Am J Cancer Res 2023;13(1):204-215
www.ajcr.us /ISSN:2156-6976/ajcr0146663

Original Article

Using nomogram, decision tree, and deep learning models to predict lymph node metastasis in patients with early gastric cancer: a multi-cohort study

Lulu Zhao[1*], Weili Han[2*], Penghui Niu[1*], Yuanyuan Lu[2*], Fan Zhang[3*], Fuzhi Jiao[4*], Xiadong Zhou[5*], Wanqing Wang[1], Xiaoyi Luan[1], Mingyan He[5], Quanlin Guan[4], Yumin Li[3], Yongzhan Nie[2], Kaichun Wu[2], Dongbing Zhao[1], Yingtai Chen[1]

[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]State Key Laboratory of Cancer Biology and National Clinical Research Center for Digestive Diseases, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, China; [3]Lanzhou University Second Hospital, Lanzhou, Gansu, China; [4]The First Hospital of Lanzhou University, Lanzhou, Gansu, China; [5]Gansu Provincial Cancer Hospital, Lanzhou, Gansu, China. [*]Equal contributors.

Received September 23, 2022; Accepted December 30, 2022; Epub January 15, 2023; Published January 30, 2023

Abstract: The accurate assessment of lymph node metastasis (LNM) in patients with early gastric cancer is critical to the selection of the most appropriate surgical treatment. This study aims to develop an optimal LNM prediction model using different methods, including nomogram, Decision Tree, Naive Bayes, and deep learning methods. In this study, we included two independent datasets: the gastrectomy set (n=3158) and the endoscopic submucosal dissection (ESD) set (n=323). The nomogram, Decision Tree, Naive Bayes, and fully convolutional neural networks (FCNN) models were established based on logistic regression analysis of the development set. The predictive power of the LNM prediction models was revealed by time-dependent receiver operating characteristic (ROC) curves and calibration plots. We then used the ESD set as an external cohort to evaluate the models' performance. In the gastrectomy set, multivariate analysis showed that gender (P=0.008), year when diagnosed (2006-2010 year, P=0.265; 2011-2015 year, P=0.001; and 2016-2020 year, P<0.001, respectively), tumor size (2-4 cm, P=0.001; and ≥4 cm, P<0.001, respectively), tumor grade (poorly-moderately, P=0.016; moderately, P<0.001; well-moderately, P<0.001; and well, P<0.001, respectively), vascular invasion (P<0.001), and pT stage (P<0.001) were independent risk factors for LNM in early gastric cancer. The area under the curve (AUC) for the validation set using the nomogram, Decision Tree, Naive Bayes, and FCNN models were 0.78, 0.76, 0.77, and 0.79, respectively. In conclusion, our multi-cohort study systematically investigated different LNM prediction methods for patients with early gastric cancer. These models were validated and shown to be reliable with AUC>0.76 for all. Specifically, the FCNN model showed the most accurate prediction of LNM risks in early gastric cancer patients with AUC=0.79. Based on the FCNN model, patients with LNM rates of >4.77% are strong candidates for gastrectomy rather than ESD surgery.

Keywords: lymph node metastasis, early gastric cancer

Introduction

Early gastric cancer is defined as gastric cancer that is confined to the mucosa and submucosa of the stomach, regardless of lymph node metastasis (LNM) [1]. For patients without LNM, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) with minimally invasive operation are most often recommended according to Japanese gastric cancer treatment guidelines [2, 3]. For patients with possible LNM, gastrectomy with D2 lymphadenectomy is most common [2]. Thus, accurately predicting LNM in early gastric cancer patients is critical to treatment decisions where ESD surgeries will better preserve gastric function and minimize complications.

Increasing efforts have been made to improve imaging technologies and establish models for

