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Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer

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ABSTRACT

Purpose
To develop and validate a radiomics nomogram for preoperative prediction of lymph node (LN) metastasis in patients with colorectal cancer (CRC).

Patients and Methods
The prediction model was developed in a primary cohort that consisted of 326 patients with clinicopathologically confirmed CRC, and data was gathered from January 2007 to April 2010. Radiomic features were extracted from portal venous–phase computed tomography (CT) of CRC. Lasso regression model was used for data dimension reduction, feature selection, and radiomics signature building. Multivariable logistic regression analysis was used to develop the predicting model, we incorporated the radiomics signature, CT-reported LN status, and independent clinicopathologic risk factors, and this was presented with a radiomics nomogram. The performance of the nomogram was assessed with respect to its calibration, discrimination, and clinical usefulness. Internal validation was assessed. An independent validation cohort contained 200 consecutive patients from May 2010 to December 2011.

Results
The radiomics signature, which consisted of 24 selected features, was significantly associated with LN status ($P < .001$ for both primary and validation cohorts). Predictors contained in the individualized prediction nomogram included the radiomics signature, CT-reported LN status, and carcinoembryonic antigen level. Addition of histologic grade to the nomogram failed to show incremental prognostic value. The model showed good discrimination, with a C-index of 0.736 (C-index, 0.759 and 0.766 through internal validation), and good calibration. Application of the nomogram in the validation cohort still gave good discrimination (C-index, 0.778 [95% CI, 0.769 to 0.787]) and good calibration. Decision curve analysis demonstrated that the radiomics nomogram was clinically useful.

Conclusion
This study presents a radiomics nomogram that incorporates the radiomics signature, CT-reported LN status, and clinical risk factors, which can be conveniently used to facilitate the preoperative individualized prediction of LN metastasis in patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and ranks fourth as a cause of cancer-related death globally.[1,2] Accurate identification of lymph node (LN) involvement in patients with CRC is crucial for prognosis and treatment strategy decisions.[3,4] Although several histopathologic findings, such as lymphatic invasion and tumor differentiation, are known to be predictors of LN metastasis, they are only available postoperatively.[5] Preoperative knowledge of LN metastasis can provide valuable information for determining the need for adjuvant therapy and the adequacy of surgical resection, thus aiding in pretreatment decision making.[6,7] A recent study revealed that serum angiopoietin-like protein 2, combined with clinical factors, could reach high predictive accuracy in the preoperative detection of LN metastasis in CRC.[7]

As an alternative, computed tomography (CT) is commonly used for preoperative work-up

and is an important part of the staging process of CRC in clinical practice[8-10]; however, a previous study has shown that the main limitation of CT in local staging of CRC is its inability to accurately identify malignant nodes.[11] The term radiomics has attracted increased attention in recent years, and it is the process of the conversion of medical images into high-dimensional, mineable data via high-throughput extraction of quantitative features, followed by subsequent data analysis for decision support.[12,13] Advances in pattern recognition tools and the increase in data set sizes have facilitated the development of radiomics, which may potentially improve predictive accuracy in oncology.[12-15] Previous studies have shown that objective and quantitative imaging descriptors could potentially be used as prognostic or predictive biomarkers.[16-18] The combined analysis of a panel of biomarkers, rather than individual analyses, as a signature is the most promising approach that is powerful enough to change clinical management.[19,20] Radiomics, which allows the investigation of multiple imaging features in parallel, can provide a combination of features. Although CT texture assessments have been applied and demonstrated to be useful for prognosis prediction in patients with CRC,[21,22] an optimal approach that combines multiple imaging biomarkers as a predictive signature has yet to be developed. To the best of our knowledge, there is no literature that has determined whether a radiomics signature would enable superior prediction of LN metastasis.

Therefore, the aim of this study was to develop and validate a radiomics nomogram that incorporated both the radiomics signature and clinicopathologic risk factors for individual preoperative prediction of LN metastasis in patients with CRC.

PATIENTS AND METHODS

Patients

Ethical approval was obtained for this retrospective analysis, and the informed consent requirement was waved. The primary cohort of this study comprised an evaluation of the institutional database for medical records from January 2007 to April 2010 to identify patients with histologically confirmed CRC who underwent surgical resection with curative intent. Data Supplement presents the patient recruitment pathway as well as the inclusion and exclusion criteria. In total, 326 patients were identified and comprise the primary cohort: 213 males and 113 females; mean age, 61.22 ± 13.91 years; range, 14 to 90 years. From May 2010 to December 2011, an independent validation cohort of 200 consecutive patients (128 males and 72 females; mean age, 62.43±12.84; range, 27 to 88 years) was screened from 631 consecutive patients using the same criteria as that for the primary cohort, with the exception of exclusion criteria (c) and (d) as listed in the Data Supplement. The level of attrition for our study was consistent with other studies in the literature.[13]

Baseline clinicopathologic data, including age, gender, preoperative histologic grade, and carcinoembryonic antigen (CEA) was derived from medical records and dates of baseline CT imaging were also recorded. Note that LN status was defined by case. Laboratory analysis of CEA was done via routine blood tests within 1 week before surgery. The threshold value for CEA level was ≤ 5 ng/mL and > 5 ng/mL, according to the normal range used at our institution.

