Machine Learning for Predicting Pathological Complete Response in Patients with Locally Advanced Rectal Cancer after Neoadjuvant Chemoradiotherapy

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Research

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Abstract

BACKGROUND For patients with locally advanced rectal cancer (LARC), achieving pathological complete response (pCR) after neoadjuvant chemoradiotherapy (CRT) results in best prognosis. So far, no reliable prediction model has been available. We aim to evaluate the performance of an artificial neural network (ANN) model in the prediction of pCR in patients with LARC.

METHODS Predictive accuracy was compared between the ANN, k-earest neighbor (KNN), support vector machines (SVM), naïve Bayes classifier (NBC), and multiple logistic regression (MLR) models.

RESULTS A total of 236 patients with LARC were used to compare the forecasting models. We trained the model with an estimation data set, and evaluated model performance with a validation data set. The ANN model significantly outperformed the KNN, SVM, NBC, and MLR models in predicting pCR. Our results revealed that post-CRT carcinoembryonic antigen was the most influential predictor of pCR, followed by intervals between CRT and surgery, chemotherapy regimens, clinical nodal stage, and clinical tumor stage.

CONCLUSIONS Compared with conventional prediction models, the ANN model was more accurate in the prediction of pCR. The predictors of pCR can be used to identify which patients with LARC can benefit from watch-and-wait approaches.

Background

Neoadjuvant chemoradiotherapy (CRT) has benefited patients with locally advanced rectal cancer (LARC) with specific respect to improvements in local control, disease-free survival, and sphincter preservation rates [1–3]. However, the patterns of tumor regression after neoadjuvant CRT vary widely, ranging from a pathological complete response (pCR) to disease progression. Patients with a pCR have the most favorable survival and tumor control, but only 10–30% of patients with LARC achieve a pCR to neoadjuvant CRT [4–7]. In addition, mounting evidence has demonstrated that in patients who achieve a pCR, radical surgery can be omitted without compromising tumor control [8, 9]. Therefore, the identification of useful predictors of a pCR in patients with LARC after neoadjuvant CRT is vital.

Few studies have compared the artificial neural network (ANN), k-nearest neighbor (KNN), support vector machine (SVM), naïve Bayes Classifier (NBC), and multiple logistic regression (MLR) prediction models with respect to internal validity (reproducibility). The validity is an important performance metric [10, 11]. However, numerous predictive models yield insufficiently reliable predictions of pCR occurrence in patients with LARC after neoadjuvant CRT.

One of the most common used methods for multivariate analysis is regression analysis, which supposes linear correlations between the dependent and independent variables. Nevertheless, studies have demonstrated that biomedical variables usually vary nonlinearly [12–16]. The KNN model is a simple classification algorithm because of its straightforward implementation [14].The KNN model predicts new

samples by the use of training samples through a majority vote on the outcome of the points that are k-nearest to the new sample. The SVM model is a supervised learning model and the model is associated with learning algorithms that analyze information utilized for regression analysis and classification [13]. An SVM model constructs multidimensional hyperplanes that separate the 2 classes while maximizing the margin between the 2 classes; it uses kernel functions and can discriminate between nonlinearly separable classes. An NBC model can efficiently develop classification tools in various health domains and can transform complex clinical problems into clear, precise, and predictive models [16]. An ANN model has 3 layers: an input one, a hidden one, and an output one. Every layer possesses nodes that are connected by links from one layer to the next [12, 15]. Nodes in the input layer represent predictors, while in the output layer are viewed as outcome variables. One common application of neural networks is in the multilayer back-propagation learning algorithm, which modeling a non-linear system. Although the interpretation of neural networks is more complicated than interpretation of other statistical models, The ANN model has been used in different medical fields.