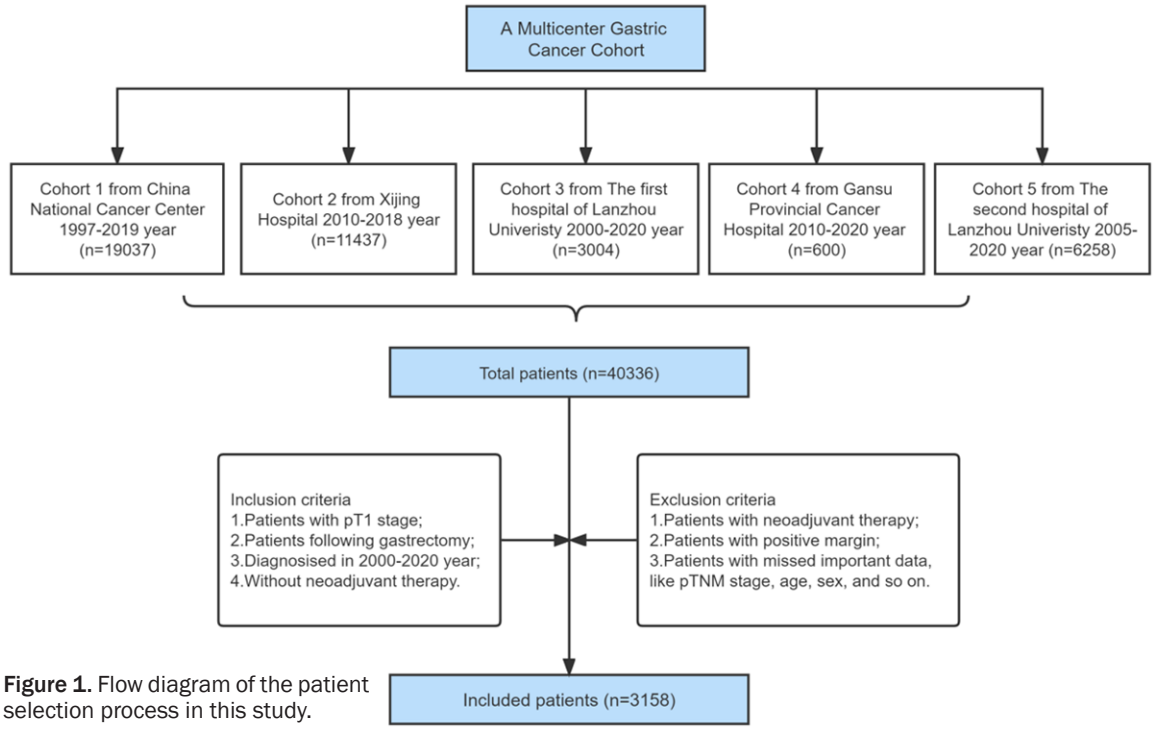

Figure 1. Flow diagram of the patient selection process in this study.

predicting the lymph nodal status of patients with early gastric cancer [4], although the diagnostic accuracy of endoscopic ultrasonography (EUS) and enhanced computed tomography (CT) for LNM prediction has remained unsatisfactory. Previous studies on LNM prediction models were limited to small sample size from a single or small number of hospitals [5-9]. Chen et al [10] have presented a prediction model based on collagen architecture and morphology to estimate the risk of LNM in patients with early gastric cancer. However, wider use is difficult given that extra equipment and additional training are needed for multiphoton imaging. In recent years, deep learning, in particular, fully convolutional neural networks (FCNN) [11-13], has emerged as a promising method for medical diagnosis, which may provide new insights into LNM prediction for patients with early gastric cancer.

Given the above considerations, we conducted the present study using five gastric cancer cohorts from the National Cancer Center of China, Xijing Hospital of Digestive Diseases, The First Hospital of Lanzhou University, The Second Hospital of Lanzhou University, and Gansu Cancer Hospital, to develop LNM prediction methods for patients with early gastric cancer. The prediction models should directly help surgeons to choose optimal and individualized treatment for patients and provide evidence for the development of guiding strategies for early gastric cancer.

Methods

Study population and data source

In this study, we used two independent datasets of gastrectomy and ESD. We searched the gastrectomy set from five gastric cancer cohorts of the National Cancer Center of China, Xijing Hospital of Digestive Diseases, The First Hospital of Lanzhou University, The Second Hospital of Lanzhou University, and Gansu Cancer Hospital for early gastric cancer. The five cohorts consist of >40,000 gastric cancer patients (**Figure 1**). Inclusion criteria of gastric cancer patients were: (1) more than 18 years old, (2) in pT1 stage, (3) gastrectomy recipients, (4) without neoadjuvant therapy; and (5) diagnosed in 2000-2020. In addition, patients with missing data were excluded. Finally, a total of 3,158 patients with early gastric cancer were included regardless of lymph node status. We also included an additional 323 patients as an external cohort who received ESD surgery from

the National Cancer Center of China between January 1, 2011 and December 31, 2019.

Development of the LNM prediction model

Four LNM prediction models ranging from traditional statistical algorithms to state-of-the-art deep learning models were developed in this study: nomogram, Decision Tree, Naive Bayes, and FCNN. In order to develop and verify the LNM prediction models, patients in the gastrectomy set were randomly divided into the development (n=2,215) and validation (n=943) sets at a 7:3 ratio. In the development set, independent risk factors with a P<0.10 in the univariate analysis were adopted for the multivariate analysis by logistic regression analysis. The hazard ratio (HR) and 95% confidence interval (CI) were used to measure LNM risks.

Based on the development set, six independent risk variables were identified on multivariate logistic regression analysis: gender, year when diagnosed, tumor size, grade, vascular invasion and pT stage. These six features plus age at diagnosis, another clinically meaningful variable, were used to formulate the logistic regression-based nomogram and Decision Tree models. Naive Bayes was assessed by all baseline model variables, including gender, age at diagnosis, tumor location, tumor size, tumor grade, ulcer, signet ring cell, nerve invasion, vascular invasion, and pT stage.

Compared to Naive Bayes, a traditional machine-learning method, FCNN can automatically learn representations of data with increasing levels of abstraction via multiple convolutional and fully-connected layers [14]. In fitting the FCNN model, we used a four-layer neural network with 10 variables in the input layer and one node in the output layer. Activation functions used were ReLU between layers and sigmoid for the final output.

Performance evaluation of the LNM prediction models

The predictive power of the LNM models was assessed by time-dependent receiver operating characteristic (ROC) curves and the calibration plot and then verified in the validation set. The predictive accuracy of the model was shown using ROC curves, which plot sensitivity versus 1-specificity for different threshold probabilities of LNM. The model's accuracy was quantified using the area under the curve (AUC) for validation. Larger AUCs indicate more accurate LNM prediction.

