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Nomogram prediction model for lymph node metastasis after neoadjuvant chemoradiotherapy in rectal cancer

CAO Chenliang*, WANG Ling, SHI Haihua

**Department of Gastrointestinal Surgery, Suzhou Municipal Hospital, the Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou, Jiangsu 215000, China*

Corresponding author: SHI Haihua, E-mail:doctorhaihua0309@163.com

Abstract: Objective To construct a nomogram prediction model for predicting lymph node metastasis in stage Ⅱ-Ⅲ rectal cancer patients after receiving neoadjuvant chemoradiotherapy (nCRT) based on LASSO regression, and to evaluate its efficacy. M**ethods** The clinical data of 150 patients admitted to Suzhou Municipal Hospital from September 2010 to December 2024 were included in this study. All patients received nRCT combined with total mesorectal excision. Data processing was conducted using R4. 3. 3 and SPSS 23. 0 software. Initially, the LASSO regression method was employed to screen for key variables, followed by a multivariate logistic regression analysis to identify risk factors for lymph node metastasis after nCRT. A nomogram prediction model was then constructed, and its performance was comprehensively evaluated using methods such as the receiver operating characteristic (ROC) curve. **Results** Four potential predictors were identified as independent risk factors, including age (*OR*=2. 949, 95%*CI* : 1.050-8. 284), body mass index (BMI) (*OR*=6.808, 95%*CI* : 2.772-16.724), post-neoadjuvant carcinoembryonic antigen (CEA) (*OR*=2.376, 95%*CI* : 1.020-4.586), and yield pathologic T (ypT) stage (*OR*=5.783, 95%*CI*:1.894-17.655) (*P*<0.05). The ROC curve area under the curve (AUC) predicted by this model for lymph node metastasis in rectal cancer patients was 0.843(95%*CI* : 0.776-0.911). **Conclusion** After nCRT, patients who were younger, had a higher BMI, had a CEA level >5 μg/L, and had deeper tumor infiltration should be vigilant for the risk of lymph node metastasis. The nomogram prediction model established based on these factors not only has high prediction accuracy but also possesses strong clinical application potential.

Keywords: Rectal cancer; Neoadjuvant chemoradiotherapy; Total mesorectal excision; LASSO regression; Lymph node metastasis; Nomogram

Neoadjuvant chemoradiotherapy (nCRT) combined with total mesorectal excision (TME) is the standard treatment for stage II-III low-lying rectal cancer [1]. Compared to direct surgery, TME after nCRT can result in lower local recurrence rates and higher anal sphincter preservation rates. However, postoperative complications such as anastomotic leakage, stenosis, sexual dysfunction, ureteral injury, and anterior resection syndrome occur in 10%-40% of cases, and some patients may also face the risk of temporary colostomy non-reversal [2-5]. Considering the incidence of early and late complications of TME and the favorable prognosis of patients who achieve complete or significant pathological remission after nCRT, performing radical surgery with TME for these cases might result in overtreatment. Therefore, some researchers have proposed strategies of observation and local excision [6-7]. Related studies show that for patients whose tumors significantly respond to nCRT, performing local excision with rectal preservation or adopting a wait-and-see strategy for patients who achieve clinical complete remission yields similar survival outcomes to those who undergo TME, while avoiding the potential postoperative complications associated with TME [8-12]. However, neither local excision nor the wait-and-see strategy involves lymph node dissection, and lymph node staging remains a critical factor influencing patient prognosis. Research indicates that in patients who have received nCRT, metastatic lymph nodes in these two non-radical treatment options become the main cause of later recurrence and metastasis [13]. Therefore, assessing lymph node metastasis after nCRT is of significant importance. This study collected clinical and pathological data from patients diagnosed with rectal cancer at Suzhou Municipal Hospital who underwent nCRT combined with TME, analyzed the risk factors for lymph node metastasis after nCRT, and developed a nomogram prediction model for lymph node metastasis risk based on the least absolute shrinkage and selection operator (LASSO) regression, evaluating its effectiveness.

1 Objects and Methods

1.1 Study Objects

Clinical data of 150 rectal cancer patients hospitalized at Suzhou Municipal Hospital between September 2010 and December 2024 were retrospectively analyzed. All

patients underwent nCRT combined with TME.

Inclusion criteria:

(1) Pathological confirmation of rectal adenocarcinoma by colonoscopic biopsy before nCRT;
(2) Pre-nCRT TNM stage II–III mid-low rectal cancer;
(3) No distant metastasis detected by enhanced CT of the chest, abdomen, and pelvis;
(4) Completion of both nCRT and TME surgery.

Exclusion criteria:

(1) Distant metastasis before nCRT or during nCRT;
(2) Concurrent other primary malignant tumors;
(3) Emergency surgery due to perforation or obstruction during treatment;
(4) Severe cardiopulmonary, hepatic, or renal dysfunction.

1.2 Treatment Protocol

1.2.1 nCRT regimen

Gross tumor volume (GTV): radiation dose 45–50.4 Gy in 25–28 fractions, once daily, 5 consecutive days/week. Clinical target volume (CTV): radiation dose 45 Gy in 25 fractions, once daily, 5 consecutive days/week. Concurrent oral capecitabine (850–1 250 mg/m², twice daily) to enhance radiosensitivity.