Although a great improvement in outcome prediction models has been achieved, there have been some major limitations in pCR prediction models [17, 18]. For example, many studies have identified effective predictors of pCR, but most of these variables have had insufficient sensitivity and specificity [19–21]. Therefore, our study utilized the ANN, KNN, SVM, NBC and MLR models to identify the most powerful factors to predict pCR in patients with LARC after neoadjuvant CRT. Thus, the primary purpose of the study was to validate the accuracy of the ANN model for predicting a pCR occurrence in patients with LARC following neoadjuvant CRT, and the secondary purpose was to investigate predictive performance among the various forecasting models.

Methods

Patients

This study identified patients with a LARC diagnosis who were undergoing neoadjuvant CRT at any period between January 2011 and December 2017 at Kaohsiung Medical University Hospital. In total, 248 consecutive patients satisfied the inclusion criteria, which were pathologically proven adenocarcinomas, tumors located within 12 cm of the anal verge, clinical stage II and III rectal tumors (T3 to 4 or N+), and the delivery of neoadjuvant CRT. We excluded twelve patients because they had incomplete neoadjuvant CRT (n = 4), rejection of resection (n = 3), unresectable tumors after CRT (n = 3), or only primary tumor excision (n = 2). The remaining 236 patients were enrolled for analysis as the training cohort. The validation cohort recruited 34 patients with LARC at Kaohsiung Municipal Ta-Tung Hospital between January 2017 and September 2018. The same inclusion and exclusion criteria were used in both the training and validation cohorts (Fig. 1). The study protocol was approved by the local ethic committee of our hospital (KMUHIRB-E(II)-20190280). Each patient gave written informed consent. Pretreatment clinical staging was determined through computed tomography (CT) of abdomen and chest, pelvic magnetic resonance imaging (MRI), and a physical examination. Participants' serum carcinoembryonic antigen (CEA) levels and routine laboratory test results were analyzed.

Treatment

All participants underwent neoadjuvant CRT. Radiotherapy was delivered from 45 to 50.4 Gy, 1.8 to 2.0 Gy per fraction. There-dimensional conformal radiotherapy was delivered in 45 patients, and intensity-modulated radiotherapy was given in 191 patients. Chemotherapy was administered concurrently with radiotherapy. Participants underwent 1 of 2 chemotherapeutic regimens. The first was the fluoropyrimidine-based regimen (n = 95), which consisted of 6 courses of capecitabine (850 mg/m2 twice daily for 14 days), followed by 7 days of rest after each course. The second was a biweekly schedule of FOLFOX, which included oxaliplatin (85 mg/m2) on day 1, in addition to folinic acid (400 mg/m2) and a 46-h infusion of 5-fluouracil (2800 mg/m2) repeated every 2 weeks during radiotherapy; patients continued to receive 3 to 4 cycles of consolidation chemotherapy with biweekly FOLFOX after completing of radiotherapy (n = 141) [7].

All of the patients in the current study underwent total mesorectal excision after completing neoadjuvant CRT. The surgical procedures included low anterior resection with colorectal or coloanal anastomosis (n = 207) and abdominoperineal resection (n = 29).

Evaluation And Follow-up

Two experienced pathologists evaluated tumor responses to neoadjuvant CRT. The definition of pCR was the absence of any malignant cells in the primary and nodes (ypT0N0) in the resected specimen following neoadjuvant CRT.

Acute side effects were assessed at each visit during neoadjuvant CRT according to the Common Terminology Criteria for Adverse Events, version 4.03. We defined anemia as hemoglobin level < 10 g/dL in the current study. Approximately 6–10 weeks after completing CRT, measurements were conducted before surgery, specifically through pelvic MRI, abdominal and chest CT, CEA test, and colonoscopy. After completion of all treatment, patients were required for visits to the hospital every three months in the initial two years and then once every six months until the present day.

Statistical analysis

In the current study, we used the individual patient who received neoadjuvant CRT with subsequent surgery as the unit of analysis. First, we used univariate logistic regression to select pCR-related significant risk factors. In the forecasting models, the dependent variable was the probability of a pCR, and the independent variables were the significant risk factors.