We further compared actual LNM rates with predicted LNM rates from our developed LNM models using the validation set to evaluate the models' performance. In addition, we used the ESD set as an external cohort to predict LNM rates based on the nomogram, Decision Tree, Naive Bayes, and FCNN models.

Statistical analysis

All statistical analyses were done using Python (version 3.6.5) and R (version 4.1.0). Comparisons between two groups were examined using the *t* test for continuous variables and chi-square test for categorical variables. A *P*-value of less than 0.05 was considered statistically significant and all the tests were two-sided.

Results

Baseline characteristics

Table 1 shows the clinicopathological characteristics of the early gastric cancer patients in the development, validation, and ESD set. The mean age of patients in the development and validation sets was 57.11±11.121 years and 56.57±10.856 years (P=0.554) respectively, and 61.05±9.374 years for the ESD set. The development and validation sets showed no statistical difference in age at diagnosis, gender, tumor location, tumor size, tumor grade, ulcer, signet ring cell, nerve invasion, vascular invasion, pT stage, or pN stage (P>0.05 for all). The actual LNM ratios of the development and validation sets were 16.8% and 16.5%, respectively.

Compared to the gastrectomy set, a smaller percentage of patients in the ESD set showed poor grade (n=20, 7.19%), ulcer (n=9, 2.79%), signet ring cell (n=37, 11.46%), vascular invasion (n=17, 5.26%), and nerve invasion (n=6, 1.86%). In addition, a significantly higher proportion of ESD patients had ≤2 cm tumor size (n=185, 57.28%) and pT1a stage (n=235, 72.76%).

Table 1. Characteristics of patients with early gastric cancer

Characteristics	Gastrectomy Set						
	Development set (n=2215)		Validation set (n=943)		*P* value	ESD set (n=323)	
	Number	%	Number	%		Number	%
Age at diagnosis (years)							
Mean (SD)	57.11	11.121	56.57	10.856	0.554	61.05	9.374
Younger (≤35)	89	4.0	30	3.2	0.293	2	0.62
Middle-aged (36-65)	1597	72.6	700	75.0		220	68.11
Older (≥66)	514	23.4	203	21.8		101	31.27
Gender							
Male	1579	71.3	657	69.7	0.361	238	73.68
Female	636	28.7	286	30.3		85	26.32
Year at diagnosis							
2000-2005	253	11.4	99	10.5	0.013	0	0.00
2006-2010	358	16.2	161	17.1		0	0.00
2011-2015	1001	45.2	378	40.1		146	45.20
2016-2020	603	27.2	305	32.3		177	54.80
Tumor location							
Proximal	171	18.1	437	19.7	0.571	126	39.01
Distal	659	69.9	1523	68.8		177	54.80
Total	113	12.0	255	11.5		20	6.19
Tumor size							
≤2 cm	432	47.8	971	45.4	0.165	185	57.28
2-4 cm	310	34.3	724	33.8		92	28.48
≥4 cm	161	17.8	444	20.8		46	14.24
Grade							
Poorly	732	35.6	309	35.8	0.996	20	7.19
Poorly-moderately	495	24.1	207	24.0		66	23.74
Moderately	439	21.4	181	20.9		123	44.24
Well-moderately	179	8.7	79	9.1		19	6.83
Well	211	10.3	88	10.2		50	17.99
Ulcer							
Yes	482	21.8	208	22.1	0.854	9	2.79
No	1733	78.2	735	77.9		314	97.21
Signet ring cell							
Yes	648	29.3	261	27.7	0.370	37	11.46
No	1567	70.7	682	72.3		286	88.54
Nerve invasion							
Yes	182	8.2	65	6.9	0.205	6	1.86
No	2033	91.8	878	93.1		317	98.14
Vascular invasion							
Yes	302	13.6	123	13.0	0.656	17	5.26
No	1913	86.4	820	87.0		306	94.74
pT stage							
T1a	1032	46.4	454	48.1	0.424	235	72.76
T1b	1183	53.4	489	51.9		88	27.24
pN stage							
N0	1843	83.2	787	83.5	0.803	-	-
N1	231	10.4	100	10.6		-	-
N2	94	4.2	41	4.3		-	-
N3	47	2.1	15	1.6		-	-

