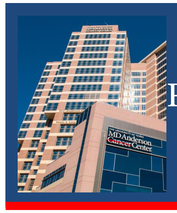

Predicting Response of Triple Negative Breast Cancer to Neoadjuvant Chemotherapy Using a Deep Convolutional Neural Network-based Artificial Intelligence Tool

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Abstract

Background: Triple-negative breast cancer (TNBC) is commonly treated with neoadjuvant chemotherapy (NAC). Pathologic complete response (pCR) to NAC is associated with improved patient outcomes. The ability to predict which patients have high likelihood to achieve pCR has important clinical implications. We developed and validated a deep convolutional neural network (CNN)–based artificial intelligence (AI) model to extract morphometric features of TNBC to predict response to NAC.

Methods: Whole-slide images (WSIs) of hematoxylin and eosin–stained core biopsies of 165 (pathologic complete response [pCR] in 60 and non-pCR in 105) and 78 (pCR in 31 and non-pCR in 47) TNBC patients, respectively, were used for training and validation of the model. The model extracted morphometric features from WSIs in an unsupervised way and transformed the image tiles from WSIs into high-dimensional vectors, generating clusters of morphologically similar patterns. Downstream ranking of clusters using neural networks provided regions of interest with high or low predictive value for NAC response. Morphometric scores combined with clinical TNM stage gave AI prediction scores; a low score close to 0 and high score close to 1, respectively, represented a high or low probability of pCR, respectively.

Results: The predictive ability of the AI score for the entire cohort of 78 TNBC patients ascertained by receiver operating characteristic (ROC) analysis demonstrated area under the curve (AUC) of 75.5%. The AUC for stage I, II, and III disease was 88.1%, 73.7%, and 74.7% respectively. The performance of the AI scores was also analyzed based on their distribution into quartiles. Patients in the highest score quartile were predicted to not have pCR and those in the lowest score quartile were predicted to have pCR. Of the 20 patients in the lowest score quartile, 15 experienced pCR yielding a positive predictive value of the AI score for pCR of 75%. Of the 20 patients in the highest score quartile, 16 did not have pCR, yielding a negative predictive value of 80%.

Conclusions: This is the first demonstration of using an AI tool to predict response to NAC in patients with TNBC. These results if validated in subsequent studies, could inform individualized decisions regarding intensity of NAC, including options to de-escalate NAC in patients with TNBC who are likely to achieve pCR.

Introduction

Triple-negative breast cancer (TNBC) is an aggressive variant of breast cancer that accounts for 15% to 20% of all breast tumors and is associated with high recurrence rates and poor overall survival. Neoadjuvant chemotherapy (NAC) including anthracycline and taxanes with immunotherapy in some cases remains the main treatment option for patients diagnosed with early and advanced stages of TNBC. Pathologic complete response (pCR) with no evidence of residual tumor in the breast and locoregional lymph nodes is achieved in approximately 30% to 65% of patients with early-stage TNBC following NAC. At present there are no validated predictive biomarkers of response to NAC in TNBC.

In recent years, the availability of whole slide digital images (WSIs) of hematoxylin and eosin (H&E)-stained tissue, together with the rapidly advancing technology of computational approaches, brings unprecedented opportunity for pathology analyses. Convolutional neural network (CNN)-based artificial intelligence (AI) analyses can be utilized for extracting the collective known and unknown sub visual features of the tumor and stroma. These features can be exploited for making predictions regarding the behavior of malignant tumors.

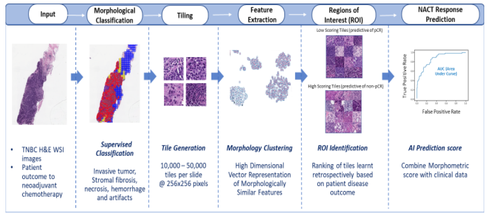
Objectives

Develop and validate a novel deep CNN-based AI prediction tool for predicting response to NAC in TNBC patients using features of the invasive tumor and stroma in H&E-stained WSIs of core biopsies of the invasive mammary tumor.

