European Journal of Surgical Oncology 45 (2019) 134–140

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

A predictive model for high/low risk group according to oncotype DX recurrence score using machine learning

Isaac Kim, Hee Jun Choi, Jai Min Ryu, Se Kyung Lee, Jong Han Yu, Seok Won Kim, Seok Jin Nam, Jeong Eon Lee*

Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 31 May 2018
Received in revised form
19 September 2018
Accepted 24 September 2018
Available online 16 October 2018

Keywords:
Breast neoplasm
Prediction
Machine learning

ABSTRACT

Background: Oncotype DX(ODX) is a 21-gene breast cancer recurrence score(RS) assay that aids in decision-making for chemotherapy in early-stage hormone receptor-positive(HR+)breast cancer. We developed a prediction tool using machine learning for high- or low-risk ODX criteria (i.e., RS < 11 for low-risk; RS > 25 for high-risk).

Methods: We performed a retrospective review of 301 breast cancer patients who underwent surgery between April 2011 and July 2017 and then an ODX test at Samsung Medical Center in Seoul, Korea. Among them, 208 cases were defined as the modeling group and 76 cases were defined as the validation group. We built a supervised machine learning classification model using the Azure ML platform.

Results: For the high RS group, accuracy was 0.903 through Two-class Decision Jungle method in test set. For the low RS group, the accuracy was 0.726 when the Two-class Neural Network method was applied. The AUC of the ROC curve was 0.917 in the high RS group and 0.744 in the low RS group in test set. In addition, we conducted an internal validation using 76 patients who underwent ODX testing between January 2017 and July 2017. The accuracy of validation was 0.880 in the high RS group and 0.790 in the low RS group.

Conclusion: We developed a predictive model using machine learning that could represent a useful and easy-to-access tool for the selection of high ODX RS patients. After additional evaluation with large data and external validation, worldwide use of our model could be expected.

Introduction

Oncotype DX (ODX) (Genomic Health, Redwood City, CA, USA) is a 21-gene breast cancer recurrence score (RS) assay that aids in decision-making for chemotherapy in early-stage hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer [1,2]. The ODX test is currently used worldwide for routine evaluations in conjunction with guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and others [3,4]. However, the ODX test is costly, and significant racial and socioeconomic disparities exist with regard to its use [5].

A few studies have attempted to predict the results of the ODX test using patients at multiple institutions who were evaluated using the ODX test [6–9]. These investigations employed histopathologic variables and statistical methods such as logistic regression for prediction; to date, no study has used machine learning method for prediction. Machine learning as an advanced computational technology has been around for several years, with research indicating it is suitable for discovering patterns among diverse biomedical datasets and that it provides excellent capabilities ranging from gene annotation to predictive phenotyping [10].

The purpose of our study was to develop a prediction tool using machine learning for high- or low-risk ODX criteria according to the TAILORx trial (i.e., RS < 11 for low-risk; RS > 25 for high-risk) [11]. Because, patients with RS < 11 do not need chemotherapy according to prospective validation study [12] and chemotherapy is recommended to patients with RS > 25 [13].

* Corresponding author. Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Republic of Korea.
E-mail address: jeongeon.lee@samsung.com (J.E. Lee).

https://doi.org/10.1016/j.ejso.2018.09.011
0748-7983/

Methods

Study population

We performed a retrospective chart review of 301 breast cancer patients who underwent surgery between April 2011 and July 2017 and then an ODX test at Samsung Medical Center in Seoul, Korea. As part of this study, not only ODX scores but also electronic medical records including pathology reports were reviewed. Seventeen cases were excluded from analysis due to incomplete medical data and 284 cases were included for analysis. Among them, 208 cases were defined as the modeling group and 76 cases were defined as the validation group. Because we tried to conduct a prospective validation with data during January and July 2017 after development of our model, we used retrospective data (total 208 patients during April 2011 and December 2016) for modeling. This study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board (IRB) of Samsung Medical Center (IRB no. 2017-03-136-002).