Table 2. Multivariate analysis of LNM in patients with early gastric cancer

Characteristics	Gastrectomy Set				
	Univariate analysis	Multivariate analysis			
	P Value	OR	95% CI		*P* Value
Gender					
Male		1.00			
Female	<0.001	1.35	1.08	1.69	0.008
Age at diagnosis					
Younger (≤35)					
Middle-aged (36-65)	0.544				
Older (≥66)	0.780				
Year at diagnosis					
2000-2005		1.00			
2006-2010	0.165	0.81	0.55	1.18	0.265
2011-2015	0.068	0.56	0.40	0.78	0.001
2016-2020	0.001	0.45	0.31	0.64	<0.001
Tumor location					
Proximal		1.00			
Distal	<0.001	1.28	0.95	1.74	0.113
Total	0.247	1.09	0.71	1.68	0.688
Tumor size					
≤2 cm		1.00			
2-4 cm	<0.001	1.51	1.19	1.92	0.001
≥4 cm	<0.001	1.97	1.51	2.56	<0.001
Grade					
Poorly		1.00			
Poorly-moderately	0.183	0.72	0.54	0.94	0.016
Moderately	<0.001	0.48	0.35	0.66	<0.001
Well-moderately	<0.001	0.17	0.09	0.31	<0.001
Well	<0.001	0.28	0.16	0.47	<0.001
Ulcer					
No					
Yes	0.116				
Signet ring cell					
No		1.00			
Yes	<0.001	0.92	0.71	1.20	0.555
Nerve invasion					
No		1.00			
Yes	<0.001	0.77	0.53	1.11	0.170
Vascular invasion					
No		1.00			
Yes	<0.001	4.36	3.35	5.67	<0.001
pT stage					
T1a		1.00			
T1b	<0.001	1.97	1.57	2.48	<0.001

Adjusted factor: Gender, Year at diagnosis, Tumor location, Tumor size, Grade, Signet ring cell, Nerve invasion, Vascular invasion and pT stage.

Risk factors of LNM in univariate and multivariate analyses

In the gastrectomy set, univariate analysis suggested that gender, year when diagnosed, tumor location, tumor size, tumor grade, signet ring cell, nerve invasion, vascular invasion, and pT stage were associated with LNM in early gastric cancer patients (P< 0.05 for all, **Table 2**). After adjusting the variables, multivariate analysis confirmed that gender (OR=1.35, 95% CI: 1.08-1.69, P=0.008), year when diagnosed (OR=0.81, 95% CI: 0.55-1.18, P=0.265; OR=0.56, 95% CI: 0.40-0.78, P=0.001; OR=0.45, 95% CI: 0.31-0.64, P<0.001), tumor size (OR=1.51, 95% CI: 1.19-1.92, P=0.001; OR=1.97, 95% CI: 1.51-2.56, P<0.001), tumor grade (OR=0.72, 95% CI: 0.54-0.94, P=0.016; OR= 0.48, 95% CI: 0.35-0.66, P<0.001; OR=0.17, 95% CI: 0.09-0.31, P<0.001; OR= 0.28, 95% CI: 0.16-0.47, P<0.001), vascular invasion (OR=4.36, 95% CI: 3.35-5.67, P<0.001), and pT stage (OR= 1.97, 95% CI: 1.57-2.48, P< 0.001) were independent risk factors of LNM for patients with early gastric cancer.

Using Nomogram to predict LNM in patients with early gastric cancer

To predict LNM in early gastric cancer patients, a nomogram was established by incorporating the following parameters: Gender, year when diagnosed, tumor size, tumor grade, vascular invasion, and pT stage (**Figure 2**). The no-