Materials & Methods

The H&E-stained glass slides of the pre-chemotherapy core needle biopsy performed at the time of initial diagnosis from the 243 patients were scanned using a Leica/Aperio AT2 scanner at 20× magnification to create WSIs. The 243 WSIs were divided to training (n = 165) and test (n = 78) sets with equitable distribution based on patient demographic (age, race), clinical (menopausal status, pre chemotherapy TNM stage), and pathological features (invasive tumor type, grade) and response to NAC (pathologic yTNM stage).

We first trained the AI model using WSIs of H&E-stained tissue sections of invasive mammary carcinoma from the National Institute of Health Cancer Genomic Atlas Breast Adenocarcinoma (TCGA-BRCA) data set. Development of the AI prediction model entailed 5 essential steps, including input, morphological classification, tiling, feature extraction, identification of regions of interest (ROI) following ranking of tiles and establishment of the final AI prediction score resulting from the combination of morphometric score and clinical information.



Statistical analysis

Receiver operating characteristic (ROC) analysis was used to evaluate the AI prediction tool's predictive ability. Higher scores were associated with a lower probability of pCR to NAC. Performance of the AI prediction model was summarized by the area under the curve (AUC). The AUC was compared with a null value of 0.60 using a 1-sided test with a 5% significance level. This comparison was made by taking bootstrap samples of the AUC and comparing those to the null rate of 0.60. The model's predictive ability in patients with different clinical disease stages was also evaluated using ROC analysis. All statistical analyses were performed using the R version 3.6.1 and a significance level of 5%. No adjustments for multiple testing were made due to the exploratory nature of the study.

Results

Table 1. Characteristics of the training and testing cohorts included in the development of the deep convolutional neural network–based AI model to predict response to neoadjuvant chemotherapy of triple negative breast cancer patients.

	Training set (N = 165)		Testing set (N = 78)	
	N	%	N	%
Race				
Caucasian	111	67.3	55	70.5
African American	30	18.2	11	14.1
Hispanic	11	6.7	4	5.1
Asian/Pacific Islander	9	5.4	5	6.4
Other	4	2.4	3	3.8
Clinical T category				
T0	2	1.2	1	1.2
T1	33	20.0	20	25.6
T2	97	58.78	40	51.2
T3	18	10.9	14	17.9
T4	15	9.09	3	3.8
Clinical N category				
N0	90	57.7	43	55.1
N1	41	26.3	20	25.6
N2	8	5.1	3	3.8
N3	17	10.9	12	36.0
Clinical stage				
Stage I	18	11.5	13	16.7
Stage II	98	62.8	45	57.7
Stage III	39	25.0	20	25.7

Table 2. Pathologic features of the training and testing cohorts included in the development of the deep convolutional neural network–based AI model to predict response to neoadjuvant chemotherapy in triple-negative breast cancer.

	Training set		Testing set	
	N	%	N	%
Primary tumor type				
Ductal	157	95	76	97.4
Lobular	2	1.2	0	0
Other	6	3.6	2	2.5
Tumor grade (pre-NAC)				
II	18	12.9	11	17.5
III	122	87.1	52	82.5
Path T (yp) stage				
T0	54	32.7	33	42.3
Tis	15	9.1	3	3.8
T1	51	32.8	23	29.3
T2	25	15.2	14	17.9
T3	16	9.7	3	3.8
T4	1	0.6	0	0
Path N (yp) stage				
N0	118	71.6	52	66.7
N0 (i+)	1	0.6	0	0
N1	25	17.5	15	19.2
N2	2	4.2	3	3.9
N3	10	6.1	3	3.8
Final path (yp) stage				
Stage 0	66	40	32	41.0
Stage I	39	23.6	20	25.6
Stage II	40	24.2	19	24.3
Stage III	20	12.2	7	8.9
Response				
pCR	60	36.4	31	39.7
No pCR	105	63.6	47	60.3

Abbreviations: NAC, neoadjuvant chemotherapy; path, pathological; pCR, pathologic complete response; yp, after neoadjuvant therapy.