The available data for the cohorts were: age at diagnosis; histopathology (e.g., invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal carcinoma and invasive lobular carcinoma); existence of ductal carcinoma in situ (DCIS), lymphovascular invasion (LVI), and extensive intraductal component (EIC); nuclear grade; histologic grade; pathologic T-stage; number of metastatic lymph nodes; lymph node metastasis size; perinodal extension; and estrogen receptor, progesterone receptor, HER2, and Ki-67 status. ER, PR positivity was defined as an Allred score in the range of 3–8 according to immunohistochemical(IHC) staining with antibodies to ER (Immunotech, France) and PR (Novocastra, UK) [14]. HER2 status was evaluated using the antibody (DAKO, CA) and/or fluorescence or silver in situ hybridization (FISH or SISH). HER2 grades of 0, 1 were defined as a negative, while grade 3 was identified as a positive result. Amplification of HER2 was confirmed by FISH or SISH for results of 2 + and HER2 amplification, defined as American society of clinical oncology guideline 2013 [15]. Ki-67 status was evaluated using the MIB1antibody (Immunotech, France) and scored by percentage of positive cells [16].

Statistical analysis

Continuous variables were compared between the modeling and validation groups using Mann–Whitney *U* tests, while categorical variables were analyzed via the chi-squared test or Fisher's exact test using SAS version 9.4 (SAS Institute, Cary, NC, USA). Receiver operating characteristic (ROC) curves and areas under the ROC curve (AUCs) were calculated. All tests were two-sided and a *p*-value of <0.05 was considered to be statistically significant.

Machine learning

Azure Machine Learning (Azure ML; Microsoft, Redmond, WA, USA) is a cloud service that enables the execution of machine learning processes; the Azure Machine Learning Studio (Microsoft, Redmond, WA, USA) is also available as a workspace to help users build and test predictive models [17]. We built a supervised machine learning classification model using the Azure ML platform (Microsoft, Redmond, WA, USA). This was accomplished using the steps of (1) edit the data, (2) split the data, (3) train the model, (4) score the model, and (5) evaluate the model (Fig. 1). We classified data as integers (e.g., age, DCIS size, metastasis size of lymph nodes) and categories (e.g., tumor type; existence of DCIS, LVI, and EIC; perinodal extension; and status of estrogen receptor, progesterone receptor, HER2, and Ki-67). We split the modeling data (208 cases) into training and testing sets using a randomized 70–30 split. We then trained our training set using a Two-class Decision Jungle method [18] for the prediction of the high RS group and a Two-class Neural Network [19] method for the prediction of the low RS group.

Results

Patient characteristics

Table 1 shows the baseline characteristics of the included patients. The modeling and validation groups consisted of 208 patients and 76 patients, respectively. The proportion of low RS patients was higher in the validation group than in the modeling group, while the proportion of high RS patients was higher in the