1.2.2 Surgical protocol

At 6–8 weeks post-nCRT, CT/MRI re-examinations were performed. After evaluation by the multidisciplinary team (MDT) of preliminary efficacy and general condition, patients without surgical contraindications underwent TME surgery. Surgical approach [laparoscopic/open low anterior resection (Dixon procedure)] was selected based on tumor location. Prophylactic colostomy/ileostomy or abdominoperineal resection (Miles procedure) was added when indicated. Postoperative pathological staging followed TNM criteria [14], and tumor regression was assessed by Mandard's tumor regression grade (TRG) [15].

1.3 Observation Indicators

All patients underwent pelvic CT/MR before and after nCRT. The following clinical parameters were analyzed: gender, age, body mass index (BMI), post-nCRT carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), tumor distance from anal verge, maximum tumor diameter, gross tumor type, tumor occupancy ratio of intestinal lumen, surgical approach, post-nCRT pathological T (ypT) stage, and TRG.

1.4 Statistical Methods

IBM SPSS Statistics 23.0 was used for statistical analysis. Categorical data were expressed as n(%), with intergroup comparisons using chi-square test. Non-normally distributed data was presented as $M(P_{25},P_{75})$, and analyzed by rank-sum test. $P<0.05$ indicated statistical significance. Potential risk factors were screened via LASSO regression. Non-zero coefficient variables were included in multivariate logistic regression to construct a nomogram predicting post-nCRT lymph node metastasis risk. R4.3.3 was used for the above analysis. Model discrimination and accuracy were evaluated by the receiver operating characteristic (ROC) curve.

2 Results

2.1 Baseline Data of Patients

Among 150 patients, the number of lymph nodes detected was 10 (2, 17), and 56 patients (37.3%) had lymph node metastasis. In the lymph node metastasis positive group, the number of lymph nodes detected was 11 (3, 17), while in the lymph node metastasis negative group it was 10 (2, 16). The difference between the two groups was not statistically significant (Z=1.717, P>0.05). In the patients with TRG grade 1, 24.0% (6/25) of them still had lymph node metastasis. A comparison of the clinical and pathological characteristics of patients with and without lymph node metastasis is shown in **Table 1.**

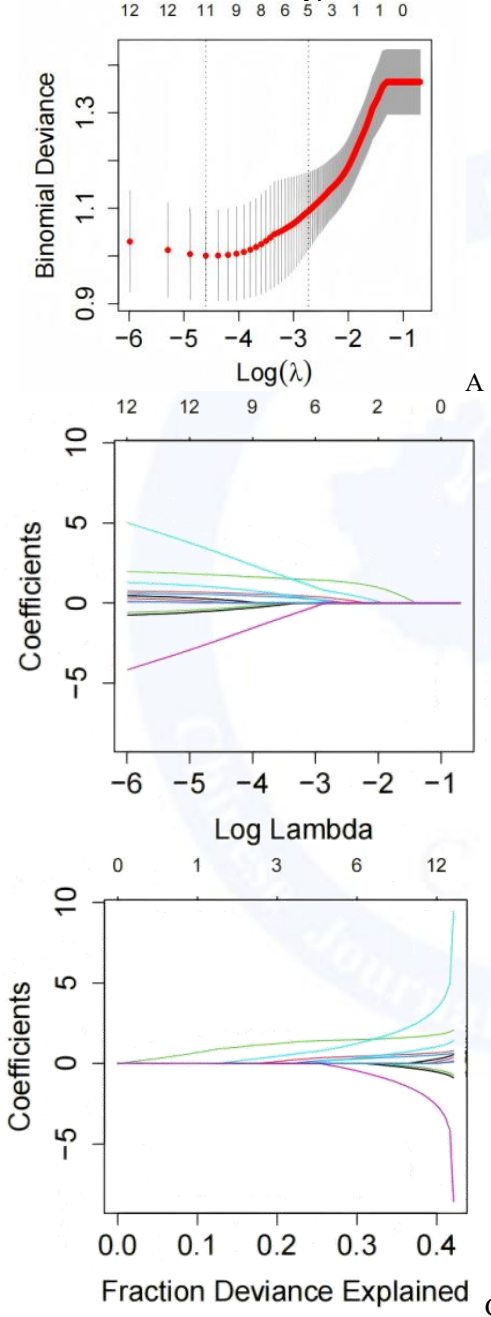
Tab.1 Comparison of clinicopathological features between two groups of patients with and without lymph node metastasis [case(%)]

