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ORIGINAL RESEARCH

# Predictive Value of TRUS and CEUS Parameters for Lymph Node Metastasis in Rectal Cancer: A Retrospective Study

Shitao Su*, Xuanzhang Huang*, Xigui Li, Jun Meng, Jianyuan Huang

Department of Medical Ultrasound, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jianyuan Huang, Department of Medical Ultrasound, the First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning, Guangxi Zhuang Autonomous Region, 530001, People's Republic of China, Tel +86 771 5356899, Email huangjianyuan@sr.gxmu.edu.cn

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**Purpose:** To assess the predictive value of transrectal ultrasound (TRUS) combined with qualitative and quantitative parameters of contrast-enhanced ultrasound (CEUS) for lymph node metastasis (LNM) in rectal cancer (RC).

**Patients and Methods:** This retrospective study analyzed preoperative clinical data, qualitative and quantitative TRUS and CEUS parameters, and postoperative pathological data from 535 patients with RC confirmed by surgical pathology. Independent predictors of LNM were identified through univariate and multivariate binary logistic regression analysis. Two predictive models were developed: one based on TRUS/CEUS parameters, and another combining ultrasonographic parameters with clinical indicators. Model calibration was evaluated using the Hosmer-Lemeshow test, and diagnostic performance was quantified via receiver operating characteristic (ROC) curve analysis.

**Results:** Multivariate analysis revealed ultrasonographic tumor (uT) stage(OR=1.751,P=0.042), ultrasonographic nodal (uN) stage (OR=2.279,P<0.001), peak intensity ratio(PI-ratio: OR=0.799,P<0.001), and slope ratio (S-ratio: OR=0.997,P=0.008) as independent predictors of LNM. When incorporating clinical indicators, the combined model identified uN stage (OR=2.351,P<0.001), PI-ratio (OR=0.784,P<0.001), PI-difference (OR=0.997,P=0.011), S-ratio (OR=1.046,P=0.048), CEA (OR=2.324,P<0.001), and CA199 (OR=3.020,P=0.003) as significant predictors. The US model demonstrated an AUC of 0.792 (95% CI: 0.755–0.829), while the combined model achieved superior performance with an AUC of 0.815 (95% CI: 0.780–0.850) (Z=−2.076, P=0.038). Both models showed satisfactory calibration (Hosmer-Lemeshow test: P>0.05).

**Conclusion:** The predictive model constructed based on preoperative TRUS combined with CEUS quantitative parameters, along with its combined model incorporating clinical biomarkers (CEA, CA199), can effectively predict LNM in RC, providing a non-invasive and quantifiable preoperative assessment tool for clinical practice.

**Keywords:** rectal cancer, transrectal ultrasound, contrast-enhanced ultrasound, lymph node metastasis, logistic regression model

## Introduction

Colorectal cancer is one of the most prevalent malignant tumors worldwide. Global Cancer Statistics reported 1,926,118 new cases and 903,859 deaths from colorectal cancer in 2022.[1] Rectal cancer (RC) accounts for approximately one-third of all colorectal cancers.[2] Both the incidence and mortality rates of colorectal cancer are rising in China.[3,4] Lymph node metastasis (LNM) is the primary pathway for RC metastasis. For early RC without lymph node involvement, transanal endoscopic local resection is a viable option, whereas the presence of lymph node metastasis around the rectum indicates the need for preoperative neoadjuvant therapy.[5] Thus, accurate preoperative assessment of LNM status in RC is crucial for determining appropriate treatment strategies. LNM is also an independent predictor of postoperative local recurrence, distant metastasis, and overall survival in RC patients, making it vital for prognosis prediction.[6] However, the status of

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lymph node metastasis can only be confirmed through surgical pathology. If LNM information could be accurately obtained preoperatively, it would significantly impact clinical treatment decisions and prognosis assessment for RC.

Transrectal ultrasound (TRUS) is one of the most commonly used imaging techniques for the preoperative evaluation of RC. TRUS can clearly display the size, morphology, depth of tumor infiltration, and lymph node involvement around the tumor. However, TRUS assessment of lymph node metastasis has shown poor agreement with the pathological diagnosis of lymph node metastasis (k=−0.164).[7] Contrast-enhanced ultrasound (CEUS) is a novel ultrasound technology that enhances images by injecting microbubbles containing gases into blood vessels, tissues, or body cavities, making normal tissues or lesions more distinct. CEUS can detect low-velocity microfluidic signals, which can be analyzed through time-intensity curve (TIC) analysis to provide quantitative information on tumor angiogenesis.[8] Studies have indicated that CEUS qualitative features and quantitative parameters are associated with LNM in various malignant tumors, such as breast, liver, and thyroid cancers.[9–13] Current evidence regarding the association between CEUS quantitative parameters and LNM in RC remains inconsistent. Studies have identified correlations of parameters such as peak intensity (PI), time-to-peak (TTP), and area under the curve (AUC) with nodal staging (N-stage),[14–16] while others report no significant associations between TIC parameters and TNM staging.[17] These discrepancies may stem from methodological heterogeneity, including variations in parameter selection and region-of-interest definitions. Notably, few studies have systematically integrated CEUS-derived perfusion metrics with TRUS parameters for preoperative prediction of LNM in RC. Consequently, the combined use of multimodal ultrasound parameters in RC prediction remains underexplored and warrants further investigation.