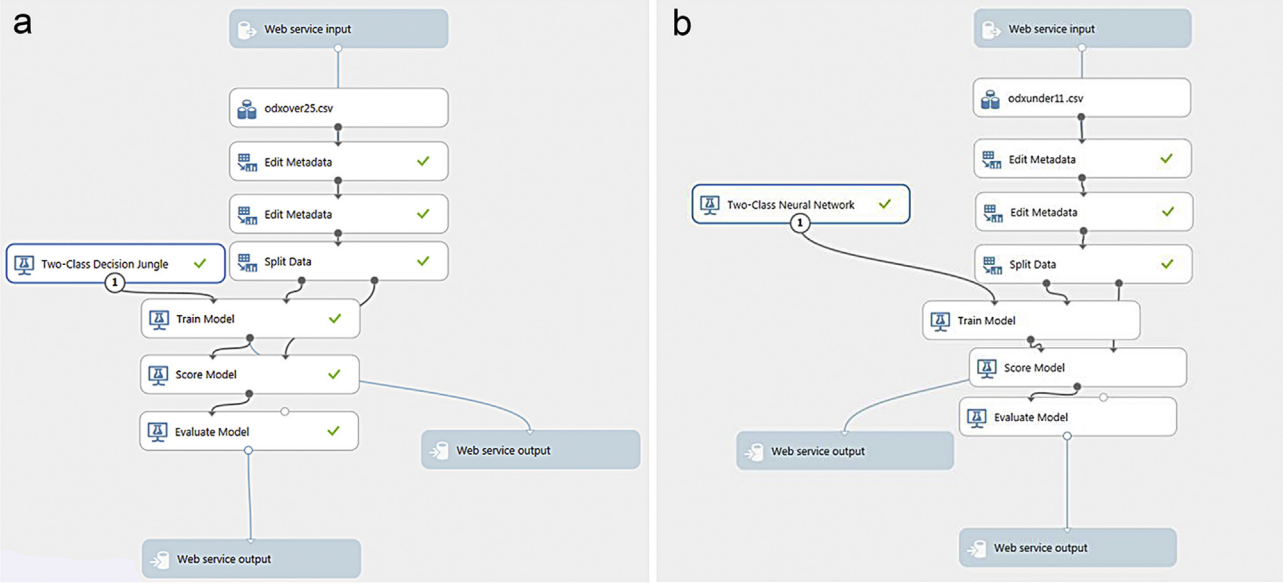

Fig. 1. The workflow of modeling using Azure ML (Microsoft, Redmond, WA, USA). It consist of establishing a dataset; editing the metadata; employing an algorithm (for example, Two-Class Decision Jungle or Two-Class Neural Network); splitting the data; training the model; scoring the model; and evaluating the model. a. The high RS group. b. The low RS group.

Table 1
The baseline characteristics of enrolled patients.

		Modeling group (n = 208)		Validation group (n = 76)		*p*-value
		No.	%	No.	%	
Recurrence Score	low (<11)	44	21.2	18	23.7	0.840
	intermediate (11–25)	143	68.8	52	68.4	
	high (>25)	21	10.1	6	7.9	
Age	<40	28	13.5	13	11.0	0.449
	40 ≤	180	86.5	63	82.9	
Age (Median±SD, yr)	44.00 (±4.0)			46.68 (±3.9)		0.052
Menopause	Pre	174	83.7	61	80.3	0.595
	Post	34	16.3	15	19.7	
Histology	Ductal	180	86.5	70	92.1	0.201
	Lobular	17	8.2	6	7.9	
	Mixed(ductal+lobular)	3	1.4	0	0.0	
	Others	8	3.8	0	0.0	
Coexistence of Ductal Carcinoma in situ	No	128	61.5	52	68.4	0.286
	Yes	80	38.5	24	31.6	
Median Size (range, cm) of DCIS	2.04 (±1.5)			1.05 (±0.9)		0.069
Excistence of Satelite nodules	No	145	69.7	54	71.1	0.827
	Yes	63	30.3	22	28.9	
Lymphovascular invasion	No	135	64.9	44	57.9	0.279
	Yes	73	35.1	32	42.1	
Extensive intraductal component	No	137	65.9	63	82.9	0.005
	Yes	71	34.1	13	17.1	
Nuclear grade	1	28	13.5	2	2.6	0.053
	2	168	80.8	67	88.2	
	3	12	5.8	7	9.2	
Histologic grade	1	58	27.9	9	11.8	0.058
	2	140	67.3	62	81.6	
	3	10	4.8	5	6.6	
T stage	1	144	69.2	46	60.5	0.211
	2	64	30.8	30	39.5	
Number of metastatic lymph node	0	140	67.3	57	75.0	0.454
	1	56	26.9	16	21.1	
	2	12	5.8	3	3.9	
Median Size (range, cm) of metastasis	0.11 (±0.1)			0.17 (±0.2)		0.455
Perinodal extension	No	195	93.8	71	93.4	0.927
	Yes	13	6.3	5	6.6	
Estrogen Receptor(ER)	negative	0	0.0	0	0.0	
	positive	208	100.0	76	100.0	
ER grade	8	171	82.2	69	90.8	0.353
	7	33	15.9	6	7.9	
	6	2	1.0	1	1.3	
	5	1	0.5	0	0.0	
	4	1	0.5	0	0.0	
	3	0	0	0	0	
Progesteron Receptor	negative	6	2.9	3	3.9	0.355
	positive	202	97.1	73	96.1	
HER2 Receptor	negative	208	100.0	76	100.0	0.325
	positive	0	0.0	0	0.0	
Ki-67	1 (<25%)	184	88.5	59	77.6	0.054
	2 (25≤ <50%)	24	11.5	17	22.4	
	3 (50 ≤ < 75%)	0	0	0	0	
	4 (75≤ <100%)	0	0	0	0	

modeling group but lower in the validation group. However, there was no statistical significance with respect to these differences ($p = 0.840$). The mean patient age was 44 years in the modeling group and 46 years in the validation group. The majority of patients had invasive ductal carcinoma with the characteristics of nuclear grade 2, histologic grade 2, and stage T1. EIC was the only different variable among the two groups ($p = 0.005$); the others were not significantly different.