Indicators	Lymph metastasis	Non-lymph metastasis	χ^2 value	P value
Gender				
Male	21(37.5)	27(28.7)	1.242	0.265
Female	35(62.5)	67(71.3)		
Age				
≤65 years	39(69.6)	48(51.1)	4.973	0.026
>65 years	17(30.4)	46(48.9)		
BMI				
≤25 kg/m²	20(35.7)	80(85.1)	38.526	<0.001
>25 kg/m²	36(64.3)	14(14.9)		
CEA				
≤5 μg/L	30(53.6)	71(75.5)	7.694	0.006
>5 μg/L	26(46.4)	23(24.5)		
CA199				
≤27 u/mL	40(71.4)	78(83.0)	2.790	0.095
>27 u/mL	16(28.6)	16(17.0)		
Distance from anal verge				
≤7 cm	29(51.8)	53(56.4)	0.299	0.584
>7 cm	27(48.2)	41(43.6)		
Maximum diameter of tumor				
≤4 cm	33(58.9)	55(58.5)	0.003	0.960
>4 cm	23(41.1)	39(41.5)		
Morphologic pattern of tumor growth				
Polypoid	10(17.9)	21(22.3)	0.430	0.512
Ulcerated/perforated	46(82.1)	73(77.7)		
Proportion of tumor in intestinal lumen				
≤1/2	33(58.9)	50(53.2)	0.467	0.494
>1/2	23(41.1)	44(46.8)		
Operation				
Dixon	31(55.4)	44(46.8)	1.026	0.311
Miles	25(44.6)	50(53.2)		
ypT				
T_0-T_2	6(10.7)	42(44.7)	18.607	<0.001
T_3-T_4	50(89.3)	52(55.3)		
TRG				
1-2	15(26.8)	20(21.3)	0.595	0.440
3-5	41(73.2)	74(78.7)		

Note: The data of CEA and CA199 were detected after nCRT.

2.2 Variable Selection

Lymph node metastasis was used as the dependent variable. LASSO regression was applied, and ten-fold cross-validation was performed during the regularization process. See **Figure 1**. The λ corresponding to the smallest bias and one standard error was selected as the optimal value for this study. Finally, five non-zero coefficient predictors were identified, including age, BMI, post-nCRT CEA and CA199, and ypT.



Note: A showed the cross-validation results of LASSO regression. And the two dashed lines represent the lg(λ) corresponding to the minimum model deviance and the lg(λ) within one standard error of the minimum deviance. B was the lg(λ) versus LASSO regression coefficients. C was model deviance versus LASSO regression coefficients.

Fig.1 LASSO regression analysis

2.3 Nomogram Prediction Model Construction

The five risk factors selected by LASSO regression were further analyzed using multivariate logistic regression. Four independent risk factors were finally identified, including age, BMI, post- nCRT CEA, and ypT (P<0.05). See **Figure 2**. Based on these four predictors, a nomogram prediction model for lymph node metastasis risk after nCRT was constructed. The score for each factor was obtained according to the patient's clinical results, and the total score was calculated by adding the four scores, corresponding to the probability of lymph node metastasis in the patient. See **Figure 3**.

2.4 Evaluation of the Nomogram Prediction Model

The ROC curve was plotted to assess the discriminatory ability of the nomogram prediction model. The area under the curve (AUC) for the nomogram prediction model was 0.843 (95% *CI*: 0.776–0.911), indicating that the prediction model has good discriminatory power and high clinical predictive value. See **Figure 4**.