Moreover, existing predictive models for LNM face critical limitations. For instance, the lack of standardized parameter definitions across studies compromises their generalizability in multi-institutional settings. Furthermore, most models are validated only in single-center cohorts, with insufficient external validation to ensure robustness in diverse populations.[18] This study aims to investigate the correlation between TRUS parameters combined with CEUS qualitative features and quantitative parameters and LNM in rectal cancer, to construct a logistic regression prediction model, and to explore the potential value of TRUS combined with CEUS parameters in the preoperative prediction of LNM in rectal cancer.

# Materials and Methods

## Study Population

A retrospective analysis was conducted on 535 patients diagnosed with RC by surgical pathology between January 2019 and September 2023 at the First Affiliated Hospital of Guangxi Medical University.

The inclusion criteria were as follows: (1) Primary rectal adenocarcinoma confirmed by surgical pathology; (2) TRUS and CEUS performed within 2 weeks before surgery; (3) No preoperative neoadjuvant radiochemotherapy; (4) Age greater than 18 years; (5) Complete clinical, laboratory, and pathology information. The exclusion criteria were as follows: (1)Poor-quality ultrasound images or inadequate CEUS dynamic video storage; (2) Mucinous adenocarcinoma, signet ring cell carcinoma, etc; (3) Comorbidities with other malignant tumors; (4) Allergy to ultrasound contrast agents; (5) Anal stenosis. The study was approved by the Ethics Committee of the hospital.

## TRUS Examination and Observed Indicators

All TRUS and CEUS examinations were performed using an Aplio 500 scanner (Canon Medical Systems, Inc., Tokyo, Japan) equipped with a transrectal end sweep intraluminal probe operating at 5–10 MHz. The ultrasound evaluations were conducted by a sonographer with 9 years of experience in TRUS and 5 years in CEUS.

### Procedure

1. Patients were given an oral laxative or a cleansing enema to clear the bowel before the TRUS examination.
2. Patients were placed in the left lateral position with legs flexed as close to the anterior abdominal wall as possible.
3. A medical ultrasound coupling agent (100–150 mL) was slowly pushed into the rectum to evacuate the local intestinal lumen of gas and to establish an acoustic window.

4. The probe was uniformly coated with a medical ultrasound coupling agent, covered with two layers of medical probe isolation sleeves, and inserted into the bowel as the patient took a deep breath to relax and cooperate with the examination.

### TRUS Evaluations

- Distance from the lower edge of the tumor to the anal verge.
- Long and short diameters of the tumor.
- Depth of tumor infiltration (ultrasonographic tumor (uT) stage).
- The lymph nodes around the rectum (ultrasonographic nodal (uN) stage) (Figure 1).
- Peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index (RI) of the tumor trunk trophoblastic vessels, each measured and averaged three times.

## CEUS Examination, CEUS Qualitative Features, and TIC Analysis

Following the TRUS examination, the largest section of the tumor was selected for the CEUS examination. The contrast agent used was SonoVue™ (Bracco SpA, Milan, Italy), a lipid-coated microbubble contrast agent. It was prepared by mixing 5 mL of 0.9% saline with 2.4 mL of SonoVue™. The contrast agent was injected via an elbow vein over 2 seconds, followed by 5 mL of 0.9% saline. The ultrasonographic performance of the RC lesion was observed dynamically in real-time, and 60 seconds of dynamic CEUS images were stored on the internal hard disk drive of the Aplio 500.

To ensure objectivity, dynamic CEUS image analysis was performed independently by another experienced sonographer who was blinded to the patient's clinical and pathological information. The qualitative features of CEUS included:

- Entry modes for contrast agents (earlier than, synchronized with, or later than the peripheral bowel wall)
- Exit modes for contrast agents (earlier than, synchronized with, or later than the peripheral bowel wall)
- Enhancement intensity (hyper-enhancement, iso-enhancement, or hypo-enhancement)
- Enhancement homogeneity (homogeneous enhancement or heterogeneous enhancement) (Figure 2).