Predictive model

We developed a predictive model with 208 cases through the Azure ML platform (Microsoft, Redmond, WA, USA) (Fig. 1). We tried to develop a model using various classification algorithms, such as Two-class Decision Forest, Two-class Decision Jungle, Two-class Bayes Point Machine, Two-class Support Vector Machine, and Two-class Neural Network. Among them, we found the most suitable method in each case for the high RS group and the low RS group, respectively. For the high RS group, the use of Two-class Decision Jungle showed the best accuracy, which was 0.903. For the low RS group, the accuracy was 0.726 when the Two-class Neural Network method was applied. We also assessed the AUC. The AUC of the ROC curve was 0.917 in the high RS group (Fig. 2a) and 0.744 in the low RS group (Fig. 2b). In addition, we conducted an internal validation initiative using 76 patients who underwent ODX testing between January 2017 and July 2017. When we applied a 0.5 threshold value with our predictive model, the accuracy of validation was 0.880 in the high RS group and 0.790 in the low RS group (Table 2). We also compared variables for modeling between other validation studies and our study (Table 3.)

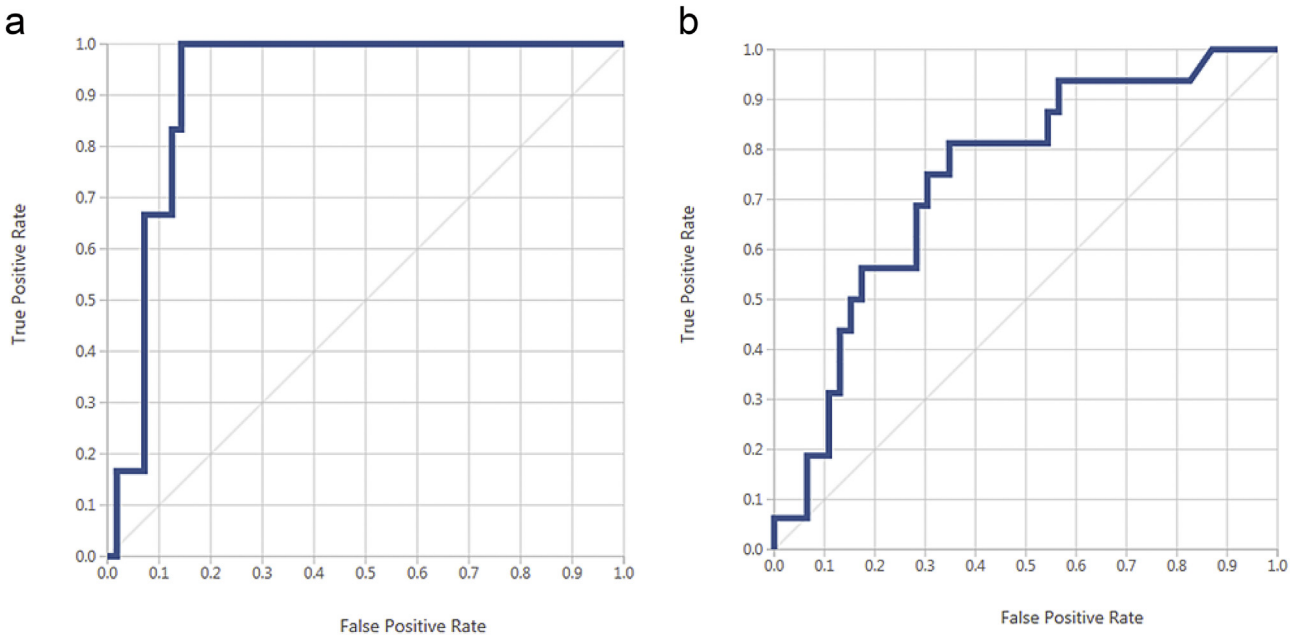

Fig. 2. The mean AUC of ROC curve. a. The high RS group (0.917). b. The low RS group (0.744).

Table 2
The predictive result of validation with 76 patients.