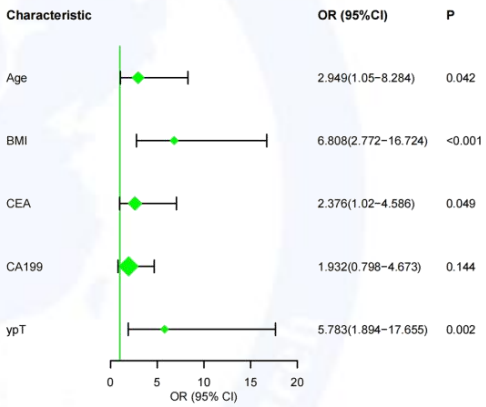


Fig.2 Forest plot for multivariate logistic regression analysis

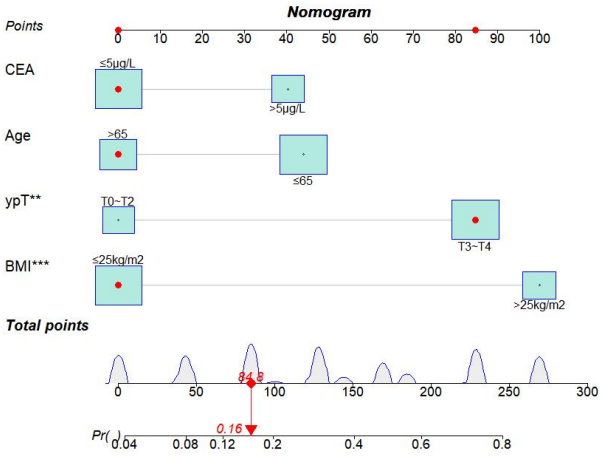


Fig.3 Nomogram for predicting lymph node metastasis risk after nCRT

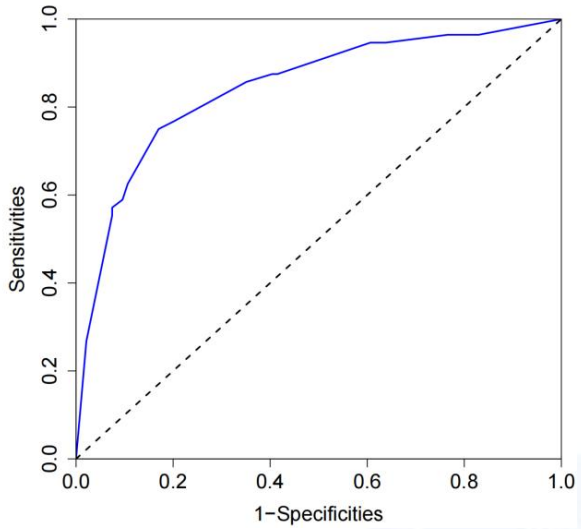


Fig.4 ROC curve of the nomogram

3 Discussion

TME surgery may cause nerve and vascular injuries, potentially leading to reproductive and urinary dysfunction. Some patients develop anterior resection syndrome (ARS) after sphincter-preserving low rectal surgery, manifesting as varying degrees of bowel and anal dysfunction, with severe cases experiencing fecal incontinence and evacuation difficulties. Others undergoing the Miles procedure develop permanent abdominal stomas, which may cause psychosocial distress, all significantly impairing quality of life [2-5]. Studies indicate that 8%–27% of patients treated with nCRT followed by TME achieve pathological complete response, with excellent 5-year overall survival rates of 88%–90% [16-17]. In this context, watch-and-wait strategies and local excision have been proposed [6-7]. Research shows that patients with significant tumor regression after nCRT who undergo rectum-preserving local excision exhibit 5-year survival comparable to TME, with lower postoperative complication and mortality rates. This approach maintains anatomical and functional rectal integrity while reducing ARS risk. For selected patients achieving clinical complete response, watch-and-wait strategies yield survival outcomes equivalent to TME [18-21]. However, these non-radical rectum-preserving approaches omit regional lymph node dissection. Metastatic lymph nodes become the primary source of recurrence and treatment failure [13]. This study revealed lymph node metastasis in 24.0% (6/25) of TRG grade 1 patients.

To identify patients at high risk of lymph node metastasis and avoid inappropriate local excision or watch-and-wait strategies, we performed LASSO-logistic regression analysis to develop a predictive model. Four independent risk factors were identified: age, BMI, post-nCRT CEA level, and ypT stage. These were incorporated into a nomogram model. Results indicate that younger age increases regional lymph node metastasis risk post-nCRT. Higher BMI also elevates risk, possibly linked to metabolic syndrome in obese patients. CEA, a crucial tumor marker for colorectal cancer diagnosis and surveillance, predicts therapeutic efficacy and prognosis. Zhao *et al.* [22] demonstrated that normal preoperative serum CEA (<5 μg/L) correlates with better nCRT response, while elevated levels (>5 μg/L) indicate adverse outcomes. Our study confirmed CEA >5 μg/L as an independent predictor of lymph node metastasis post-nCRT. Although primary tumor T-stage correlates with perirectal lymph node metastasis [23], the relationship between ypT and nodal involvement remains controversial. Wang *et al.* [24] reported increased metastasis risk with deeper tumor invasion, whereas Hueman *et al.* [25] found no significant association. Our data show escalating lymph node metastasis risk with higher ypT stages. Even in TRG stage 2 patients, deeper tumor infiltration post-nCRT predicts substantial metastasis risk.

Traditional univariate/multivariate methods face computational inefficiency, overfitting, and multicollinearity. LASSO regression overcomes these by constraining coefficients, applying regularization, and using cross-validation. Our model achieved an AUC of 0.843 (95%*CI*: 0.776–0.911), indicating strong discriminative power and clinical utility.

In summary, patients aged ≤65 years, with BMI >25 kg/m^2, post-nCRT CEA >5 μg/L, or deep tumor infiltration should be monitored for lymph node metastasis risk. The developed nomogram provides a practical tool for risk stratification. Limitations include potential biases and data gaps inherent to retrospective studies. Future validation with larger cohorts is warranted to enhance model accuracy.

Conflict of Interest None

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·论　著·

直肠癌新辅助放化疗后淋巴结转移的列线图预测模型

曹晨亮[1]，　汪玲[2]，　施海华[1]

1. 南京医科大学附属苏州医院　苏州市立医院胃肠外科，　江苏 苏州 215000；

2. 苏州大学附属第一医院放射科，　江苏 苏州 215000

摘要：目的　通过LASSO回归构建一个用于预测接受新辅助放化疗（nCRT）后的Ⅱ~Ⅲ期直肠癌患者淋巴结转移情况的列线图预测模型，并评估其效能。**方法**　收集苏州市立医院2010年9月至2024年12月收治的150例直肠癌患者的临床资料，均接受nCRT联合全直肠系膜切除术，采用R4.3.3与SPSS 23.0软件进行数据处理，首先运用LASSO回归方法筛选关键变量，随后实施多因素logistic回归分析以识别nCRT后导致淋巴结转移的风险因素。据此构建列线图预测模型，并采用受试者工作特征（ROC）曲线对其性能进行全面评价。**结果**　最终纳入预测模型的危险因素包括年龄（*OR*=2.949，95%*CI*：1.050~8.284）、身体质量指数（BMI）（*OR*=6.808，95%*CI*：2.772~16.724）、nCRT后癌胚抗原（CEA）水平（*OR*=2.376，95%*CI*：1.020~4.586）、nCRT后T分期（ypT分期）（*OR*=5.783，95%*CI*：1.894~17.655）（*P*<0.05）。该模型预测直肠癌患者淋巴结转移情况的ROC曲线下面积（AUC）为0.843（95%*CI*：0.776~0.911）。**结论**　nCRT后，对于年龄偏低、BMI较大、放化疗后CEA>5 μg/L、肿瘤病灶浸润较深的直肠癌患者，应警惕存在淋巴结转移风险。而基于这些因素建立起来的列线图预测模型不仅预测准确性高，而且具有较强的临床应用潜力。