TIC analysis was performed using the quantitative analysis software provided with the Aplio 500 instrument. A circular region of interest (ROI) with a diameter of 5 mm was manually placed in the maximum and minimum enhancement regions in the CEUS peak-phase images, labeled as ROI-max and ROI-min, respectively. Time-intensity curves (TICs) were generated after setting the ROIs.[19]

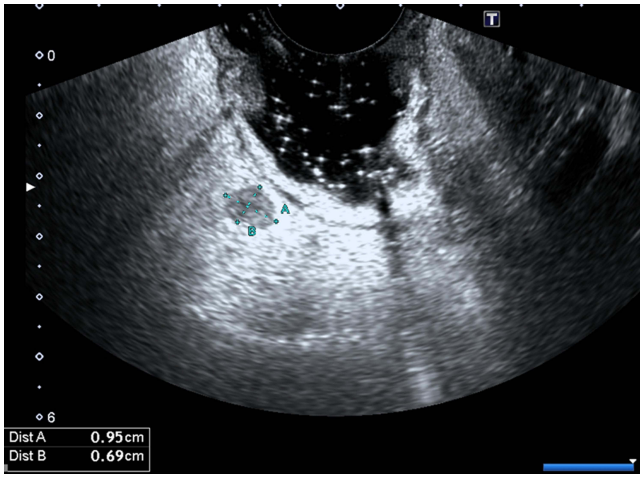


**Figure 1** TRUS showed abnormal lymph nodes(size:9.5mm×6.9mm).


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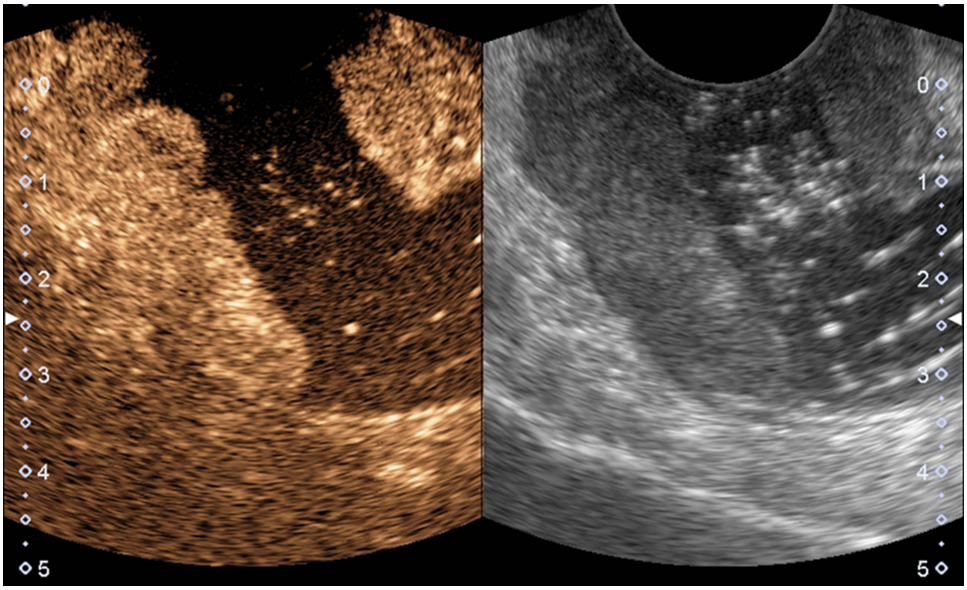

**Figure 2** The CEUS image at the peak phase shows a hyper-enhanced lesion with heterogeneity enhancement. Left: CEUS. Right: Gray-scale US image.

Absolute quantitative parameters were obtained, including peak intensity (PI), time to peak (TTP), mean transit time (MTT), and slope (S) (Figure 3). Each ROI-max and ROI-min was measured three times, and the average of the three quantitative parameters was taken. Relative quantitative parameters were calculated, including the difference and ratio of PI, TTP, MTT, and S. The difference was calculated as the quantitative parameter value obtained by ROI-max minus the quantitative parameter value obtained by ROI-min, eg, PI-difference = PImax - PImin; the ratio was calculated as the quantitative parameter value obtained by ROI-max divided by the quantitative parameter value obtained by ROI-min, eg, PI-ratio = PImax / PImin. Calculating the relative parameters aims to minimize potential confounding factors, such as heterogeneity of rectal lesions and differences in contrast injection rates.

To evaluate inter-observer reproducibility, dynamic CEUS images from 100 randomly selected patients were reanalyzed by a second sonographer with 5 years of CEUS experience after a 1-week interval, following the same TIC analysis protocol.

## Clinical-Pathologic Data Collection

Clinical-pathologic data were collected, including age, gender, preoperative carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), and postoperative pathological lymph node metastasis status.

## Sample Size

This study employed the events per variable (EPV) method to determine the sample size, ensuring sufficient statistical power for the development of the prediction model. Based on the principle that multivariable logistic regression requires at least 10–15 positive events per variable, and considering the anticipated inclusion of 5–6 predictors in the model, a minimum of 50–90 positive outcome events (ie, lymph node metastasis-positive events) was required to ensure model stability.

## Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R software package (version 4.5.0). Normally distributed measures were expressed as mean ± standard deviation (X ± SD), and an independent samples *t*-test was used for comparison between two groups. Non-normally distributed measures were expressed as median (interquartile range) [M(IQR)], and Mann–Whitney *U*-test was used for comparison between two groups. Comparisons of rates or component ratios between two groups were performed using the $\chi 2$ test. Variables that were statistically different between the two groups were included in multivariate binary logistic regression analysis to identify independent predictors of LNM in RC.

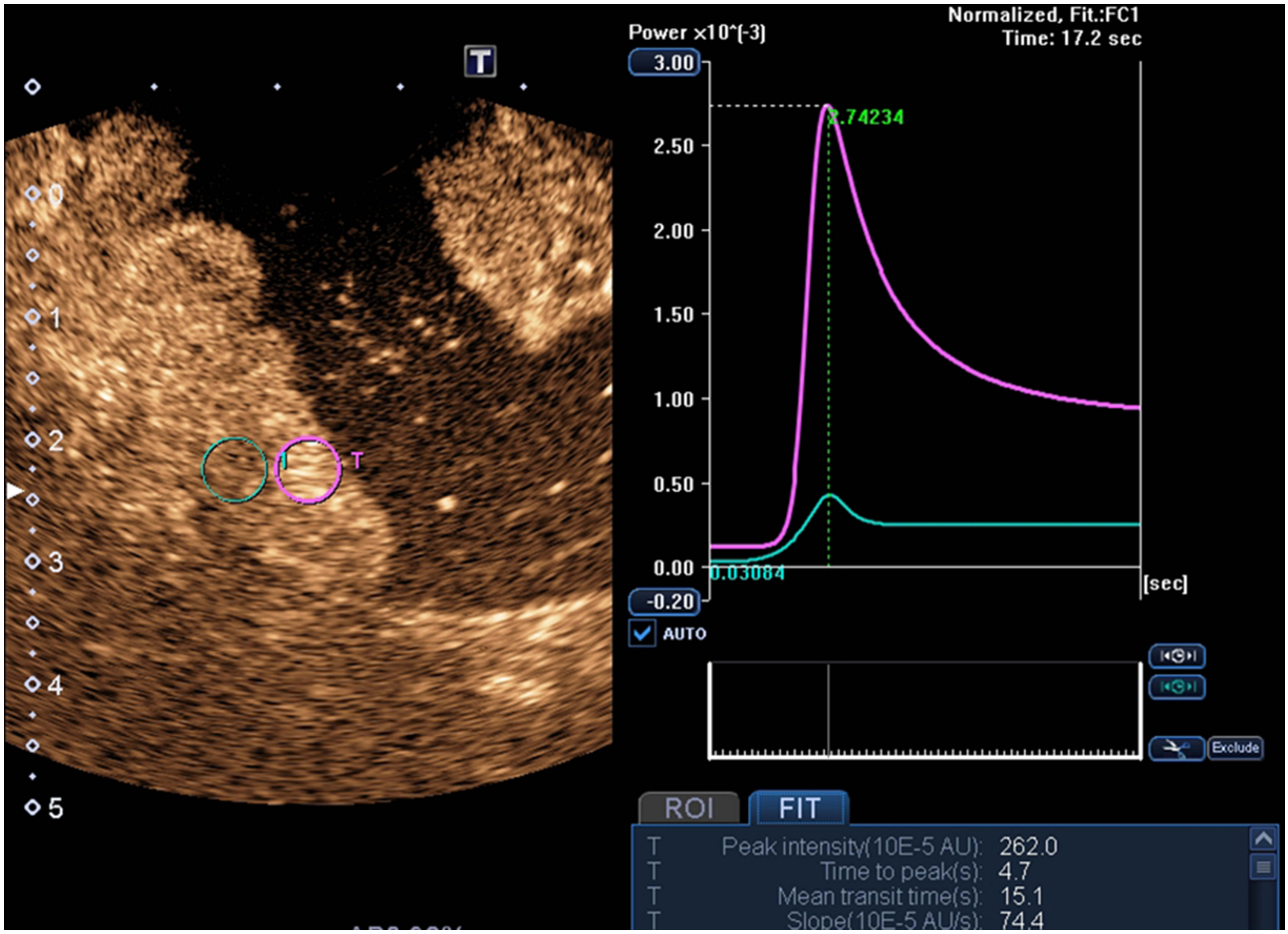


**Figure 3** CEUS region of interest (ROI) and time-intensity curves (TICs).

A logistic regression prediction model was developed with LNM as the dependent variable and independent predictors as independent variables. The Hosmer-Lemeshow test was used to test the model fit. The model was subjected to internal validation using the 10-fold cross-validation method. Receiver operating characteristic(ROC) curves were plotted to assess the predictive performance of the prediction model for LNM, and the DeLong test was used to compare the differences between the prediction models. Intra-class correlation coefficients (ICCs) were used to assess reproducibility, with ICC $\geq$ 0.75 indicating excellent agreement. A two-tailed P-value less than 0.05 was considered statistically significant.