Second, the data set was randomly segmented into training and testing sets, comprising 70% and 30% of the whole data set, respectively. From a probabilistic perspective with respect to the forecasting models, this randomization was a form of statistical sampling (e.g., Monte Carlo sampling). We used the training set to construct the forecasting models. The independent variables fitted to the forecasting models were

the significant risk factors, and the dependent variable was the outcome (pCR probability). Upon completing training, the forecasting model was exposed to the testing set, and the model outputs were calculated for each testing set. Additionally, for cross-validation, data from 34 new patients were used to construct the validation set for the prediction of pCR in patients with LARC after neoadjuvant CRT.

Third, the performance indices including sensitivity, 1-specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the receiver operating characteristic (AUROC) were employed to evaluate the accuracy of the models. Bootstrapping with 1,000 replications was also performed to further amplify the training, testing, and validation data sets to reduce variability in assessing model performance.

Finally, global sensitivity analysis was conducted to evaluate the relative significance and importance of input variables in the prediction models, with these variables ranked by their importance. The ratio of the network error, sum of squared residuals, represented the global sensitivity of the input variables against the output variables. In general, a variable sensitivity ratio (VSR) level of ≤ 1 demonstrates that the variable decreases predictive performance and should be removed. STATISTICA 13.0 software (StatSoft, Inc., Tulsa, OK, USA) was executed for statistical analyses.

Results

Patient characteristics

A total of 270 LARC patients were enrolled for analysis. There were 236 patients in the training cohort and 34 patients in the validation cohort (Table 1). The median post-CRT carcinoembryonic antigen (CEA) level was 2.2 ng/mL (range: 0.48 to 197.5). Accordingly, the cut-off value of post-CRT CEA level was 2 ng/mL. Patients who achieved pCR following CRT were found in 23.7% and 20.6% of the training cohort and validation cohorts, respectively (P = .16).

Table 1

Patient Characteristics.

Variables		The training cohort Mean ± SD/ N(%)	The validation cohort Mean ± SD/ N(%)
Number of patients Patient attributes Gender	Female	236 82(34.7)	34 12(35.3)
	Male	154(65.3)	22(64.7)
Age		62.1 ± 11.5	62.8 ± 12.2
Clinical attributes Chemotherapy	Fluoropyrimidine	95(40.3)	15(44.1)
	FOLFOX	141(59.7)	19(55.9)
Tumor location	Low/middle	141(59.7)	20(58.8)
	Upper	95(40.3)	14(41.2)
Clinical T stage	T2	13(5.5)	2(5.9)
	T3	184(78)	27(79.4)
	T4	39(16.5)	5(14.7)
Clinical N stage	N0	36(15.3)	6(17.7)
	N1	145(61.4)	20(58.8)
	N2	55(23.3)	8(23.5)
TNM stage	II	36(15.3)	6(17.6)
	III	200(84.7)	28(82.4)
Tumor grade	Well differentiated	16(6.8)	2(5.8)
	Moderate differentiated	212(89.8)	31(91.3)
	Poor differentiated	8(3.4)	1(2.9)

Abbreviation:

CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; Hb, hemoglobin; ; pCR, pathological complete response; SD, standard deviation; RT, radiation therapy; WBC, white blood cell.

Variables		The training cohort Mean ± SD/ N(%)	The validation cohort Mean ± SD/ N(%)
Pre-CRT CEA (ng/mL)	≦ 5	144(61)	20(58.8)
	> 5	92(39.0)	14(41.2)
Anemia	Hb (g/dL) ≦ 10	76(32.2)	10(29.4)
	Hb (g/dL) > 10	160(67.8)	24(70.6)
Diarrhea	Grade 0–1	102(43.2)	14(41.2)
	Grade 2–3	134(56.8)	20(58.8)
Urinary symptoms	Grade 0–1	218(92.4)	31(91.2)
	Grade 2–3	18(7.6)	3(8.8)
Dermatitis	Grade 0–1	166(70.3)	24(70.6)
	Grade 2–3	70(29.7)	10(29.4)
leukopenia	WBC ≦ 3000 (/uL)	65(27.5)	11(32.4)
	WBC > 3000 (/uL)	171(72.5)	23(67.6)
RT dose (cGy)	5040	11(4.7)	1(2.9)
	5000	181(76.7)	27(79.5)
	4500	44(18.6)	6(17.6)
RT-surgery interval	≦ 8 weeks	81(34.3)	14(41.2)
	> 8 weeks	155(65.7)	20(58.8)
Post-CRT CEA (ng/mL)	≦ 2	90(38.1)	13(38.2)
	> 2	146(61.9)	21(61.8)
Treatment response	pCR	56(23.7)	7(20.6)