关键词：直肠癌；新辅助放化疗；全直肠系膜切除术；LASSO回归；淋巴结转移；列线图

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CAO Chenliang*, WANG Ling, SHI Haihua

*Department of Gastrointestinal Surgery, Suzhou Municipal Hospital, Suzhou Hospital Affiliated to Nanjing Medical University, Suzhou, Jiangsu 215000, China

Corresponding author: SHI Haihua, E-mail: doctorhaihua0309@163.com

Abstract: Objective　To construct a nomogram prediction model for predicting lymph node metastasis in stage Ⅱ-Ⅲ rectal cancer patients after receiving neoadjuvant chemoradiotherapy (nCRT) based on LASSO regression, and to evaluate its efficacy. **Methods**　The clinical data of 150 patients admitted to Suzhou Municipal Hospital from September 2010 to December 2024 were included in this study. All patients received nRCT combined with total mesorectal excision. Data processing was conducted using R4.3.3 and SPSS 23.0 software. Initially, the LASSO regression method was employed to screen for key variables, followed by a multivariate logistic regression analysis to identify risk factors for lymph node metastasis after nCRT. A nomogram prediction model was then constructed, and its performance was comprehensively evaluated using methods such as the receiver operating characteristic (ROC) curve. **Results**　Four potential predictors were identified as independent risk factors, including age (*OR*=2.949, 95%*CI*: 1.050-8.284), body mass index (BMI) (*OR*=6.808, 95%*CI*: 2.772-16.724), post-neoadjuvant carcinoembryonic antigen (CEA) (*OR* =2.376, 95%*CI*: 1.020-4.586), and yield pathologic T (ypT) stage (*OR*=5.783, 95%*CI*: 1.894-17.655) (*P*<0.05). The ROC

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通信作者：施海华，E-mail: doctorhaihua0309@163.com

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curve area under the curve (AUC) predicted by this model for lymph node metastasis in rectal cancer patients was 0.843 (95%*CI*: 0.776-0.911). **Conclusion** After nCRT, patients who were younger, had a higher BMI, had a CEA level >5 μg/L, and had deeper tumor infiltration should be vigilant for the risk of lymph node metastasis. The nomogram prediction model established based on these factors not only has high prediction accuracy but also possesses strong clinical application potential.

Keywords: Rectal cancer; Neoadjuvant chemoradiotherapy; Total mesorectal excision; LASSO regression; Lymph node metastasis; Nomogram

新辅助放化疗(neoadjuvant chemoradiotherapy, nCRT)联合全直肠系膜切除术(total mesorectal excision, TME)是目前Ⅱ~Ⅲ期中低位直肠癌的标准治疗方法[1]。与直接进行手术相比,nCRT后再行TME,局部复发率低,保肛率高,但是吻合口漏、狭窄、性功能障碍和输尿管损伤及直肠前切除综合征等术后并发症发生率高,为10%~40%,部分患者可能面临临时性造口无法回纳的风险[2-5]。考虑到TME的早期和晚期并发症发生率,以及nRCT后达到完全或显著病理缓解的患者预后较好,采用TME进行根治性手术可能意味着过度治疗。据此,有学者提出等待观察策略及局部切除术的方法[6-7]。相关研究显示,nCRT后肿瘤病灶达到显著缓解的患者采取保留直肠的局部切除术,以及对部分达到临床完全缓解的患者群体实施等待观察策略,生存预后与行TME手术者无明显差异,并且避免了TME术后可能产生的相关手术并发症[8-12]。然而,采取局部切除术或者等待观察策略并没有进行淋巴结清扫,研究显示,接受nCRT治疗的患者在采取这两种非根治性治疗方案后,已发生转移的淋巴结成为后期复发和转移的主要原因[13]。因此,在nCRT后评估淋巴结是否转移具有重要意义。本研究收集确诊为直肠癌并且行nCRT联合TME手术患者的临床资料,分析影响nCRT后淋巴结转移的危险因素,基于最小绝对收缩与选择算子算法(least absolute shrinkage and selection operator, LASSO)回归,构建nCRT后淋巴结转移风险的列线图预测模型并评估其效能。