# Results

## Univariate Analysis of Clinical and Ultrasonic Parameters to Predict LNM in RC

Among the 535 patients with RC, 319 were male and 216 were female, with ages ranging from 24 to 90 years and a mean age of 60.4±11.4 years. There were 236 cases in the LNM+ group and 299 cases in the LNM- group. The univariate analysis results showed that CEA, CA199, TRUS parameters (tumor location, uT stage, uN stage), CEUS qualitative features (entry modes for contrast agents, exit modes for contrast agents, enhancement intensity), and CEUS quantitative parameters (difference and ratio of PI, S) were statistically different between the LNM- and LNM+ groups (P< 0.05)(Table 1).

## Multivariate Logistic Regression Analysis

Ultrasonic parameters and clinical indicators with statistically significant differences between the two groups were included in a multivariate binary logistic regression analysis to identify independent predictors of LNM. The variable assignments are described in Table 2.


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**Table 1** Comparison of Clinical and Ultrasonic Parameters Between LNM- Group and LNM+ Group, n(%)/M(IQR)

| Variables | LNM- | LNM+ | $Z/\chi^2$ | *P* |
|---|---|---|---|---|
| Gender | | | | |
| Male | 182(57.1) | 137(42.9) | 0.435 | 0.509 |
| Female | 117(54.2) | 99(45.8) | | |
| Age (years) | | | | |
| <65 | 180(55.6) | 144 (44.4) | 0.037 | 0.848 |
| ≥65 | 119(56.4) | 92(43.6) | | |
| CEA(ng/mL) | | | | |
| 0~5 | 218(66.1) | 112(33.9) | 36.151 | <0.001* |
| >5 | 81(40.2) | 124(60.5) | | |
| CA199(U/mL) | | | | |
| 0~37 | 284(59.9) | 190(40.1) | 27.356 | <0.001* |
| >37 | 15(24.6) | 46(75.4) | | |
| Tumor location | | | | |
| Upper | 88(47.8) | 96(52.2) | 7.393 | 0.007* |
| Mid-lower | 211(60.1) | 140 (39.9) | | |
| uT stage | | | | |
| uT1-2 | 73(71.6) | 29(28.4) | 12.570 | <0.001* |
| uT3-4 | 226(52.2) | 207(47.8) | | |
| uN stage | | | | |
| uN0 | 197(61.9) | 121 (38.1) | 11.686 | 0.001* |
| uN1-2 | 102(47.0) | 115(53.0) | | |
| Length (cm) | 3.90(1.80) | 3.80(1.68) | −0.189 | 0.850 |
| Thickness (cm) | 1.30(0.60) | 1.30(0.58) | −1.871 | 0.061 |
| PSV(cm/s) | 18.90(12.20) | 17.50(10.15) | −1.700 | 0.089 |
| EDV(cm/s) | 6.00(4.90) | 6.00(4.88) | −0.582 | 0.560 |
| RI | 0.62(0.16) | 0.63(0.15) | −0.081 | 0.936 |
| Entry modes for contrast agents(comparison with peripheral bowel wall) | | | | |
| Synchronized with, or later | 60(43.2) | 79(56.8) | 12.329 | <0.001* |
| Earlier | 239(60.4) | 157(39.6) | | |
| Exit modes for contrast agents(comparison with peripheral bowel wall) | | | | |
| Synchronized with, or later | 76(45.2) | 92(54.8) | 11.267 | 0.001* |
| Earlier | 223(60.8) | 144(39.2) | | |
| Enhancement intensity | | | | |
| Iso-/hypo | 52(36.6) | 90(63.4) | 29.111 | <0.001* |
| Hyper | 247(62.8) | 146(37.2) | | |
| Enhancement homogeneity | | | | |
| Heterogeneous | 52(48.6) | 55(51.4) | 2.883 | 0.090 |
| Homogeneous | 247(57.7) | 181(42.3) | | |
| PI-ratio | 5.18(5.96) | 3.31(2.42) | −8.676 | <0.001* |
| PI-difference(10E-5 AU) | 220.10(439.30) | 81.90(126.75) | −9.810 | <0.001* |
| TTP-ratio | 0.96(0.35) | 0.95(0.38) | −0.377 | 0.706 |
| TTP-difference(s) | −0.30(2.20) | −0.30(2.68) | −0.366 | 0.715 |
| MTT-ratio | 0.74(0.61) | 0.78(0.60) | −1.431 | 0.153 |
| MTT-difference(s) | −3.00(14.20) | −2.85(13.38) | −1.198 | 0.231 |
| S-ratio | 5.29(6.74) | 3.11 (3.58) | −7.417 | <0.001* |
| S-difference (10E-5 AU/s) | 42.00(103.50) | 16.35(26.32) | −8.604 | <0.001* |

**Notes**: *Statistically significant difference.

Multivariate logistic regression analysis of TRUS and CEUS parameters for predicting LNM showed that uT stage (OR=1.751, P=0.042), uN stage (OR=2.279, P<0.001), PI-ratio (OR=0.799, P<0.001), and S-ratio (OR=0.997, P=0.008) were independent predictors of LNM in RC.