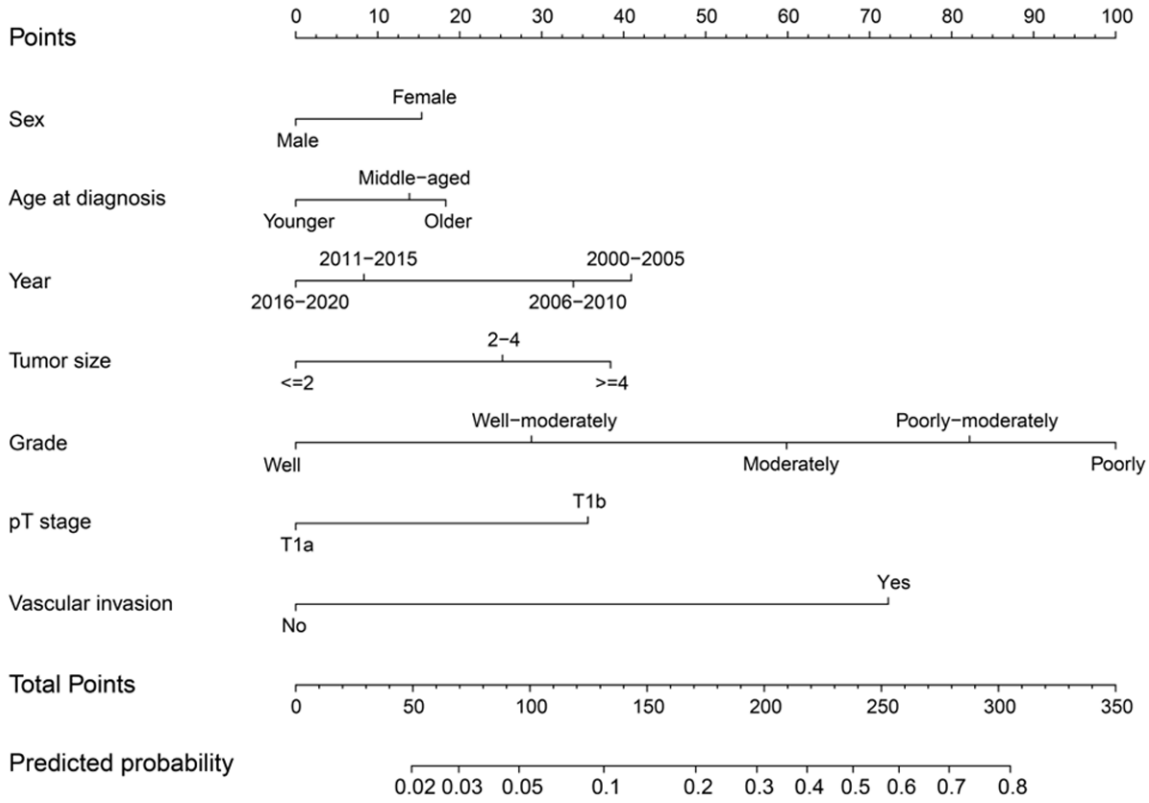

Figure 2. LNM nomogram for patients with early gastric cancer. The scores of each variable were combined to obtain the total score, and then a vertical line was subtracted from the row of total-points to estimate the risk of LNM.

mogram for predicting LNM is as follows: the sum of the total scores can be obtained by adding each score of the clinicopathological variable. The predictive risk corresponding to the total score is the risk of LNM in early gastric cancer patients.

To examine the nomogram model's performance, ROC curves were constructed with AUC values of 0.80 and 0.78 for the development and validation sets (**Figure 3A**), which suggests high accuracy of the nomogram in predicting LNM. In addition, **Figure 3B** shows the calibration plot of the nomogram using the validation set, which indicates high agreements between the ideal curves and calibration curves.

Using the decision tree to predict LNM in patients with early gastric cancer

A Decision Tree model was developed using the development set of patients with early gastric cancer (**Figure 4**). We plugged the clinicopathological characteristics from the multivariate analysis into the Decision Tree, and obtained the final model with five levels of depth and 19 decision nodes. We found that LNM risk was likely affected by vascular invasion (node 1, P<0.001), tumor grade (node 2, P=0.004; node 7, P<0.001), tumor size (node 3, P=0.007), pT stage (node 8, P=0.002; node 13, P<0.001), and gender (node 16, P=0.017) in turn.

As for the model's performance, the AUC for predicting LNM was 0.79 and 0.76 in the development set and validation set, respectively (**Figure 5**). Examples of LNM risk prediction using the Decision Tree are shown in Table S1.

Using Naive Bayes and FCNN models to predict LNM in patients with early gastric cancer

We further developed Naive Bayes and FCNN models for LNM probability (Table S2). Figure S1 shows the loss curve of the FCNN model for predicting LNM in the validation set, indicating a good fit ability. The AUC of the FCNN model for predicting LNM risks was 0.79, which is higher than the AUC value of 0.77 from the machine learning method Naive Bayes (**Figure 6**).