	Sensitivity	Specificity	Precision	Accuracy
low recurrence score group (<11)	0.110	1.000	1.000	0.790
high recurrence score group (>25)	0.170	0.960	0.250	0.880

Clinical application

The Azure ML platform (Microsoft, Redmond, WA, USA) provides a function for the set-up of web services(http://docs.microsoft.com/en-us/azure/machine-learning/studio/consume-web-services). After deploying the Azure ML predictive model as a web service, we used a Representational State Transfer application programming interface to send data and obtain predictions in real-time. For example, when we input data according to each variable excluding the final value "ODX" (Fig. 3), an external application communicated with a machine learning workflow scoring model in real-time, enabling the predicted value to be calculated in only a few seconds.

Clinical follow up

We performed clinical follow up in 284 patients (208 patients for modeling group and 76 patients for validation group) and median follow up period was 38.1 months(range 11–80). Among them, 1 patient had distant metastasis and 2 patients had local recurrence (Table 4). These patients were all real high RS group but only 1 patient was not high RS group through our predictive model. There were also 3 cases for contra lateral breast cancer (Table 4). Among them, 2 cases were real high RS group but only 1 case was predictive high RS group.

Discussion

ODX is one of several genomic tests that has been developed for the identification of early breast cancer and is currently used worldwide [20]. There have been several reports published to date about the cost-effectiveness of ODX [21,22] and it remains an expensive test.

In previous studies, prediction for ODX score was performed using logistic regression models [8,23,24] or equations [7,25]. Our study is unique in that it is a validation study that employs machine learning. The Azure ML platform (Microsoft, Redmond, WA, USA) that we used has several advantages. First, real-time analysis is possible in the clinical field. Second, it is free of charge to use—-there is an option tool that has a charge associated with it in the Azure ML platform (Microsoft, Redmond, WA, USA), but our study was performed with the free option tool sufficiently. Third, using this program, the development of a suitable model is possible for each hospital. The findings of a predictive study with large data conducted at one center may not always be suitable for use by other institutions. Our center performed a validation study using an online nomogram calculator provided by the University of Tennessee Medical Center (Knoxville, TN, USA) on their website (https://gsm.utmck.edu/nomograms) in order to calculate the probability of a low-risk or a high-risk ODX score for each patient [26]. Notably, the nomogram calculations cannot be generalized to patients in Asia, although they are based on a large dataset of the United States-based National Cancer Database. This may be because of differences in race or variable values. The accurate results of ODX testing were dependent on accurate histology grading and high-quality estrogen receptor, progesterone receptor, HER2, and Ki-67 immunohistochemical results. These factors were measured according to the official international standard; however, there could be minimally differences among centers or individual patients. Our predictive model can incorporate data from other centers or hospitals

Table 3
The Comparison for Variables between previous validation studies and present study.

Study	Group	Variables for modeling	Character of variables	Meaning
Gage,M et al. [9]	low risk (ODX RS ≤ 10)	low tumor grade	categorical variable	Nottingham Combined histologic grade
		progesterone receptor positive	categorical variable	1–100%
	high risk (ODX RS 26≤)	high tumor grade	categorical variable	Nottingham Combined histologic grade
		low estrogen receptor	categorical variable	<20%
Orucevic,A et al. [6]	low risk (ODX RS ≤ 10) and	age	continuous variable	
	high risk (ODX RS 26≤)	tumor size	continuous variable (millimeter)	
		histologic grade 1,2,3	categorical variable	Nottingham Combined histologic grade
		progesterone receptor(positive or negative)	categorical variable	≤1%
		lymphovascular invasion(positive or negative)	categorical variable	
		histologic type (IDC, ILC, IDC+ILC, IDC+Others)	categorical variable	
Present Study	low risk (ODX RS ≤ 10) and	age	continuous variable	
	high risk (ODX RS 26≤)	DCIS size	continuous variable (centimeter)	
		metastatic size of lymph node	continuous variable (centimeter)	
		histologic type IDC (yes = 1 or no = 0)	categorical variable	
		histologic type ILC (yes = 1 or no = 0)	categorical variable	
		histologic type IDC + ILC (yes = 1 or no = 0)	categorical variable	
		histologic type Others (yes = 1 or no = 0)	categorical variable	
		existence of DCIS (yes = 1 or no = 0)	categorical variable	
		existence of satelite nodule (yes = 1 or no = 0)	categorical variable	
		lymphovascular invasion (yes = 1 or no = 0)	categorical variable	
		Extensive intraductal component (yes = 1 or no = 0)	categorical variable	
		Nuclear grade 1,2,3	categorical variable	Fisher grading nuclear system
		Histologic grade 1,2,3	categorical variable	Nottingham Combined histologic grade
		pathologic T stage 1,2	categorical variable	AJCC 7th edition
		number of metastatic lymph node	continuous variable	
		Perinodal extension (yes = 1 or no = 0)	categorical variable	
		estrogen receptor 3,4,5,6,7,8	categorical variable	Allered score
		progesteron receptor (positive = 1 or negative = 0)	categorical variable	Allered score 3 ≤ : positive
		HER2 receptor 1,2,3	categorical variable	IHC staining HER2 score
		Ki-67 1(<25%),2(25≤<50%),3(50≤<75%) 4(75≤<100%)	categorical variable	Percentage of positive cell by IHC staining