**Table 2** Assign Values to Variables

| Variables | Parameters | Variable Description |
|---|---|---|
| X1 | Tumor location | 0=Upper,1=Mid-lower |
| X2 | uT stage | 0=uT1-2,1=uT3-4 |
| X3 | uN stage | 0=uN0,1=uN1-2 |
| X4 | Entry modes for contrast agents | 0=Synchronized with, or later than the peripheral bowel wall, 1=Earlier than the peripheral bowel wall |
| X5 | Exit modes for contrast agents | 0=Synchronized with, or later than the peripheral bowel wall, 1=Earlier than the peripheral bowel wall |
| X6 | Enhancement intensity | 0=Iso-/hypo-enhancement,1=Hyper- enhancement |
| X7 | PI-ratio | Continuous variable |
| X8 | PI-difference(10E-5 AU) | Continuous variable |
| X9 | S-ratio | Continuous variable |
| X10 | S-difference(10E-5 AU/s) | Continuous variable |
| X11 | CEA(ng/mL) | 0=0~5,1=>5 |
| X12 | CA199(U/mL) | 0=0~37,1=>37 |

Multivariate logistic regression analysis of TRUS+CEUS parameters +clinical indicators for predicting LNM showed that uN stage (OR=2.351, P<0.001), PI-ratio (OR=0.784, P<0.001), PI-difference (OR=0.997, P=0.011), S-ratio (OR=1.046, P=0.048), CEA (OR=2.324, P<0.001) and CA199 (OR=3.020, P=0.003) were independent predictors of LNM in RC(Table 3).

## Logistic Regression Model for Predicting LNM in RC

### US Model (Based on TRUS and CEUS Parameters)

Y=0.588+0.560×X2+0.824×X3-0.224×X7-0.003×X8(Y=Logit [P], P LNM rate,X2 uT stage; X3 uN stage; X7 PI-ratio; X8 PI-difference). Hosmer–Lemeshow goodness of fit test showed $\chi 2$=3.850, P=0.870(P>0.05), indicating that the fitting effect of the model was good.

### Combined Model (Based on TRUS,CEUS Parameters, and Clinical Indicators)

Y=0.340+0.855×X3-0.243×X7-0.003×X8+0.045×X9+0.843×X11+1.105×X12 (Y=Logit [P], P LNM rate, X3 uN stage; X7 PI-ratio, X8 PI-difference, X9 S-ratio, X11 CEA, X12 CA199).Hosmer–Lemeshow goodness of fit test showed $\chi 2$=13.646, P=0.091 (P>0.05), indicating that the fitting effect of the model was good.

**Table 3** Multivariate Logistic Regression Analysis of TRUS+CEUS Parameters and TRUS+CEUS Parameters+clinical Indicators for Predicting LNM

| Method | Variate | B | SE | *P* | OR (95% CI) |
|---|---|---|---|---|---|
| TRUS+CEUS parameters | X2 | 0.560 | 0.276 | 0.042 | 1.751 (1.020~3.004) |
| | X3 | 0.824 | 0.215 | <0.001 | 2.279 (1.496~3.471) |
| | X7 | −0.224 | 0.057 | <0.001 | 0.799(0.715~0.893) |
| | X8 | −0.003 | 0.001 | 0.008 | 0.997(0.995~0.999) |
| | Constant | 0.588 | 0.354 | 0.097 | 1.801 |
| TRUS+CEUS parameters +clinical indicators | X3 | 0.855 | 0.223 | <0.001 | 2.351(1.518~3.640) |
| | X7 | −0.243 | 0.058 | <0.001 | 0.784(0.700~0.879) |
| | X8 | −0.003 | 0.001 | 0.011 | 0.997(0.995~0.999) |
| | X9 | 0.045 | 0.023 | 0.048 | 1.046(1.000~1.094) |
| | X11 | 0.843 | 0.222 | <0.001 | 2.324(1.503~3.592) |
| | X12 | 1.105 | 0.371 | 0.003 | 3.020(1.461~6.244) |
| | Constant | 0.340 | 0.366 | 0.353 | 1.405 |

