate a new predictive model with the potential to change clinical management.

Neoadjuvant chemotherapy and systemic disease progression

Death after NACT is associated with progression of systemic disease. The ANN correctly predicted whether patients would be alive or dead after NACT 82.2% of the time, with a specificity of 98.7%; on subsequent prospective testing, 77.5% accuracy was achieved. Several factors have been described in the literature

Table 3. Predictive performance of an artificial neural network trained on clinicopathologic data alone to assess response to neoadjuvant chemotherapy in patients with breast cancer.

	Pathologic complete response		Systemic progression		Locoregional recurrence		Survival	
	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)
Accuracy	83.3	80	82.2	77.5	95.6	95	90	87.5
Sensitivity	84.4	81.8	0	100	0	0	95.1	94.3
Specificity	82.8	79.3	98.7	76.9	100	95	44.4	40
Positive predictive value	73	60	0	10	0	0	93.9	91.7
Negative predictive value	90.6	92	83.1	100	95.6	100	50	50

Retro: retrospective; Prosp: prospective.

as potential predictors of systemic progression. HER-2 expression and triple-negative status are two factors reported as such by Yiqun et al.[14].

A previous study evaluated the ability of an ANN to predict survival after BC without assessing the response to NACT. Based only on the Surveillance, Epidemiology, and End Results (SEER) Program[15] dataset, composed of 162,500 records with 16 main characteristics (the most informative ones being tumor size, number of affected lymph nodes, and age at diagnosis, all parameters which were also included in our model), this ANN achieved 65% accuracy[16].

Artificial intelligence-based forecasting

The use of AI in healthcare has been growing exponentially, with particular interest in the development of systems to guide clinical management. Specifically regarding BC, studies have focused on the ability of AI to interpret imaging findings[17-19]. There is very little published data on chemosensitivity and resistance[7,20], and, so far, no studies have demonstrated predictive ability based exclusively on clinicopathologic data. The present study is thus the first of its kind.

Some prior research has investigated the ability of ANNs and their learning models to predict risk in BC, including disease progression[21-25]. However, to date, no published research has used clinicopathologic data to predict the response to NACT in patients with BC, thus highlighting the importance of the present study in advancing science.

Limitations include the lack of validation of the model in a larger sample, which justifies the expansion of the present project. For this reason, we have requested this extension in an effort to minimize its limitations and hence contribute more significantly to the clinical management of patients with BC.

CONCLUSIONS

Breast cancer is a heterogeneous and complex disease. Considering their ability to adapt, learn from examples, organize data, and recognize patterns, ANNs may become an interesting tool for predicting response to NACT, locoregional recurrence, systemic disease progression, and survival in patients with BC.

AUTHORS' CONTRIBUTION

KOBG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MCK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. BC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. LLC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. MRE: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JAPH: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. JB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing

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