Fig. 3. An illustration of web service usage for prediction in the high RS group.
AbbreviationODX25, oncotype DX > 25; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PNE, perinodal extension; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

and still provide proper results for each center, so any disparity among centers or hospitals could be diminished.

We established a prediction model using a modeling group (208 patients) and performed an internal validation with 76 patients.

Table 4
The results of clinical follow up in 284 patients (modeling group 208 + validation group 76).

	Site	Time to event from operation date	Real ODX RS group	Predictive ODX RS group
Distant metastasis	Multiple bone(Skull, Spine, Sternum, Humerus)	59 months	high	high
Local recurrence	Operation site	52 months	high	high
	Ipsilateral internal mammary lymph node	33 months	high	intermediate[a]
Contra lateral breast cancer	–	56 months	high	high
	_	52 months	high	intermediate
	_	34 months	intermediate	intermediate

[a] Our model was made for prediction of high or low RS group. Intermediate means the group which could not be predicted through high RS model as well as low RS model.

Between the two groups, EIC was the only factor that showed a statistical difference. EIC is defined as the presence of intraductal carcinoma representing more than 25% of the area of the entire invasive carcinoma [27] and it has been reported to be a very important risk factor for local disease recurrence after breast-conserving therapy [28]. However, the association between ODX RS (low, intermediate, high) and EIC (yes, no) was not important statistically according to linear-by-linear association analysis ($p = 0.083$). Therefore, we believe that EIC did not have an influence on the results of internal validation.

We also investigated recurrence or contralateral breast cancer cases in 284 patients (208 patients for modeling group and 76 patients for validation group) and then only 6 cases were observed.

Among them, 5 cases were real high RS group and 3 cases were predictive high RS group. These results did not reflect the utility of our predictive model because our study was focused on the prediction for RS low or high group, not recurrence. In addition, it was limited to check accurate prognosis due to short follow up period. For more reliable results, additional analysis with a larger number of patients and long term follow up time is needed.

Our study has several limitations. First, the predictive accuracy for the low RS group was lower (0.790) than that for the high RS group (0.880). However, the predictive value for the high RS group showed reliable results, so it can be said that our predictive model is more suitable for the prediction of high RS patients. This could be the merit for assortment of patients who need chemotherapy in clinical field. Second, the number of patients enrolled in the current study was not a large one and, third, only internal validation was performed. To increase study reliability, an analysis with a larger number of patients and external validation regardless of race is needed.

Conclusion

We developed a predictive model using machine learning that could represent a useful and easy-to-access tool for the selection of high RS patients. After additional evaluation with large data and external validation, worldwide use of our model could be expected.

Conflicts of interest statement

The authors declare that they have no competing interests.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (2015R1D1A1A01057585); by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare of the Republic of Korea (HI14C3418); and by a National Research Foundation of Korea grant funded by Ministry of Science, ICT and Future Planning (2016R1A5A2945889).