1 对象与方法

1.1 *研究对象* 回顾性分析苏州市立医院2010年9月至2024年12月150例直肠癌患者的临床资料,均接受nCRT联合TME手术治疗。纳入标准:(1) nCRT前肠镜活检病理证实为直肠腺癌;(2) nCRT前TNM分期为Ⅱ~Ⅲ期中低位直肠癌;(3) 胸腹盆腔增强CT未发现远处转移;(4) 均接受nCRT及TME手术治疗。排除标准:(1) nCRT前有远处转移或nCRT期间发现远处转移;(2) 合并其他原发恶性肿瘤;(3) 治疗期间并发穿孔、梗阻行急诊手术;(4) 合并严重心肺、肝肾功能障碍。本研究获得苏州市立医院伦理委员会批准(伦理号:KL-2025-019-K01)。

1.2 *治疗方案* nCRT方案:大体肿瘤靶区(gross tumor volume, GTV),放疗剂量为45~50.4 Gy/25~28次,1次/d,每周连续照射5次。临床靶区(clinical tumor volume, CTV),放疗剂量为45 Gy/25次,1次/d,每周连续照射5次。放疗期间同步口服卡培他滨(850~1 250 mg/m^2,2次/d),增加放疗敏感性。手术方案:nCRT结束后6~8周,复查CT、MRI等检查,经过多学科综合治疗协作组(multidisciplinary team, MDT)讨论后,评估患者新辅助治疗后的初步疗效以及全身一般状况,排除相关手术禁忌证后接受TME手术,并根据术中具体情况,肿瘤的具体位置,选择腹腔镜或开腹直肠低位前切除术(Dixon术),根据情况需要,加做预防性结肠造瘘或者回肠造瘘,或者腹会阴联合切除术(Miles术)。根据TNM分期[14]进行术后病理分期,按照Mandard等[15]的肿瘤消退分级(tumor regression grade, TRG),评估nCRT后肿瘤退缩程度。

1.3 *观察指标* 所有患者nCRT前以及nCRT后均进行盆腔CT或MR检查,评估nCRT疗效,本研究纳入了以下临床因素进行观察分析,包括性别、年龄、身体质量指数(body mass index, BMI)、nCRT后癌胚抗原(carcinoembryonic antigen, CEA)、糖类抗原199(carbohydrate antigen 199, CA199)、肿瘤距肛缘距离、肿瘤最大径、肿瘤大体分型、肿瘤占肠腔比例,手术方式、nCRT后病理T(yield pathologic T, ypT)分期及TRG。

1.4 *统计学方法* 计数资料以例(%)表示,组间比较采用χ^2检验;淋巴结清扫数量呈非正态分布,以$M(P_{25}, P_{75})$表示,组间比较采用秩和检验,$P<0.05$为差异有统计学意义,由IBM SPSS Statistics 23.0软件完成上述分析。基于LASSO回归,分析可能的危险因素变量,将筛选出的非零系数变量纳入多因素logistic回归分析,最终得到可用于预测模型拟合的变

量，并构建nCRT后淋巴结转移风险的列线图预测模型，上述操作通过R4.3.3软件完成，绘制受试者工作特征（receiver operative characteristic，ROC）曲线对预测模型的区分能力和准确性进行评价。

2　结　果

2.1　患者基线资料　150例患者中检出淋巴结数量为10（2，17）枚，共有56例（37.3%）发生淋巴结转移。淋巴结转移阳性患者中检出淋巴结数量为11（3，17）枚，而淋巴结转移阴性患者为10（2，16）枚，两者比较差异无统计学意义（Z=1.717，P>0.05）。TRG 1级的患者中仍有24.0%（6/25）的患者发生淋巴结转移。有无淋巴结转移患者临床病理特征的比较见表1。

表1　有无淋巴结转移患者临床病理特征的比较　［例(%)］

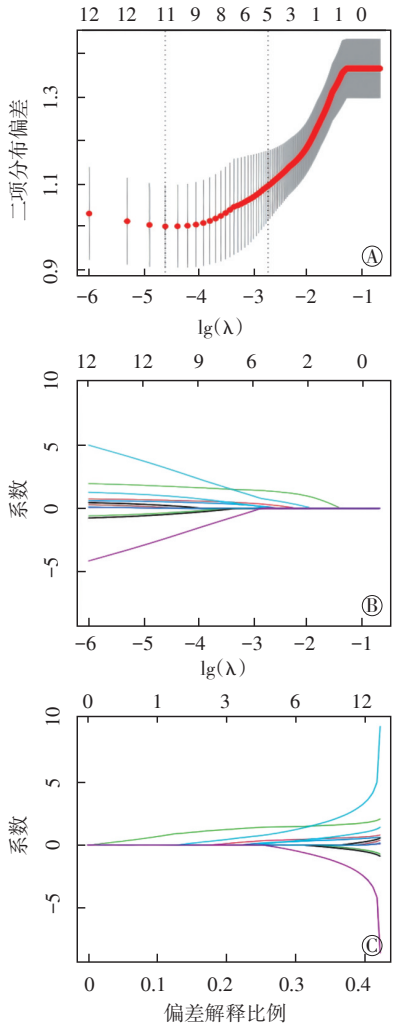
Tab.1　Comparison of clinicopathological features between patients with and without lymph node metastasis　［case(%)］