CT Image Acquisition, Retrieval Procedure, Radiomics Feature Extraction Methodology, and Determination of CT-Reported LN Status

The Data Supplement describes CT image acquisition, the image retrieval procedure, the algorithms for radiomics feature extraction along with intraobserver (reader 1 twice) and interobserver (reader 1 *v* reader 2) reproducibility evaluation, and the determination of CT-reported LN status.

Statistical Analysis

Statistical analysis was conducted with R software (version 3.0.1; http://www.Rproject.org). The packages in R that were used in this study are reported in the Data Supplement. The reported statistical significance levels were all two-sided, with statistical significance set at .05.

Demographic Comparison Between LN-Positive and LN-Negative Group and Between Primary and Validation Cohort

The univariable association between clinicopathologic risk factor and LN status and the difference in LN prevalence and clinicopathologic characteristics—regarding LN-positive and LN-negative groups separately—between primary and validation cohorts were assessed by statistical methods described in the Data Supplement.

Feature Selection and Radiomics Signature Building

The least absolute shrinkage and selection operator (LASSO) method, which is suitable for the regression of high-dimensional data,[23] was used to select the most useful predictive features from the primary data set. A radiomics score (Rad-score) calculated for each patient via a linear combination of selected features that were weighted by their respective coefficients.

Diagnostic Validation of Radiomics Signature

The potential association of the radiomics signature with LN status was first assessed in the primary cohort and then validated in the validation cohort by using a Mann-Whitney *U* test. Stratified analyses were performed (Data Supplement).

Development of an Individualized Prediction Model

Multivariable logistic regression analysis began with the following clinical candidate predictors: age, gender, site, CEA level, and CT-reported LN status. Radiomics signature was applied to develop a diagnostic model for LN metastasis by using the primary cohort. Backward step-wise selection was applied by using the likelihood ratio test with Akaike's information criterion as the stopping rule.[24,25]

To provide the clinician with a quantitative tool to predict individual probability of LN metastasis, we built the radiomics nomogram on the basis of multivariable logistic analysis in the primary cohort.

Apparent Performance of the Nomogram in the Primary Cohort

Calibration curves were plotted to assess the calibration of the radiomics nomogram, accompanied with the Hosmer-Lemeshow test. (A significant test statistic implies that the model does not calibrate perfectly.)[26] To quantify the discrimination performance of the radiomics nomogram, Harrell's C-index was measured. The radiomics nomogram was subjected to bootstrapping validation (1,000 bootstrap resamples) to calculate a relatively corrected C-index.

Validation of the Radiomics Nomogram

Internal validation. Internal validation was performed using the data set of the second measurement by reader 1 as well as the measurement by reader 2 of the 60 patients.

Independent validation. The performance of the internally validated nomogram was tested in the validation cohort. The logistic regression formula formed in the primary cohort was applied to all

patients of the validation cohort, with total points for each patient calculated. Logistic regression in this cohort was then performed by using the total points as a factor. Finally, the C-index and calibration curve were derived on the basis of the regression analysis.

Incremental predictive value of histologic grade for the nomogram. A major concern with the addition of histologic grade to the radiomics nomogram was that histologic grade was obtained from presurgery biopsy, which may introduce sampling bias compared with surgical tissue, and, hence, was prone to a high false-negative rate.[26] Therefore, the incremental value of histologic grade as an additional candidate predictor was evaluated, with C-index and calibration curve derived and the net reclassification improvement (NRI) calculated.[27,28]

Clinical Use

Decision curve analysis was conducted to determine the clinical usefulness of the radiomics nomogram by quantifying the net benefits at different threshold probabilities in the validation dataset.[29] The decision curve was also plotted for the model after the addition of histologic grade.

RESULTS

Clinical Characteristics

Patient characteristics in the primary and validation cohorts are given in Table 1. There are no significant differences between the two cohorts in LN prevalence (P = .925). LN metastasis positivity was 50.9% and 50.5% in the primary and validation cohorts, respectively. Although there was a temporal disconnect, there were no significant differences in the clinical characteristics between the primary and the validation cohort, either within the LN-positive cohort or in the LN-negative cohort, which justified their use as training and validation cohorts (Data Supplement).