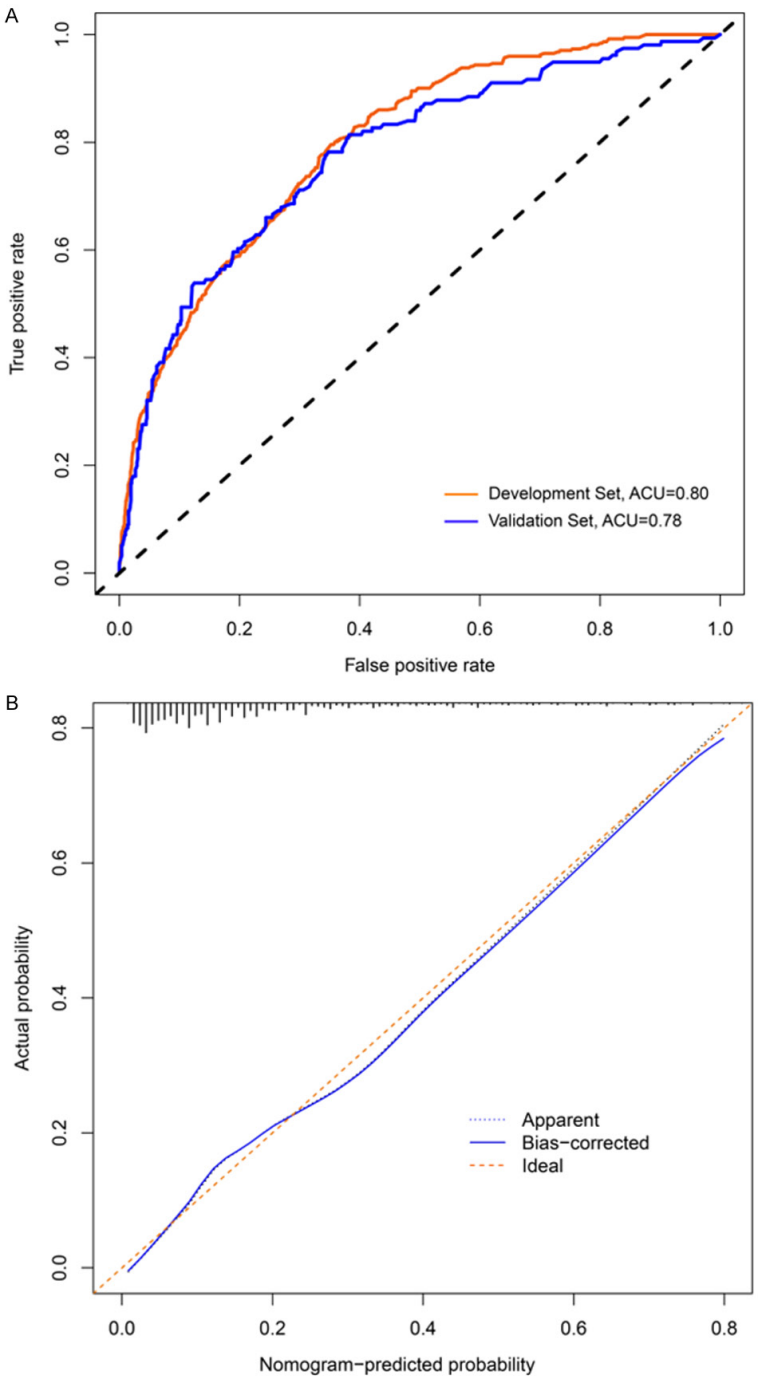

Figure 3. Validation of nomogram in predicting LNM for patients with early gastric cancer. A. The ROC curve of the nomogram, with the AUC=0.80 in the development set and 0.78 in the validation set. B. The calibration plot, the reference line represents perfect agreement of the predicted probability and the actual incidence of LNM.

Predicting LNM risks using the validation set and an external cohort

Next, we used different models to predict LNM risks for patients with early gastric cancer using the validation set and ESD set (**Table 3**). In the nomogram model, the mean and median LNM risks of the validation set were 16.16% and 13.37%, respectively. From the Decision Tree, Naive Bayes, and FCNN models, mean LNM risks of the validation set were 15.82%, 18.99%, and 15.96%, respectively. The actual LNM rate of the validation set was 16.5%, suggesting that the nomogram, Decision Tree and FCNN models exhibit high accuracies in predicting LNM risks for patients with early gastric cancer.

In addition, the predicated mean LNM risks of the ESD set were 5.87%, 6.78%, 7.24%, and 4.77% from the nomogram, Decision Tree, Naive Bayes, and FCNN models, respectively. It is clear that the ESD set showed significantly lower LNM risks than the gastrectomy set.

Discussion

Our multi-cohort study systematically investigated how to develop multiple models to predict LNM in patients with early gastric cancer, which also demonstrated the independent risk factors of LNM. To the best of our knowledge, our analysis represents the largest study of different LNM prediction models for early gastric cancer in China to date. One of the main findings from our work is that the FCNN model appeared the most accurate in predicting LNM risks of gastric cancer patients, with AUC= 0.79 in the validation set.

Notably, the LNM rate of early gastric cancer was approximately 16% (pN stage N1-N3) in our study, which is consistent with previous studies that showed rates of 0-22% [15-17]. The relatively low LNM rate in patients with early gastric

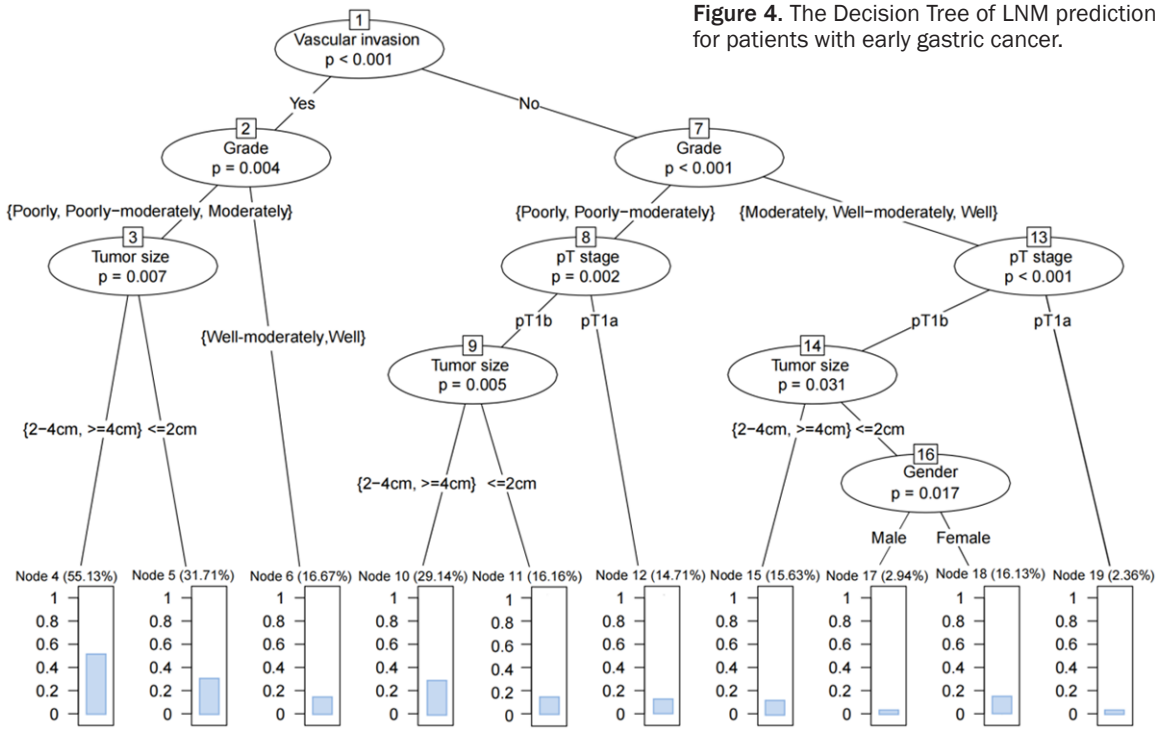

Figure 4. The Decision Tree of LNM prediction for patients with early gastric cancer.