临床因素	淋巴结阳性（n=56）	淋巴结阴性（n=94）	χ^2值	P值
性别				
男性	21(37.5)	27(28.7)	1.242	0.265
女性	35(62.5)	67(71.3)		
年龄				
≤65岁	39(69.6)	48(51.1)	4.973	0.026
>65岁	17(30.4)	46(48.9)		
BMI				
≤25 kg/m^2	20(35.7)	80(85.1)	38.526	<0.001
>25 kg/m^2	36(64.3)	14(14.9)		
CEA				
≤5 μg/L	30(53.6)	71(75.5)	7.694	0.006
>5 μg/L	26(46.4)	23(24.5)		
CA199				
≤27 u/mL	40(71.4)	78(83.0)	2.790	0.095
>27 u/mL	16(28.6)	16(17.0)		
肿瘤距肛缘距离				
≤7 cm	29(51.8)	53(56.4)	0.299	0.584
>7 cm	27(48.2)	41(43.6)		
肿瘤最大径				
≤4 cm	33(58.9)	55(58.5)	0.003	0.960
>4 cm	23(41.1)	39(41.5)		
肿瘤大体分型				
隆起型	10(17.9)	21(22.3)	0.430	0.512
溃疡、浸润型	46(82.1)	73(77.7)		
肿瘤占肠腔比例				
≤1/2	33(58.9)	50(53.2)	0.467	0.494
>1/2	23(41.1)	44(46.8)		
手术方式				
Dixon术	31(55.4)	44(46.8)	1.026	0.311
Miles术	25(44.6)	50(53.2)		
ypT				
T0~T2	6(10.7)	42(44.7)	18.607	<0.001
T3~T4	50(89.3)	52(55.3)		
TRG				
1~2级	15(26.8)	20(21.3)	0.595	0.440
3~5级	41(73.2)	74(78.7)		

注：CEA、CA199为nCRT后的临床资料。

2.2　变量筛选　以淋巴结是否转移作为因变量，使用LASSO回归，在正则化的过程中，对数据集进行十折交叉验证。见图1。本研究选取距离最小偏差一个标准误时对应的lambda作为最优值，最终筛选出5个非零系数的预测变量，包括年龄、BMI、nCRT后CEA和CA199、ypT。

2.3　列线图预测模型构建　将LASSO回归分析筛选出的5个危险因素进一步进行多因素logistic回归分析，最终筛选出4个独立危险因素，包括年龄、BMI、nCRT后CEA、ypT（P<0.05）。见图2。纳入这4个预测因素，构建nCRT后淋巴结转移风险的列线图预测



注：A为LASSO回归交叉验证结果，2条虚线分别表示模型偏差最小时对应的lg(λ)值及模型距离最小偏差一个标准误时对应的lg(λ)值；B为lg(λ)值与LASSO回归系数；C为模型偏差与LASSO回归系数。

图1　LASSO回归分析

Fig.1　LASSO regression analysis

模型。按患者的临床因素结果得到每个影响因素的评分，4 个评分相加得到总分，对应得到该患者发生淋巴结转移的概率。见图 3。

2.4　列线图预测模型的评价　绘制 ROC 曲线对列线图预测模型进行区分度评估，列线图预测模型 ROC 曲线下面积（area under curve，AUC）为 0.843（95%*CI*：0.776～0.911），表明该预测模型具有良好的区分能力，临床预测价值较高。见图 4。