Satisfactory interobserver and intraobserver reproducibility of radiomics features extraction was achieved (Data Supplement). Accuracy of the subjective CT report of LN status was 0.63. In the whole cohort, 103 patients were reported to be LN-negative but confirmed to have LN metastases, whereas 102 patients were reported to be LN-positive but confirmed to have LN metastases.

Feature Selection and Radiomics Signature Building

Of texture features, 150 features were reduced to 24 potential predictors on the basis of 326 patients in the primary cohort (14:1 ratio; Figs 1A and 1B), and were features with nonzero coefficients in the LASSO logistic regression model. These features were presented in the Rad-score calculation formula (Data Supplement). Distributions of the Rad-score and LN status in primary and validation cohorts are given in the Data Supplement.

Diagnostic Validation of Radiomics Signature

There was a significant difference in Rad-score between LN-positive and LN-negative patients in the primary cohort ($P <$ .001), which was then confirmed in the validation cohort ($P <$ .001). LN-positive patients generally had higher Rad-scores in the primary cohort (Table 1). The radiomics

Table 1. Characteristics of Patients in the Primary and Validation Cohorts

Characteristic	Primary Cohort			Validation Cohort		
	LN Metastasis (+)	LN Metastasis (−)	*P*	LN Metastasis (+)	LN Metastasis (−)	*P*
Age, mean ± SD, years	59.31 ± 13.90	63.19 ± 13.68	.008*	60.02 ± 13.45	64.88 ± 11.75	.007*
Gender, No. (%)			.720			.167
Male	110 (66.3)	103 (64.4)		61 (60.4)	67 (67.7)	
Female	56 (33.7)	57 (35.6)		40 (39.6)	32 (32.3)	
Primary site			.027*			.283
Cecum-ascending colon	44 (26.5)	23 (14.4)		26 (25.7)	13 (13.1)	
Transverse colon	5 (3.0)	3 (1.9)		3 (3.0)	7 (7.1)	
Descending colon	4 (2.4)	9 (5.6)		5 (5.0)	5 (5.1)	
Sigmoid colon	34 (20.5)	47 (29.4)		22 (21.8)	27 (27.3)	
Rectum	79 (47.6)	78 (48.8)		45 (44.6)	47 (47.5)	
CEA level, No (%)			.006*			.456
Normal	94 (56.6)	114 (71.2)		57 (59.0)	61 (61.6)	
Abnormal	72 (43.4)	46 (28.7)		44 (41.0)	38 (38.4)	
Histologic grade			.001*			.017*
Well differentiated	2 (1.2)	4 (2.5)		0 (0)	5 (5.1)	
Moderately differentiated	137 (82.5)	147 (91.9)		86 (85.1)	90 (90.9)	
Poorly differentiated	27 (16.3)	9 (5.6)		15(14.9)	4 (4.0)	
CT-reported LN status, No (%)			.001*			< .001
LN-negative	60 (40.5)	88 (59.5)		43 (38.4)	69 (61.6)	
LN-positive	106 (59.6)	72 (40.4)		58 (65.9)	30 (34.1)	
Radiomics score, median (interquartile range)	0.211 (−0.075 to 0.480)	−0.101 (−0.387 to 0.101)	< .001*	0.136 (−0.009 to 0.435)	−0.093 (−0.312 to 0.116)	< .001*

NOTE. *P* value is derived from the univariable association analyses between each of the clinicopahologic variables and LN status.
Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; LN, lymph node; SD, standard deviation.
*P value < .05.