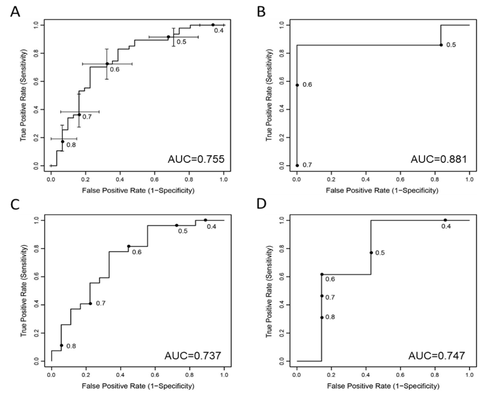


Figure 1. (A) Receiver operating characteristic (ROC) analysis demonstrating the performance of the deep convolutional neural network–based artificial intelligence (AI) model to predict response of the entire testing cohort of 78 patients with triple-negative breast cancer showing the area under the curve (AUC) of 75.5%. **(B)** ROC analysis of the AI prediction model in patients with stage I disease shows an AUC of 88.1%. **(C)** ROC analysis of patients with stage II disease shows an AUC of 73.7%. **(D)** ROC analysis of patients with stage III disease shows an AUC of 74.7%.

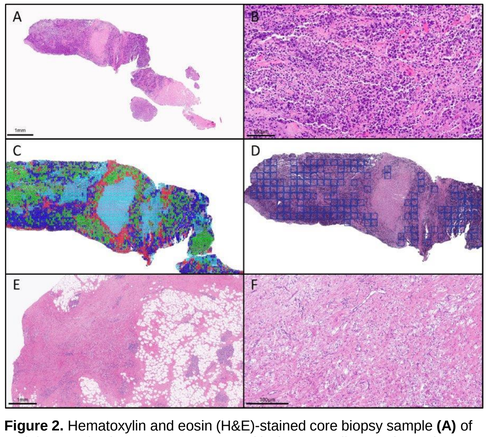


Figure 2. Hematoxylin and eosin (H&E)-stained core biopsy sample **(A)** of a triple-negative breast cancer procured before neoadjuvant chemotherapy showing high Nottingham histologic grade and infiltration of tumor-infiltrating lymphocytes (TILs) **(B)**. The tiling and labeling of a whole-slide digital image of the H&E-stained section of the core biopsy to include features of the tumor, stroma, and TILs to obtain the final score is shown in panels **(C)**. The deep convolutional neural network–based artificial intelligence prediction score resulting from the collective scores of regions of interest in the tissue indicated as blue colored tiles in this case with AI prediction score of 0.13, indicating a high likelihood of response is shown **(D)**. The prediction of probability of response to neoadjuvant chemotherapy was accurate, as evidenced by complete response to neoadjuvant chemotherapy. The tumor bed with no residual tumor is shown in panels **(E)** and **(F)**.

Patient demographics and clinical and pathologic features

The demographic and clinical characteristics of the patients in the training and testing cohorts are summarized in **Table 1**. The pathological findings for both cohorts are summarized in Ta**ble 2**.

AI scores of testing cohort tumors

The AI model was trained on the training dataset (n=165), and the model performance was 73% AUC (Area under the Curve) for the ROC (Receiver operating characteristics) curve, using 10-fold cross-validation. The model was then used to measure accuracy on the test dataset (n=78). The AI prediction scores of the 78 patients in the testing cohort ranged from 0 to 1.0. The predictive ability of the AI score for the entire testing cohort ascertained by ROC analysis demonstrated an AUC of 75.5%. This AUC was significantly higher than the protocol-specified null hypothesis of 0.60 (P = 0.016). The performance of the AI score was also estimated across the clinical stages of the TNBC patients. Of the 13 patients with stage I disease, 6 experienced pCR and 7 did not. Of the 45 patients with stage II disease, 18 experienced pCR and 27 did not. Of the 20 patients with stage III disease, 7 experienced pCR and 13 did not. The AUC in the ROC analysis for patients with stage I, II, and III disease was 88.1%, 73.7%, and 74.7%, respectively.

Conclusion

This study is the first demonstration of using an AI tool on digitized H&E images to predict response to NAC in TNBC patients with high accuracy. Our study exemplifies the utility of WSIs for building CNN-based AI prediction model for TNBC patients and has the potential to function as a robust ancillary digital pathology predictive tool that can be used in conjunction with standard-of-care pathologic evaluation of the invasive mammary tumor in the clinical management of TNBC patients.

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