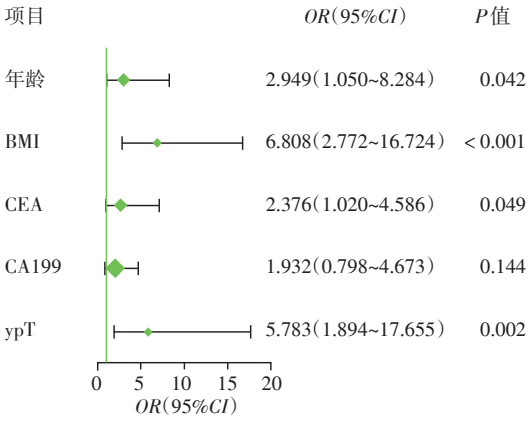


图 2　多因素 logistic 回归分析的森林图

Fig.2　Forest plot for multivariate logistic regression analysis

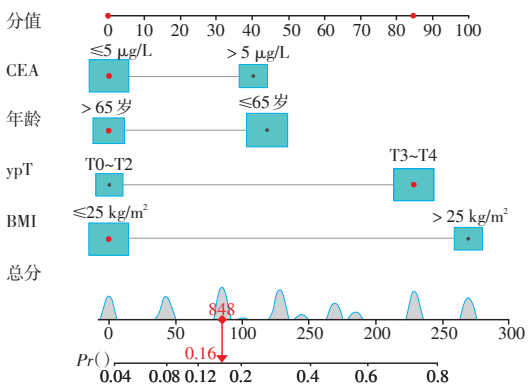


图 3　预测 nCRT 后淋巴结转移风险的列线图

Fig.3　Nomogram for predicting lymph node metastasis risk after nCRT

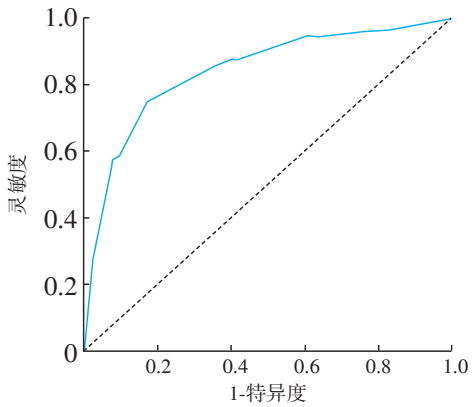


图 4　列线图预测模型的 ROC 曲线

Fig.4　ROC curve of the nomogram

3　讨　论

TME 可能出现神经、血管损伤以及由此导致的生殖、排尿功能障碍，部分患者低位保肛后出现直肠前切除综合征，表现为不同程度的肠道功能障碍和肛门功能障碍，严重者出现排粪失禁和排空障碍，另一部分患者在经历 Miles 术后，会形成腹壁永久性造瘘口，这可能导致社交心理障碍，以上种种均严重影响患者生活质量[2-5]。相关研究显示，nCRT 后接受 TME 的患者中，有 8%～27%的患者出现病理完全缓解，其 5 年总生存率为 88%～90%，预后极佳[16-17]。在这种背景下，有学者提出了等待观察策略及局部切除术的方法[6-7]。相关研究显示，nCRT 后肿瘤病灶达到显著缓解的患者采取保留直肠的局部切除术，其 5 年生存率与行 TME 手术患者无明显差异，且术后并发症发生率和死亡率明显低于 TME 术后，并且保留了直肠的解剖和功能完整性，降低了 TME 术后直肠前切除综合征的风险。对于部分达到临床完全缓解的患者群体，实施等待观察策略，生存预后与行 TME 手术者无差异[18-21]。然而，这两种保留直肠的非根治性治疗措施并没有对区域淋巴结进行清扫，已发生转移的淋巴结成为后期复发和转移的主要原因，最终导致治疗失败[13]。本研究显示，TRG 1 级的患者中仍有 24.0%（6/25）的患者发生淋巴结转移。

本研究通过对直肠癌 nCRT 后淋巴结转移相关危险因素进行 LASSO-logistic 回归分析，旨在建立 nCRT 后淋巴结转移风险的预测模型，以判断哪些患者更容易发生淋巴结转移，避免对这类患者采取局部切除术或等待观察策略。本研究最终筛选出 4 个独立危险因素，包括年龄、BMI、nCRT 后 CEA 水平、ypT，并以此构建淋巴结转移风险的列线图预测模型。本研究结果显示，nCRT 后其区域淋巴结转移的风险随着年龄的降低而增加。此外，BMI 较高的患者，nCRT 后淋巴结转移的风险也有所增加，这可能与肥胖患者往往合并有代谢综合征有关。CEA 是结直肠癌诊断和术后随访中常用的肿瘤标志物。它对于评估直肠癌的治疗效果、监测术后病情以及预测疾病预后都具有重要的意义。Zhao 等[22]研究发现，CEA 水平能够作为预测 nCRT 反应的指标，术前血清 CEA 水平正常提示患者对 nCRT 灵敏度较好，而术前血清 CEA > 5 μg/L，被认为是 nCRT 后出现不良反应的一个风险因素。本研究显示，nCRT 后 CEA > 5 μg/L 的患者相比 CEA 水平正常的患者更容易出现淋巴结转移，多因素 logistic 回归分析显示 CEA 可作为 nCRT 后评估淋巴结转移风险的预测指标。研究表明直肠肿

瘤T分期与肠周淋巴结转移具有相关性[23]，T分期越高，转移风险越大，而ypT与淋巴结转移是否有关仍不明确。Wang等[24]研究显示，随着原发肿瘤灶浸润深度的增加，淋巴结转移风险显著增加，而Hueman等[25]的研究则显示ypT与淋巴结转移无明显相关性。本研究显示随着ypT的增加，淋巴结转移风险也随之增加，在nCRT治疗后，若肿瘤病灶浸润较深，即便TRG 2级的患者，其淋巴结转移的风险仍然较高。

传统的单因素、多因素变量筛选方法，需要消耗高昂的的计算机算力成本，也难以避免模型的过度拟合，以及自变量间的多重共线性问题。本研究采用LASSO回归，可以对估计系数进行限制，避免多重共线性的发生，在正则化的过程中，对数据集进行交叉验证，可以有效避免过度拟合。本预测模型的AUC为0.843（95%*CI*：0.776～0.911），表明该预测模型具有良好的区分能力以及较高的临床预测价值。

综上所述，nCRT后，对于年龄≤65岁、BMI>25 kg/m^2、nCRT后CEA > 5 μg/L、肿瘤病灶浸润较深的患者，应警惕存在淋巴结转移风险。基于上述因素建立的列线图预测模型可用于评估nCRT后淋巴结转移风险。本研究也存在一定的局限性，由于本研究为回顾性分析，临床资料的收集过程中难免会产生数据的偏差、缺失，未来还需纳入更多的临床病例进行研究，进一步提高模型的准确性。

利益冲突　无

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