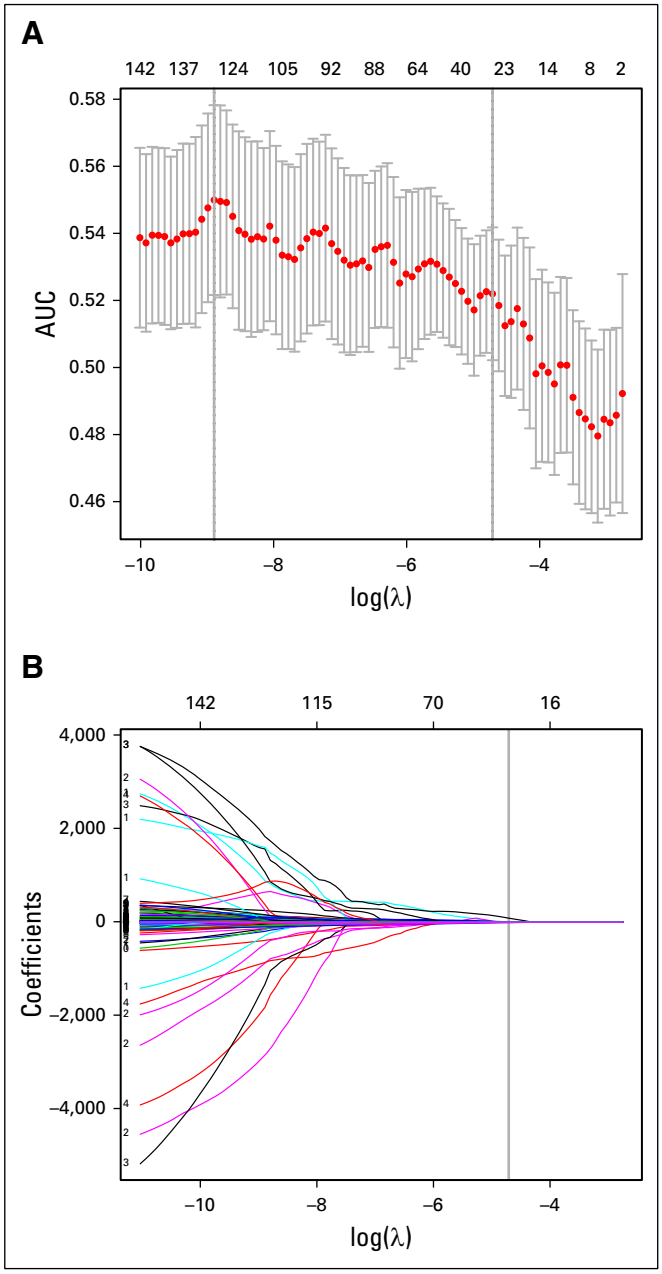

Fig 1. Texture feature selection using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model. (A) Tuning parameter (λ) selection in the LASSO model used 10-fold cross-validation via minimum criteria. The area under the receiver operating characteristic (AUC) curve was plotted versus log(λ). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 standard error of the minimum criteria (the 1-SE criteria). A λ value of 0.009, with log (λ), −4.709 was chosen (1-SE criteria) according to 10-fold cross-validation. (B) LASSO coefficient profiles of the 150 texture features. A coefficient profile plot was produced against the log (λ) sequence. Vertical line was drawn at the value selected using 10-fold cross-validation, where optimal λ resulted in 24 nonzero coefficients.

signature yielded a C-index of 0.718 (95% CI, 0.712 to 0.724) in primary cohort and 0.773 (95% CI, 0.764 to 0.782) in validation cohort. Significant association between the radiomics signature and LN status was found when stratified analysis was performed (Data Supplement)

Development of an Individualized Prediction Model

A logistic regression analysis identified the radiomics signature, CEA level, and the CT-reported LN status as independent predictors (Table 2). The model that incorporated the above independent predictors was developed and presented as the nomogram (Fig 2).

Apparent Performance of the Radiomics Nomogram in the Primary Cohort

The calibration curve of the radiomics nomogram for the probability of LN metastasis demonstrated good agreement between prediction and observation in the primary cohort (Fig 3A). The Hosmer-Lemeshow test yielded a nonsignificant statistic (P = .916), which suggested that there was no departure from perfect fit. The C-index for the prediction nomogram was 0.736 (95% CI, 0.730 to 0.742) for the primary cohort, which was confirmed to be 0.731 via bootstrapping validation.

Validation of the Radiomics Nomogram

Internal validation. Using the second radiomics feature measurements of the 60 patients done by reader 1 and the extraction of the data by reader 2 as the internal validation data set, the prediction model yielded a C-index of 0.759 (95% CI, 0.727 to 0.791) for reader 1 and 0.766 (95% CI, 0.735 to 0.797) for reader 2.

Independent validation. Good calibration was observed for the probability of LN metastasis in the validation cohort (Fig 3B). The Hosmer-Lemeshow test yielded a nonsignificant statistic (P = .196), And the C-index of the nomogram for the prediction of LN status was 0.778 (95% CI, 0.769 to 0.787).

Incremental Predictive Value of Histologic Grade to the Radiomics Nomogram

The prediction model after the addition of histologic grade is shown in Table 2. The calibration curve for the probability of LN metastasis in the primary and validation cohorts demonstrated good agreement between prediction and observation (Figs 3C and 3D). Although a slightly higher C-index was observed for the model with histologic grade integrated into the validation cohort (0.788; 95% CI, 0.779 to 0.797), integration of the histologic grade into the prediction model did not show significantly improved prediction performance (NRI, 0.014; P = .44; event NRI, −0.70; nonevent NRI, 0.72; negative percentage for the event NRI indicates a net worsening in risk classification for patients with LN metastases).