Abbreviation:

CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; Hb, hemoglobin; ; pCR, pathological complete response; SD, standard deviation; RT, radiation therapy; WBC, white blood cell.

Variables		The training cohort Mean ± SD/ N(%)	The validation cohort Mean ± SD/ N(%)
	Non-pCR	180(76.3)	27(79.4)
Abbreviation:			
CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; Hb, hemoglobin; ; pCR, pathological complete response; SD, standard deviation; RT, radiation therapy; WBC, white blood cell.			

Study Characteristics

Table 2 presents the training data set's pCR odds ratio (OR). The univariate analysis indicated that pCR occurrence in patients with LARC after neoadjuvant CRT was significantly associated with gender, age, tumor location, type of chemotherapy, clinical tumor stage, clinical nodal stage, tumor-node-metastasis stage, tumor grade, post-CRT CEA level, anemia, diarrhea, urinary symptoms, dermatitis, leukopenia, dose of radiation therapy, and the radiation to surgery interval ($p < 0.01$). As a result, the significant variables were further analyzed in the forecasting models.

Table 2
The Univariate Analysis of Logistic Regression Model Using Selected Risk Factors Related to pCR (N = 236).

Variables		OR	95% C.I.	P-value
Gender	Male vs. Female	3.53	2.41–5.17	< 0.001
Age		1.02	1.01–1.02	< 0.001
Chemotherapy	FOLFOX vs. Fluoropyrimidine	2.53	1.75–3.64	< 0.001
Tumor location	Upper vs. Low/middle	4.28	2.56–7.15	< 0.001
Clinical T stage	T2 vs. T3	2.92	2.09–4.06	< 0.001
	T2 vs. T4	6.80	2.66–17.4	< 0.001
Clinical N stage	N0 vs. N1	3.68	2.47–5.47	< 0.001
	N0 vs. N2	4.00	2.07–7.75	< 0.001
TNM stage	II vs. III	3.76	2.68–5.29	< 0.001
Tumor grade	Well differentiated vs. Moderate differentiated	3.00	2.20–4.09	< 0.001
	Well differentiated vs. Poor differentiated	3.68	2.40–6.97	< 0.001
Pre-CRT CEA (ng/mL)	≦ 5 vs. > 5	4.75	2.77–8.14	< 0.001
Anemia	Grade 0–1 vs. Grade 2–3	3.32	2.30–4.80	< 0.001
Diarrhea	Grade 0–1 vs. Grade 2–3	2.62	1.80–3.83	< 0.001
Urinary symptoms	Grade 0–1 vs. Grade 2–3	8.00	1.84–34.79	0.006

Abbreviation: CEA, carcinoembryonic antigen; CI, confidence interval, CRT, chemoradiotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; Hb, hemoglobin; OR, odds ratio; pCR, pathological complete response; RT, radiation therapy; WBC, white blood cell.