**Abbreviations**: B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

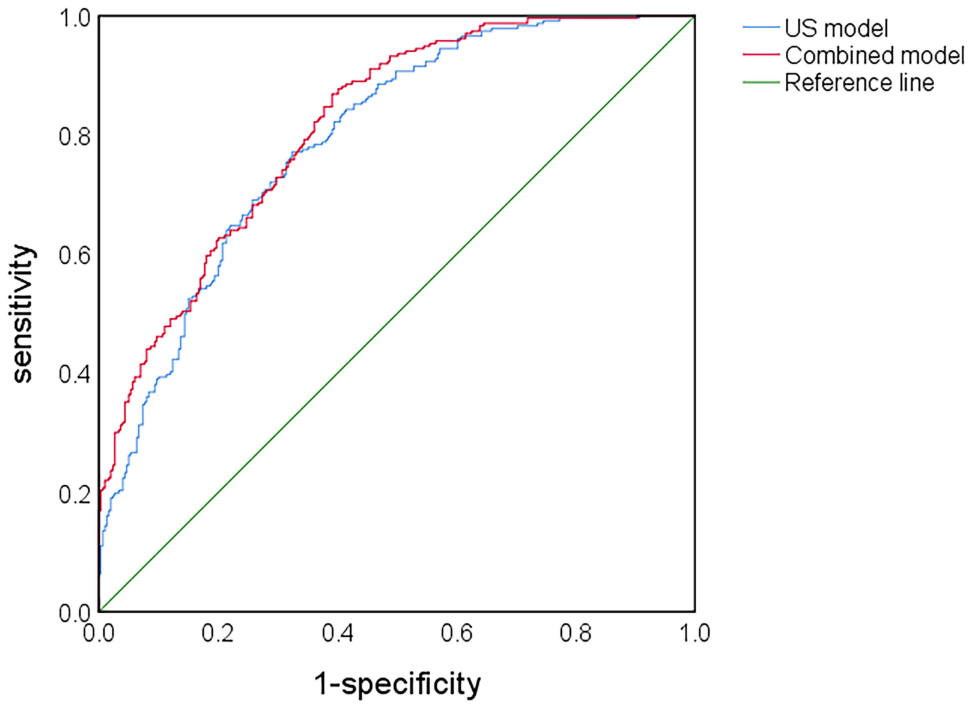


**Figure 4** ROCs of predictive models.

## The Predictive Efficacy of the Models

The AUCs of the US model and Combined model for predicting LNM in RC were 0.792 (95% CI 0.755–0.829) and 0.815 (95% CI 0.780–0.850), with a sensitivity of 77.1% and 86.9%, and a specificity of 67.6% and 60.9%, respectively. The difference in AUC between the two models was statistically significant (Z=−2.076, P=0.038) (Figure 4). The results of the internal validation showed that the AUC of the US model was 0.807 and the AUC of the combined model was 0.830. DeLong's test indicated that the AUC of the combined model was higher than that of the US model (Z = −2.254, P = 0.024).

## Inter-Observer Reproducibility of TIC Parameters

The ICC values for PI-max, TTP-max, MTT-max, S-max, PI-min, TTP-min, MTT-min, S-min, PI-difference, TTP-difference, MTT-difference, S-difference, PI-ratio, TTP-ratio, MTT-ratio, and S-ratio were 0.970, 0.931, 0.973, 0.945, 0.994, 0.964, 0.878, 0.964, 0.965, 0.885, 0.870, 0.941, 0.774, 0.762, 0.825, and 0.924, respectively.

# Discussion

Predicting lymph node metastatic status in RC patients remains a challenge in preoperative diagnosis. A meta-analysis by Gao et al reported that the predictive sensitivities of MRI, TRUS, and CT for lymph node metastasis of RC were 0.69, 0.57, and 0.63, respectively. MRI showed higher predictive sensitivity than TRUS and CT, but all three modalities had relatively low sensitivity for predicting lymph node metastasis.[20] Another study indicated that MRI, EUS, and CT had similar accuracy in evaluating RC lymph node metastasis, but none could reliably predict it.[21] Currently, there is no standard for ultrasound evaluation of lymph node metastasis. Yan et al considered round, hypoechoic lymph nodes with a diameter >5 mm as metastatic lymph nodes, but this method showed limited efficacy, with an accuracy of 79% and sensitivity of 67% compared with postoperative pathology.[22] Huang et al reported an accuracy of 65.87%(83/126) for TRUS in diagnosing RC lymph node metastasis.[23] In this study, the accuracy of TRUS was lower at 58.3%(312/535) compared with postoperative pathology. TRUS parameters (tumor location, uT stage, uN stage) showed statistically significant differences between LNM+ and LNM- groups, and multivariate logistic regression analysis indicated that TRUS parameters (uT stage, uN stage) were independent predictors of lymph node metastasis in RC. Therefore, routine TRUS uT and uN stages remain important in the preoperative diagnosis of rectal cancer LNM.