Clinical Use

The decision curve analysis for the radiomics nomogram and that for the model with histologic grade integrated is presented in Figure 4. The decision curve showed that if the threshold probability of a patient or doctor is > 10%, using the radiomics nomogram to predict LN metastases adds more benefit than either the treat-all-patients scheme or the treat-none scheme. Within this range, net benefit was comparable, with several overlaps, on the

Table 2. Risk Factors for Lymph Node Metastasis in Colorectal Cancer

Intercept and Variable	Model 1			Model 2		
	β	Odds Ratio (95% CI)	*P*	β	Odds Ratio (95% CI)	*P*
Intercept	−0.493		.011	−0.578		.004
Radiomics signature	1.701	5.479 (3.029 to 9.909)	< .001	1.629	5.099 (2.816 to 9.235)	< .001
CEA level	0.538	1.712 (1.035 to 2.832)	.036	0.550	1.733 (1.043 to 2.879)	.034
CT-reported LN status	0.528	1.694 (1.045 to 2.748)	.032	0.517	1.677 (1.031 to 2.728)	.037
Histologic grade	NA	NA	NA	0.862	2.367 (1.022 to 5.480)	.044
C-index						
Primary cohort		0.736 (0.730 to 0.742)			0.741 (0.735 to 0.747)	
Validation cohort		0.778 (0.769 to 0.787)			0.788 (0.779 to 0.797)	

NOTE. β is the regression coefficient. Histologic grade was entered into the logistic model as binary covariate by combing the patients with well-differentiated colorectal cancer and those with moderately differentiated colorectal cancer into the group of well-to-moderately differentiated colorectal cancer because of the limited number of patients with well-differentiated colorectal cancer in both cohorts (n = 6 in the primary cohort; n = 5 in the validation cohort).
Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; LN, lymph node; NA, not available.

basis of the radiomics nomogram and the model with histologic grade integrated.

DISCUSSION

We developed and validated a diagnostic, radiomics signature–based nomogram for the preoperative individualized prediction of LN metastasis in patients with CRC. The nomogram incorporates three items of the radiomics signature, CEA status, and CT-reported LN status. The radiomics signature successfully stratified patients according to their risk of LN metastases. Incorporating the radiomics signature and clinical risk factors into an easy-to-use nomogram facilitates the preoperative individualized prediction of LN metastasis.

For the construction of the radiomics signature, 150 candidate radiomics features were reduced to 24 potential predictors by examining the predictor-outcome association by shrinking the regression coefficients with the LASSO method. This method not only surpasses the method of choosing predictors on the basis of the strength of their univariable association with outcome,[30] but also enables the panel of selected features to be combined into a radiomics signature. Multimarker analyses that incorporate individual markers into marker panels have been embraced in recent studies,[19,31-33] such as in the 21-gene assay that was identified and validated to spare the use of chemotherapy in certain groups of patients who have breast cancer.[32,33] Similarly, the radiomics signature that combine multiple individual imaging features demonstrated adequate discrimination in the primary cohort (C-index, 0.718), which was then surprisingly improved in the validation cohort (C-index, 0.773). Given that LN metastasis positivity was comparable in the two cohorts, the improved discrimination implies that the radiomics signature was robust for prediction and could be applied directly in the validation