Variables		OR	95% C.I.	P-value
Dermatitis	Grade 0–1 vs. Grade 2–3	3.67	2.07–6.49	< 0.001
Leukopenia	Grade 0–1 vs. Grade 2–3	2.89	2.05–4.07	< 0.001
RT-dose (cGy)	5000 vs. 4500	2.69	1.94–3.74	< 0.001
	5040 vs. 4500	7.80	3.07–19.79	< 0.001
RT-surgery interval	> 8wk vs. ≦8wk	2.44	1.73–3.46	< 0.001
Post-CRT CEA (ng/mL)	≦ 2 vs. > 2	1.58	0.86–2.88	< 0.001

Abbreviation: CEA, carcinoembryonic antigen; CI, confidence interval, CRT, chemoradiotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; Hb, hemoglobin; OR, odds ratio; pCR, pathological complete response; RT, radiation therapy; WBC, white blood cell.

Comparisons Between These Forecasting Models

The differences in patient attributes, clinical attributes, and pCR occurrence between the training and testing data sets were insignificant (data not shown). Consequently, samples from these 2 data sets could be compared to improve the reliability of the validation data sets. The ANN-based approaches provide the three-layer networks and the relative weights of neurons used for prediction of pCR. The ANN 16-4-1 model contains 16 input neurons, 4 hidden neurons, 1 bias neuron in the hidden layer, and 1 output neuron. Table 3 shows comparisons between the training and testing data sets and indicates that the ANN model outperformed the KNN, SVM, NBC, and MLR models with respect to sensitivity, 1-specificity, PPV, NPV, accuracy, and AUROC. For cross-validation, data from 34 new patients were used to construct the validation set for the prediction of pCR, and the ANN model remained the most accurate (Table 4).

Table 3

Comparison of 1,000 Pairs of Prediction Models for Predicting Pathological Complete Response.

	Sensitivity	1-Specificity	PPV	NPV	Accuracy	AUROC
Training dataset (n = 165)						
ANN	0.93	0.84	0.87	0.90	0.87	0.79
KNN	0.81	0.64	0.86	0.64	0.78	0.72
SVM	0.91	0.57	0.85	0.57	0.64	0.73
NBC	0.91	0.49	0.75	0.87	0.75	0.50
MLR	0.90	0.47	0.83	0.39	0.80	0.79
Testing dataset (n = 71)						
ANN	0.94	0.87	0.89	0.88	0.86	0.81
KNN	0.89	0.49	0.87	0.46	0.84	0.72
SVM	0.90	0.82	0.85	0.71	0.85	0.74
NBC	0.90	0.85	0.82	0.75	0.78	0.51
MLR	0.84	0.61	0.88	0.69	0.85	0.77

Abbreviation: ANN, artificial neural network; KNN, K nearest neighbor; SVM, support vector machines; NBC, Naive Bayes classifier; MLR, multiple logistic regression; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristic.

Table 4

Comparative Performance Indices of Prediction Models When Using 34 New Validation Datasets to Predict Pathological Complete Response.

	Sensitivity	1-Specificity	PPV	NPV	Accuracy	AUROC
ANN	0.94	0.80	0.89	0.87	0.88	0.84
KNN	0.80	0.67	0.87	0.60	0.80	0.74
SVM	0.91	0.76	0.86	0.72	0.71	0.76
NBC	0.90	0.53	0.79	0.84	0.80	0.63
MLR	0.88	0.79	0.84	0.49	0.83	0.77

Abbreviation: ANN, artificial neural network; KNN, K nearest neighbor; SVM, support vector machines; NBC, Naive Bayes classifier; MLR, multiple logistic regression; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristic.

Significant Predictors In The ANN Model

We used the training data sets to compute the VSR for the ANN model. The global sensitivity analysis demonstrated that the most sensitive variable for predicting pCR occurrence in patients with LARC after neoadjuvant CRT was post-CRT CEA levels (VSR = 1.57), followed by intervals between radiation and surgery (VSR = 1.50), types of chemotherapy (VSR = 1.45), clinical nodal stages (VSR = 1.37), and clinical tumor stages (VSR = 1.32) (Table 5). All VSR values in the current study exceeded 1, which indicated that the network operated better when we took all variables into consideration.

Table 5
Global Sensitivity Analysis of the ANN Model in Predicting Pathological Complete Response.