References

[1] Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817–26.
[2] Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726–34.
[3] Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: american society of clinical oncology clinical practice guideline. J Clin Oncol 2016;34:1134–50.
[4] Henry NL, Somerfield MR, Abramson VG, Allison KH, Anders CK, Chingos DT, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: american society of clinical oncology endorsement of cancer care ontario guideline recommendations. J Clin Oncol 2016;34:2303–11.
[5] Orucevic A, Heidel RE, Bell JL. Utilization and impact of 21-gene recurrence score assay for breast cancer in clinical practice across the United States: lessons learned from the 2010 to 2012 National Cancer Data Base analysis. Breast Canc Res Treat 2016;157:427–35.
[6] Orucevic A, Bell JL, McNabb AP, Heidel RE. Oncotype DX breast cancer recurrence score can be predicted with a novel nomogram using clinico-pathologic data. Breast Canc Res Treat 2017;163:51–61.
[7] Klein ME, Dabbs DJ, Shuai Y, Brufsky AM, Jankowitz R, Puhalla SL, et al. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. Mod Pathol 2013;26:658–64.
[8] Ingoldsby H, Webber M, Wall D, Scarrott C, Newell J, Callagy G. Prediction of Oncotype DX and TAILORx risk categories using histopathological and immunohistochemical markers by classification and regression tree (CART) analysis. Breast 2013;22:879–86.
[9] Gage MM, Rosman M, Mylander WC, Giblin E, Kim HS, Cope L, et al. A validated model for identifying patients unlikely to benefit from the 21-gene recurrence score assay. Clin Breast Canc 2015;15:467–72.
[10] Tafti AP, LaRose E, Badger JC, Kleiman R, Peissig P. Machine learning-as-a-service and its application to medical informatics. In: International conference on machine learning and data mining in pattern recognition. 13th international conference, MLDM 2017, New York, NY, USA, July 15-20, 2017, proceedings; 2017. p. 206–19.
[11] Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). Clin Breast Canc 2006;7:347–50.
[12] Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015;373:2005–14.
[13] Wong WB, Ramsey SD, Barlow WE, Garrison Jr LP, Veenstra DL. The value of comparative effectiveness research: projected return on investment of the RxPONDER trial (SWOG S1007). Contemp Clin Trials 2012;33:1117–23.
[14] Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med 2010;134:e48–72.
[15] Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2013;138:241–56.
[16] Dowsett M, Nielsen TO, A'hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the international Ki67 in breast cancer working group. J Natl Cancer Inst 2011;103:1656–64.
[17] Miller S, Curran K, Lunney T. Cloud-based machine learning for the detection of anonymous web proxies. In: Signals and systems conference. ISSC); 2016. p. 1–6. 2016 27th Irish.
[18] Shotton J, Sharp T, Kohli P, Nowozin S, Winn J, Criminisi A. Decision jungles: compact and rich models for classification. Adv Neural Inf Process Syst 2013:234–42. 2013.
[19] Hinton G, Vinyals O, Dean J. Distilling the knowledge in a neural network. 2015. arXiv preprint arXiv:1503.02531.
[20] Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in

patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. Breast Canc Res Treat 2017;163:303–10.
[21] Kondo M, Hoshi SL, Yamanaka T, Ishiguro H, Toi M. Economic evaluation of the 21-gene signature (Oncotype DX) in lymph node-negative/positive, hormone receptor-positive early-stage breast cancer based on Japanese validation study (JBCRG-TR03). Breast Canc Res Treat 2011;127:739–49.
[22] Lyman GH, Cosler LE, Kuderer NM, Hornberger J. Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation studies. Cancer 2007;109:1011–8.
[23] Geradts J, Bean SM, Bentley RC, Barry WT. The oncotype DX recurrence score is correlated with a composite index including routinely reported pathobiologic features. Cancer Invest 2010;28:969–77.
[24] Allison KH, Kandalaft PL, Sitlani CM, Dintzis SM, Gown AM. Routine pathologic parameters can predict Oncotype DX recurrence scores in subsets of ER positive patients: who does not always need testing? Breast Canc Res Treat 2012;131:413–24.
[25] Turner BM, Skinner KA, Tang P, Jackson MC, Soukiazian N, Shayne M, et al. Use of modified Magee equations and histologic criteria to predict the Oncotype DX recurrence score. Mod Pathol 2015;28:921–31.
[26] Kim JM, Ryu JM, Kim I, Choi HJ, Nam SJ, Kim SW, et al. The accuracy of nomograms based on large dataset using clinico-pathologic variables for prediction of oncotype DX breast cancer recurrence score [abstract]. Cancer Res 2018;78. Abstract nr P5-11-01.
[27] Kang DK, Jeon GS, Yim H, Jung YS. Diagnosis of the intraductal component of invasive breast cancer: assessment with mammography and sonography. J Ultrasound Med 2007;26:1587–600.
[28] Alrahbi S, Chan PM, Ho BC, Seah MD, Chen JJ, Tan EY. Extent of margin involvement, lymphovascular invasion, and extensive intraductal component predict for residual disease after wide local excision for breast cancer. Clin Breast Canc 2015;15:219–26.