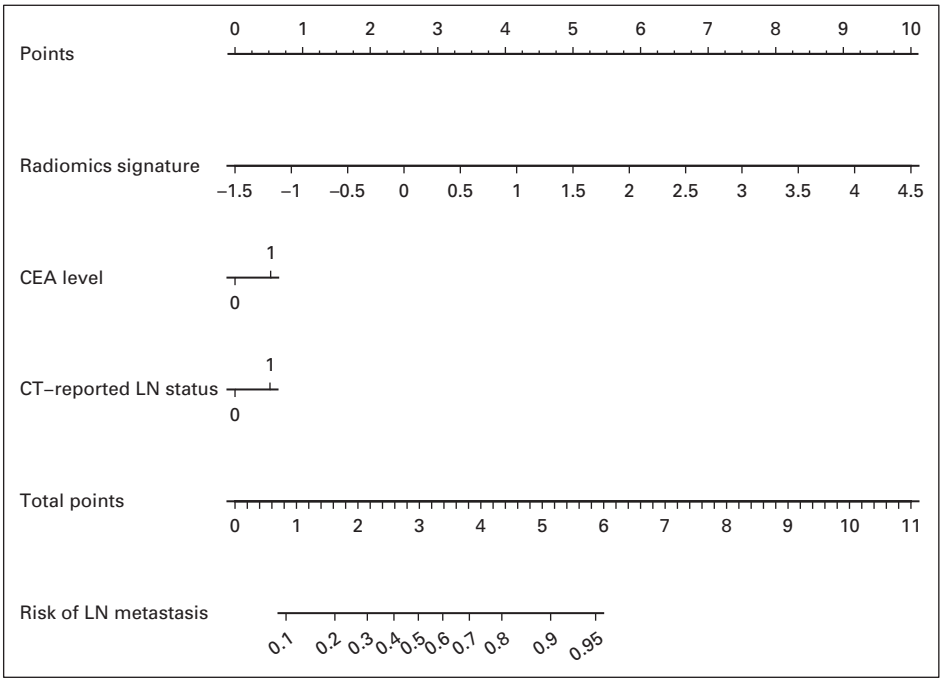

Fig 2. Developed radiomics nomogram. The radiomics nomogram was developed in the primary cohort, with the radiomics signature, carcinoembryonic antigen (CEA) level, and computed tomography (CT)–reported lymph node (LN) status incorporated.