	Rank 1st	Rank 2nd	Rank 3rd	Rank 4th	Rank 5th
Variables	post-CRT CEA	RT-surgery interval	chemotherapy regimen	clinical N stage	clinical T stage
VSR	1.57	1.50	1.45	1.37	1.32

Abbreviation: ANN = artificial neural network; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; RT, radiation therapy; VSR = variable sensitivity ratio.

Discussion

We used performance indices to compare the forecasting models with respect to their accuracy in predicting pCR occurrence in patients with LARC after neoadjuvant CRT. Overall, the ANN model exhibited higher accuracy than the KNN, SVM, NBC, and MLR models. When we used actual validation data sets to compare performance among various forecasting models based on a pCR occurrence, the ANN model significantly outperformed the KNN, SVM, NBC, and MLR models, which were constructed by using the same limited number of clinical parameters.

Recent studies have consistently demonstrated the ANN model's superiority relative to the KNN, SVM, NBC, or MLR models [22–24]. Statistical analyses have proved the advantages of the ANN model as well [23]. Particularly, high fault tolerance of the ANN model facilitates the accurate and appropriate processing of incomplete or noise-added inputs. In addition, we can use non-normally distributed and highly correlated data to develop nonlinear and linear ANN models, with extensive applications in medical big data analysis. In medicine, clinical studies have commonly used the ANN model for prognosis prediction [11, 22, 24]. This study's comparison of various models indicated that the ANN model exhibited the best performance of expanding the set of predictive variables; this facilitates the evaluation of the effectiveness of research methods and comprehensive prediction of pCR occurrence. Other cancer types can use the established model to predict clinical outcomes or events.

The global sensitivity analysis was performed to evaluate the value of significant predictors that affected pCR occurrence. We determined post-CRT CEA level to be the most important predictor of pCR occurrence

in LARC patients after neoadjuvant CRT. The CEA level has been commonly evaluated in colorectal cancer–related predictions. Several studies have shown predictive value of post-CRT CEA levels in patients with LARC treated with neoadjuvant CRT. Peng et al [25] revealed that a post-CRT CEA levels ≤ 2 ng/ml was an independent predictors for pCR (OR = 1.57, 95% confidence interval [CI], 1.02–2.43, P = 0.03). Yang et al [26] identified post-CRT CEA level ≤ 2.61 ng/ml was to be significantly associated with pCR (OR = 0.61, 95% CI, 0.41–0.89, P = 0.01) and improved overall survival. Kleiman et al [27] reported a significant correlation between decreased post-CRT CEA levels and pCR occurrence (OR = 1.74, 95% CI, 1.06–3.81). The possible explanation might be that decreased post-CRT CEA levels indicated prominent effects of CRT and consequently favorable tumor regression. However, the literature on the exact mechanism remains scarce.

Because radiation-induced necrosis requires time to develop, a prolonged interval between radiation and surgery potentially increases pCR occurrence. In the current study, a radiation-surgery interval > 8 weeks was associated with high pCR rates. The association between longer intervals and pCR occurrence has been studied in several retrospective cohorts, with inconsistent findings. Kalady et al [28] and Probst et al [29] have demonstrated that intervals > 8 weeks are associated with increased pCR occurrence, but Stein et al [30] and Sun et al [31] have reported the opposite result. In our previous study, we demonstrated that a longer CRT-surgery interval was associated with increased pCR rates [7]. Several recent randomized trials have been published to resolve this inconsistency. Two randomized trials by Akgun et al [32] and Terzi et al [33] have demonstrated that pCR rates are higher for long intervals (> 8 weeks) than for short intervals, although both intervals have exhibited similar rates in postoperative mortality and morbidity. However, the GRECCAR-6 trial revealed no significant difference between long (11 week) and short intervals (7 weeks) with respect to pCR occurrence, although greater complications and difficulties in surgery were observed for participants with an 11-week interval [34]. More data is required to adjudicate this dispute over which interval best increases pCR occurrence.