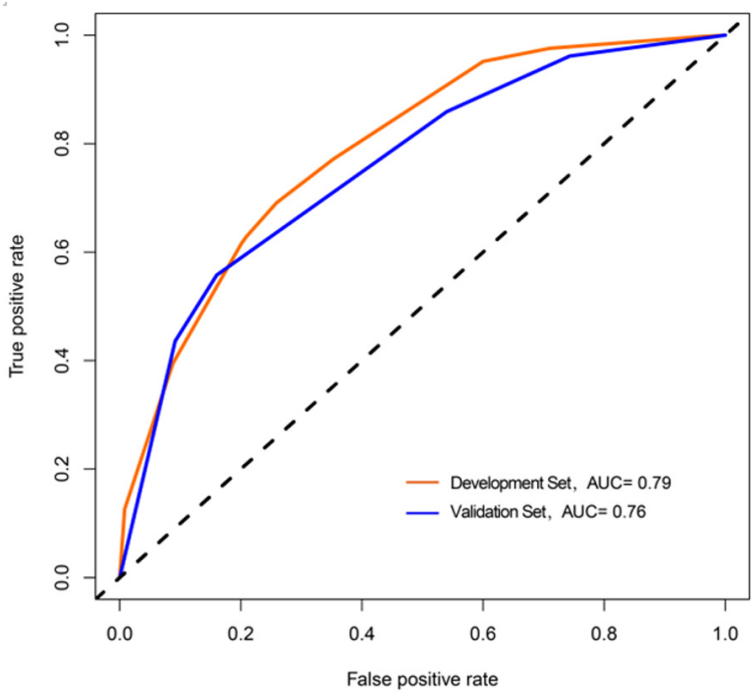

Figure 5. The ROC curve of the Decision Tree model, with the AUC=0.79 in the development set and 0.76 in the validation set.

cancer underscores the importance of avoiding unnecessary gastrectomies. Therefore, it is crucial to more accurately predict LNM risks preoperatively in order to select the most optimal treatment strategies.

In the present study, we used the following six independent variables identified through multivariate logistic regression analysis: gender, year when diagnosed, tumor size, tumor grade, vascular invasion, and pT stage. We also selected age, a clinically significant variable, to develop the nomogram. The high AUC value and calibration curve indicate a good discriminative ability and universal clinical applicability of our nomogram. We then compared the actual vs. Predicted LNM rate of the validation set using the nomogram, which are 15.89% and 16.16% respectively. Based on our nomogram, the mean LNM rate of the ESD set was 5.87%, much lower than that in the gastrectomy group. Previous studies [18-21] showed that about 5-10% patients with early gastric cancer need-

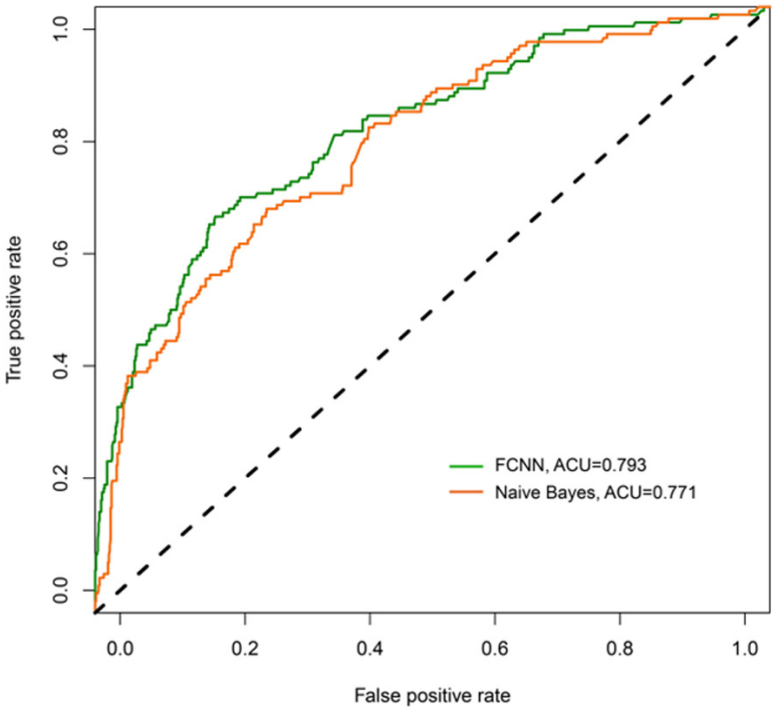

Figure 6. Comparison between the FCNN and Naive Bayes models using the validation set. The AUC was 0.79 in the FCNN model and 0.77 in the Naive Bayes model.