We also analyzed the correlation of CEUS qualitative features and quantitative parameters with LNM in RC. Differences in CEUS qualitative features (entry modes for contrast agents, exit modes for contrast agents, enhancement intensity) and CEUS quantitative parameters (ratio and difference of PI and S) were statistically significant between LNM- and LNM+ groups. Multivariate logistic regression analysis revealed that CEUS quantitative parameters (PI-ratio, PI-difference) were independent predictors of LNM in RC. Huang et al observed similar findings with PI-ratio, AREA-ratio, and MTT-difference as the main quantitative ultrasound parameters for predicting LNM.[19] Su et al identified PI-ratio and S-ratio as independent predictive factors for the pN stage of RC.[16] Similar results were seen in a study on CEUS quantitative parameters of axillary lymph nodes in breast cancer, where the PI-ratio differentiated between metastatic and non-metastatic lymph nodes.[24] Thus, the CEUS quantitative parameters have significant value in predicting LNM in RC.

The AUC values for the logistic regression models (US model and Combined model) constructed in this study were 0.792 and 0.815, respectively, indicating high predictive efficacy. The Combined model, which includes TRUS, CEUS parameters, and clinical indicators, had a relatively higher AUC. Both models may provide valuable clinical tools for predicting LNM status preoperatively in RC patients. The integration of CEUS quantitative parameters with TRUS parameters (uN staging, uT staging) significantly reduces the subjective variability inherent in traditional imaging assessments. The combined model, which merges clinical indicators (CEA, CA199) with ultrasound parameters, maintains predictive accuracy while leveraging routine laboratory and imaging data. This approach minimizes the need for additional costly testing, making it particularly suitable for resource-limited healthcare environments. By providing a non-invasive preoperative prediction of LNM risk, the model assists clinicians in tailoring surgical plans (eg, extent of lymph node dissection) and neoadjuvant therapy strategies, thereby avoiding overtreatment or under-treatment and improving patient prognosis.

Huang et al constructed various machine learning models for predicting rectal cancer LNM based on preoperative TRUS and CEUS parameters, and the AUC of the machine learning models was 0.517–0.941, among which the LightGBM model achieved the highest AUC (AUC=0.941).[19] Another study developed machine learning models based on preoperative three-dimensional TRUS and clinical data, with the XGBoost model showing the best performance (AUC=0.82).[23] Yan et al created a logistic regression model with a high predictive efficacy (AUC=0.95) based on preoperative TRUS and strain ratio.[22] However, these models were based on single-center retrospective studies without external validation, and there is no standardized predictive model available.

Recent advancements in radiomics have shown potential for predicting lymph node metastasis in RC with high diagnostic efficacy. Niu et al found that MRI radiomics outperformed CT radiomics, and a multimodal radiomics model combining clinical, MRI, and CT data had the best performance (AUC=0.947).[25] Therefore, combining multiple imaging techniques might provide a more reliable prediction of lymph node metastatic status in RC. However, the limitations of radiomics include poor reproducibility and lack of uniform standards, making it unable to replace pathology. Future research should focus on prospective multicenter studies, expanding sample sizes, and developing more comprehensive prediction models to enhance the preoperative diagnosis and individualized treatment of RC patients.

The following critical limitations must be considered when interpreting the findings of this study: (1) Potential selection bias exists due to its retrospective, single-center design focusing exclusively on rectal adenocarcinoma while excluding specific histological subtypes (eg, mucinous/signet-ring cell carcinomas). (2) While standardized ROI placement and averaged multiple measurements were implemented, TIC parameter results remain susceptible to ROI positioning variability. Future studies could employ whole-lesion analysis or AI-driven automated ROI selection. (3) Technical constraints of transrectal end sweep intraluminal probes suggest biplane endoluminal ultrasound as a potential improvement. (4) The exclusive use of logistic regression models warrants the exploration of radiomics and machine learning approaches for predicting LNM in RC using ultrasound imaging. (5) The generalizability of the predictive model remains to be validated in external independent cohorts. Future multicenter prospective studies are warranted to further confirm its clinical applicability.

## Conclusion

The predictive model developed using preoperative TRUS and CEUS quantitative parameters, as well as the integrated model incorporating clinical biomarkers (CEA, CA199), effectively predicts lymph node metastasis in rectal cancer,

offering a non-invasive and quantifiable preoperative assessment tool for clinical use. Future efforts should prioritize external validation using multi-center datasets, expansion of sample sizes, and integration of multimodal imaging predictors to enhance the accuracy and reliability of predictive models. Concurrently, prospective validation studies are essential to advance their translation into routine clinical workflows.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (No 2024-E502-01). Informed consent was waived by the First Affiliated Hospital of Guangxi Medical University in view of the retrospective nature of the study. In this study, we respect and protect the rights and privacy of participants and ensure the confidentiality of their personal information.

## Consent for Publication

Ultrasound images can be published.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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