To enhance response to CRT, several chemotherapeutic drugs were added to standard fluoropyrimidine-based CRT. Two randomized trials [5, 6] have reported an increase in pCR after the addition of oxaliplatin to CRT, but other trials observed no such increase [4, 35, 36]. To resolve this inconsistency, Yang et al [37] reviewed the published randomized trials and demonstrated that the addition of oxaliplatin to CRT significantly increased pCR rates (risk ratio = 1.24, 95% CI, 1.02–1.51, P = 0.03). Our previous study revealed that FOLFOX-based CRT resulted in improved pCR rates relative to fluoropyrimidine-based CRT [7]. In the current study, we also determined that FOLFOX-based CRT constituted an independent predictor of pCR in machine-learning prediction models.

In agreement with our results, several studies have demonstrated that having clinically node-negative rectal cancer is independently associated with an increase in pCR occurrence [38–40]. Our previous study reviewed 236 patients with LARC undergoing neoadjuvant CRT with subsequent surgery. According to the results, pCR rates in clinically node-negative disease were three times higher than those in node-positive disease (OR = 3.2, 95% CI, 1.27–8.41, P = 0.01) [41]. Based on these studies, clinical node positivity may

indicate more advanced disease, which results in poor response to CRT. Therefore, patients with clinically node-negative rectal cancer are likely to be suitable for watch-and-wait treatment.

In this study, the ANN model identified clinical T4 as an independent predictor for the absence of pCR. This finding is consistent with other published studies that have demonstrated that advanced tumor stage is associated with unfavorable tumor regression [38–40]. Despite contradictory findings on the association between clinical tumor stage and pCR occurrence [28, 42], clinical experience suggests highly advanced tumor stage is associated with highly aggressive tumor behavior, which indicates lower sensitivity to CRT.

In addition to improving the analysis of variance in the correlation between clinical parameters and pCR occurrence, predictive models have broad clinical applications as well. The methods used in the current study can be applied to investigate the effectiveness of medical care methods, and the quality of care can be improved thus. Because the proposed ANN model exhibited high accuracy in predicting pCR, the model can help clinicians to identify which patients can benefit from watch-and-wait treatment after neoadjuvant CRT. More studies are required to confirm the reliability of the ANN model and to clarify whether the model can be used effectively to predict clinical outcomes and to optimize treatment for cancer.

There were some limitations in the current study. First, magnetic resonance imaging (MRI) features were not assessed: comparisons are of limited validity because of incompleteness in MRI data. Second, the focus on pCR as the endpoint of this prediction model potentially limits the overall clinical use of the ANN model to a small subset of patients who have a high likelihood of pCR. Third, we only ran forecasting models to predict pCR in patients with LARC after neoadjuvant CRT. Because of the robust magnitude and the statistical significance of the effects in the current study, these limitations are considered not to compromise the validity of the results.

Conclusions

Relative to the KNN, SVM, NBC, and MLR models, this study's ANN model was more accurate in predicting pCR in patients with LARC after neoadjuvant CRT, at higher overall performance indices. Preoperative consultations can address this study's predictors to educate candidates for choices of LARC surgery on health outcomes and the expected prognosis. These findings can serve as a vital and empirical foundation for improving quality of life in patients with LARC because of omitting radical surgery.

Declarations

Ethics approval and consent to participate

The study protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the local ethic committee of our hospital (KMUHIRB-E(II)-20190280). Each patient gave written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no conflicts of interests.

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Authors' contributions

Conceptualization, Hon-Yi Shi; Data curation, Hsiang-Lin Tsai; Formal analysis, Hon-Yi Shi; Investigation, Wei-Chiao Chang; Resources, Ming-Yii Huang, Ching-Wen Huang, Wei-Chih Su and Jaw-Yuan Wang; Supervision, Jaw-Yuan Wang; Writing – original draft, Chun-Ming Huang.