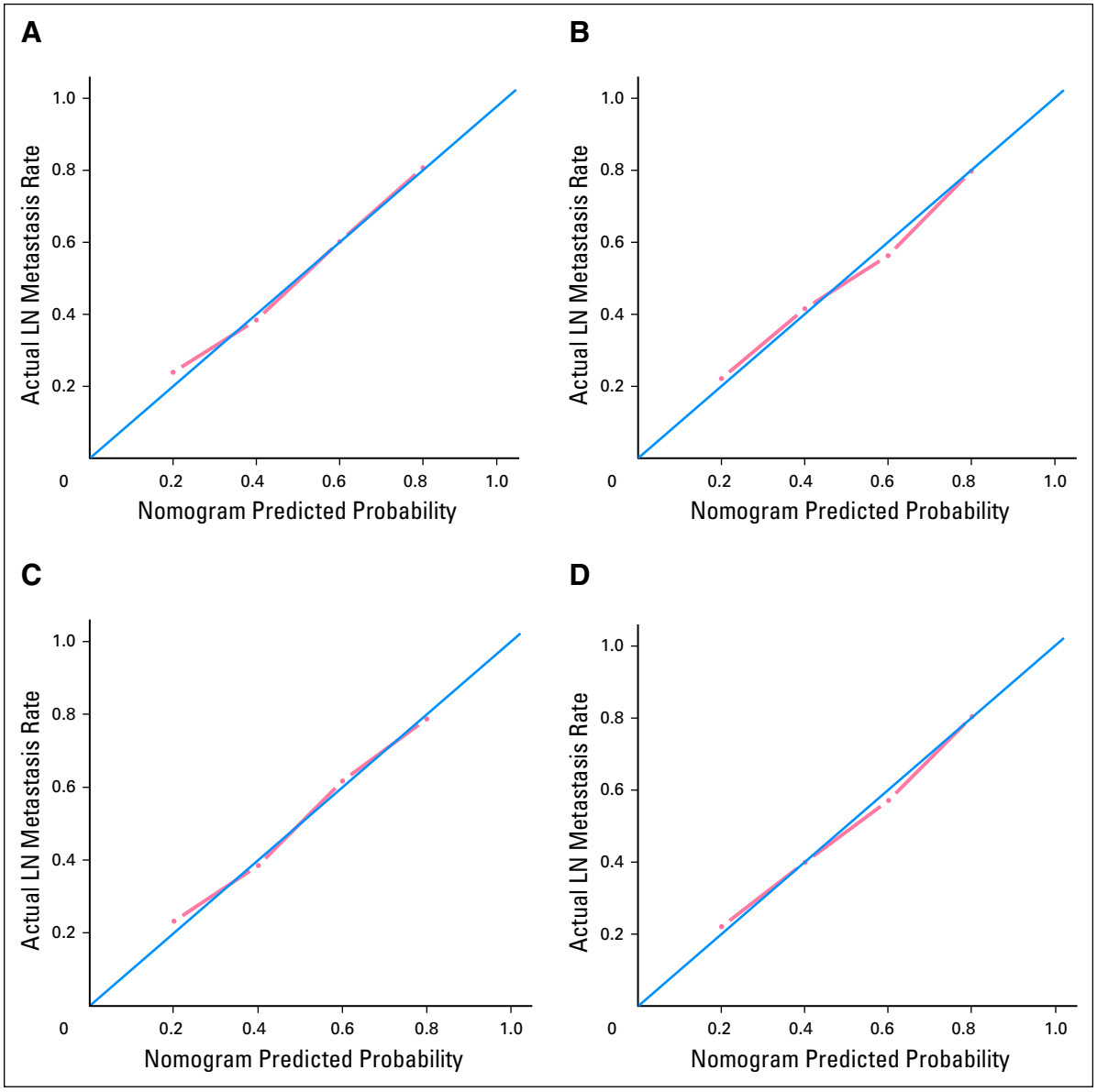

Fig 3. Calibration curves of the radiomics nomogram and the model with the addition of histologic grade prediction in each cohort. (A) Calibration curve of the radiomics nomogram in the primary cohort. (B) Calibration curve of the radiomics nomogram in the validation cohort. (C) Calibration curve of the model with addition of histologic grade in the primary cohort. (D) Calibration curve of the model with addition of histologic grade in the validation cohort. Calibration curves depict the calibration of each model in terms of the agreement between the predicted risks of lymph node (LN) metastasis and observed outcomes of LN metastasis. The *y*-axis represents the actual LN metastasis rate. The *x*-axis represents the predicted LN metastasis risk. The diagonal dotted line represents a perfect prediction by an ideal model. The pink solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction. The calibration curve was drawn by plotting $\hat{P}$ on the *x*-axis and $P_C = [1 + exp - (\gamma_0 + \gamma_1 L)]^{-1}$ on the *y*-axis, where P_C is the actual probability, L = logit ($\hat{P}$), $\hat{P}$ is the predicted probability, γ_0 is the corrected intercept, and γ_1 is the slope estimates.

cohort, omitting the process of adjusting intercept and regression coefficients regarding the signature building. In a recent study that investigated the diagnostic accuracy of using preoperative tumor marker CEA and serum inflammatory markers for LN metastasis in CRC, the derived accuracy of each single factor was $< 70\%$, which is lower than the C-index of the radiomics signature we constructed.[7] Thus, the noninvasive radiomics signature, which makes use of the images we already have for free, could serve as a more convenient biomarker for the prediction of LN metastasis.

Note that CEA level did not show enough predictive strength on the basis of univariable association with LN metastasis, which makes the exclusion of this variable a common strategy for model development; however, the rejection of important predictors may be a result of nuances in the data set or confounding by other predictors,[24,30] for which nonsignificant statistical association with LN metastasis does not definitively imply that CEA level is unimportant. In addition, existing studies have shown that CEA could serve as an important marker for prognosis in patients with CRC[34-36]; therefore, we kept CEA level as a candidate factor in the

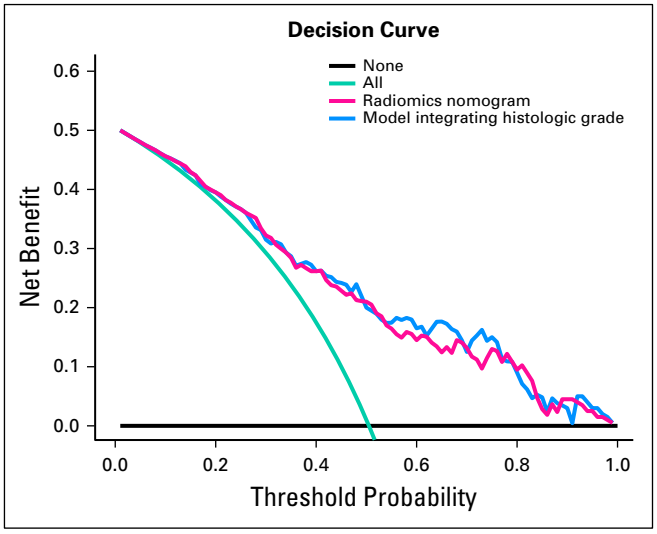

Fig 4. Decision curve analysis for the radiomics nomogram and the model with addition of histologic grade. The *y*-axis measures the net benefit. The pink line represents the radiomics nomogram. The blue line represents the model with addition of histologic grade. The green line represents the assumption that all patients have LN metastases. Thin black line represents the assumption that no patients have LN metastases. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion who are true positive, weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment.[29] Here, the relative harm was calculated by $(\frac{p_t}{1-p_t})$. "p_t" (threshold probability) is where the expected benefit of treatment is equal to the expected benefit of avoiding treatment; at which time a patient will opt for treatment informs us of how a patient weighs the relative harms of false-positive results and false-negative results ($[a - c]/[b - d] = [1 - p_t]/p_t$); $a - c$ is the harm from a false-negative result; $b - d$ is the harm from a false-positive result. a, b, c and d give, respectively, the value of true positive, false positive, false negative, and true negative.[29] The decision curve showed that if the threshold probability of a patient or doctor is $> 10\%$, using the radiomics nomogram in the current study to predict LN metastases adds more benefit than the treat-all-patients scheme or the treat-none scheme. For example, if the personal threshold probability of a patient is 60% (ie, the patient would opt for treatment if his probability of cancer was $> 60\%$), then the net benefit is 0.145 when using the radiomics nomogram to make the decision of whether to undergo treatment, with added benefit than the treat-all scheme or the treat-none scheme. The net benefit was comparable, with several overlaps, on the basis of the radiomics nomogram and the model that integrated histologic grade.