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Figures

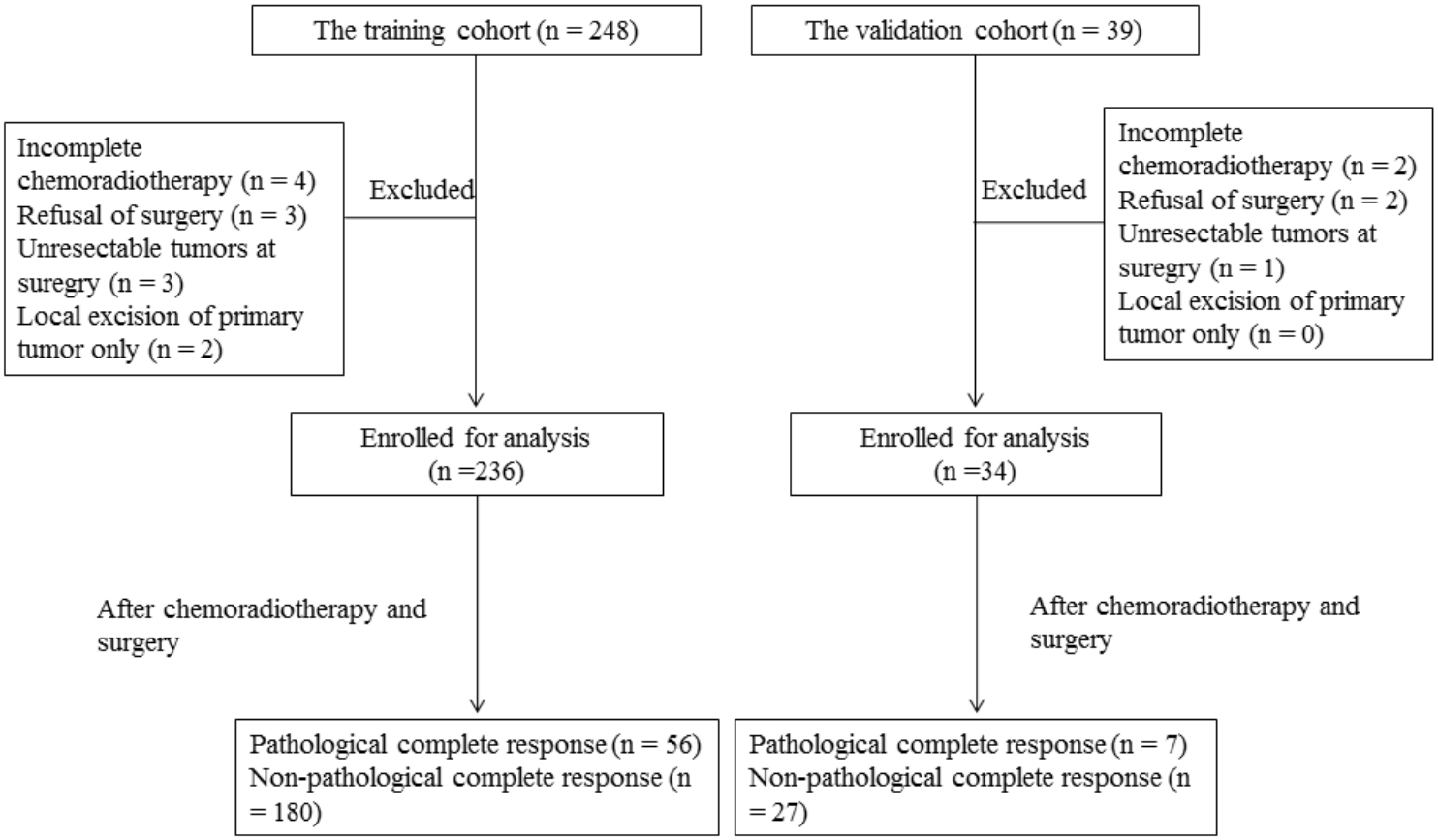

Figure 1

The flow chart of patient selection in both the training and validation cohorts.