process of model development. As a qualitative radiomics feature, preoperative CT-reported LN status can be easily obtained. Our study showed that CT-reported LN status was associated with actual LN status and was identified as an independent risk factor for the prediction of LN status.

Histologic grade can be obtained through presurgery biopsy; it is of interest whether it is a independent risk factor for LN metastasis. Unexpectedly, on one hand, the addition of histologic grade to the prediction model along with other risk factors did not improve the reclassification performance (NRI, 0.014; $P = .44$; event NRI, −0.70; nonevent NRI, 0.72). On the other hand, the integration of histologic grade may introduce sampling bias compared with surgical tissue, and, hence, may be prone to high false-negative rate. Therefore, we recommended that the nomogram integrate radiomics signature, CEA level, and CT-reported LN status for LN status prediction, with satisfactory discrimination achieved (C-index, 0.736, in primary cohort, and C-index, 0.778, in validation cohort). Similarly, when Toiyama et al[7] added serum biomarker to the prediction model along with clinicopathologic risk factors for preoperative detection of LN metastasis in patients with CRC, they observed improved predictive accuracy (the generated area under curve increased to 0.801 [95% CI, 0.725 to 0.857] when the multivariable model modification was conducted). This finding may support the idea that taking into account markers that span different aspects is the most promising approach to change clinical management.[19] Although comparable results were presented, the study by Toiyama et al[7] suffered from the inherent limitation of the lack of independent validation, and the combined receiver operating characteristic (ROC) analyses used still have a long way to go to be incorporated into clinical practice for individualized risk prediction.[7] As an alternative, we presented and validated a radiomics nomogram in our study, which has the ability to generate an individual probability of LN metastases by integrating both the radiomics signature and determinant preoperative clinical variables that are easily available preoperatively. Both physicians and patients could perform a preoperative individualized prediction of the risk of LN metastasis with this easy-to-use scoring system, which is in line with the current trend toward personalized medicine.[37]

The most important and final argument for the use of the nomogram is based on the need to interpret individual need of additional treatment or care. However, the risk-prediction performance, discrimination and calibration, could not capture the clinical consequences of a particular level of discrimination or degree of miscalibration.[24,38,39] Therefore, to justify the clinical usefulness, we assessed whether the radiomics nomogram-assisted decisions would improve patient outcomes. With this aim, instead of the multi-institutional prospective validation of the nomogram that is largely impractical because of the heterogeneity in CT image acquisition and clinical data collection in different institutions, decision curve analysis was applied in this study. This novel method offers insight into clinical consequences on the basis of threshold probability, from which the net benefit could be derived. (Net benefit is defined as the proportion of true positives minus the proportion of false positives, weighted by the relative harm of false-positive and false-negative results.)[24,37] The decision curve showed that if the threshold probability of a patient or doctor is $> 10\%$, using the radiomics nomogram in the current study to predict LN metastases adds more benefit than either the treat-all-patients scheme or the treat-none scheme.

Study limitations include the fact that genomic characteristics were not considered currently. In recent years, to detect LN metastases, increased research with gene markers, such as AKR1C3 and calponin3, in patients with CRC has been proposed.[40] Recently, radiogenomics, which focuses on the relationship between imaging phenotypes and genomics, has emerged in the field of cancer research and attracted increasing interest; however, though it might be an interesting attempt, it is yet to be decided whether simply building a model that applies the imaging features to predict outcomes directly (radiomics) is preferable to radiogenomic analysis.[18]

In conclusion, this study presents a radiomics nomogram that incorporates both the radiomics signature and clinical risk

factors, and can be conveniently used to facilitate the preoperative individualized prediction of LN metastasis in patients with CRC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Yan-qi Huang, Chang-hong Liang, Lan He, Jie Tian, Zai-yi Liu
Collection and assembly of data: Yan-qi Huang, Chang-hong Liang, Lan He, Jie Tian, Cui-shan Liang, Zai-yi Liu
Data analysis and interpretation: Yan-qi Huang, Chang-hong Liang, Lan He, Jie Tian, Xin Chen, Ze-lan Ma, Zai-yi Liu
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer

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