Table 3. The LNM risk for validation set and ESD set using the four prediction models

Set/Risk	Mean (%)	Median (%)
Nomogram model		
Validation set	15.89	13.37
ESD set	5.87	3.47
Decision Tree		
Validation set	15.82	10.22
ESD set	6.78	-
Naive Bayes		
Validation set	18.99	5.80
ESD set	7.24	-
FCNN model		
Validation set	15.96	10.72
ESD set	4.77	-

ed additional gastrectomy when ESD resulted in non-curative resection or lingering risks of LNM. These observations demonstrate that the nomogram developed in the present study can serve as a reliable prognosis prediction model.

The use of Decision Tree analysis in the study of disease diagnosis and survival prediction has proven its usefulness and effectiveness in clinical practice and the treatment decision-making process [22-24]. In the present study, we interpreted the tree in **Figure 4** as follows: vascular invasion, tumor grade, tumor size, pT stage, and gender were of relative importance to predicting LNM risks in patients with early gastric cancer. More importantly, we should first pay attention to vascular invasion following ESD surgery, given the higher LNM rate of the positive vascular invasion group (nodes 4-6, all LNM rates >15%). Compared to other models, a significant benefit of the Decision Tree is the ease and speed with which it can be applied to daily clinical practice for assessing LNM risks in patients with early gastric cancer. This can best be seen in the examples in Table S1.

A published study [25] based on machine learning models had previously performed LNM prediction. Recently, deep learning has provided us new insights into prediction models. FCNN is a deep learning method used in our study to predict LNM in patients with early gastric cancer. The AUC of FCNN was 0.79, which is slightly higher than other models, including 0.78 for nomogram, 0.76 for Decision tree, and 0.77 for the traditional machine method Naive Bayes. These models could predict LMN incidence for individual patient or entire cohorts, which should greatly help both clinicians and patients to make wiser and more customized decisions on treatment options. We further predicted the LNM risk of the ESD set using the FCNN method, and the result was 4.77%. We can conclude from these observations that patients with >5% LNM rates are more suited to receiving gastrectomy instead of ESD surgery.

Currently radiomics has allowed noninvasive approaches to extract quantitative features

from medical images, which has exhibited great potential in lymph node metastasis, not only for early stage [26] but also in locally advanced or advanced gastric cancer [27-29]. In addition, a published study showed that the collagen signature-associated prediction model in tumor microenvironment may be useful in the treatment decision-making process for patients with early gastric cancer [10]. Continued efforts are still needed to better predict LNM in patients with early gastric cancer at different levels in the future.

Several limitations need to be considered in this study. The gastrectomy set and ESD set were from total retrospective or bidirectional cohorts. Therefore, clinical trials are needed to verify and confirm the conclusions from this study. Additionally, we included patients who had been monitored for over 20 years, a significant length of time during which dramatic differences in LNM rates could be observed between different operative periods. Nonetheless, our unprecedented study clearly benefited from the large number of patients who were included and the diverse patient sources. Our data can therefore serve as a reference for future large-scale population-based studies in China.

In conclusion, this multi-cohort study systematically investigated different LNM prediction methods for patients with early gastric cancer. These models were validated and shown as reliable with AUC>0.76 for all. Specifically, the FCNN model proved to be the most accurate in predicting LNM in early gastric cancer patients with AUC=0.79. Based on this model, patients with a LNM rate of >4.77% are strongly recommend to receive gastrectomy rather than ESD surgery.

Acknowledgements

This work was supported by the grant from National Key R&D Program of China (No. 2017YFC0908300) and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2021-RC310-009).

Disclosure of conflict of interest

None.

Address correspondence to: Mingyan He, Gansu Provincial Cancer Hospital, Lanzhou, Gansu, China. E-mail: 119273873@qq.com; Quanlin Guan, The First Hospital of Lanzhou University, Lanzhou, Gansu, China. E-mail: guanquanlin@163.com; Yumin Li, Lanzhou University Second Hospital, Lanzhou, Gansu, China. E-mail: liym@lzu.edu.cn; Yongzhan Nie and Kaichun Wu, State Key Laboratory of Cancer Biology and National Clinical Research Center for Digestive Diseases, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, China. E-mail: yongznie@fmmu.edu.cn (YZN); kaicwu@fmmu.edu.cn (KCW); Dongbing Zhao and Yingtai Chen, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. E-mail: dbzhao2003@sina.com (DBZ); yingtaichen@126.com (YTC)

References

[1] Choi IJ, Kook MC, Kim YI, Cho SJ, Lee JY, Kim CG, Park B and Nam BH. Helicobacter pylori therapy for the prevention of metachronous gastric Cancer. N Engl J Med 2018; 378: 1085-1095.

[2] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021; 24: 1-21.

[3] Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y and Fujimoto K. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021; 33: 4-20.

[4] Renzulli M, Clemente A, Spinelli D, Ierardi AM, Marasco G, Farina D, Brocchi S, Ravaioli M, Pettinari I, Cescon M, Reginelli A, Cappabianca S, Carrafiello G and Golfieri R. Gastric cancer staging: is it time for magnetic resonance imaging? Cancers (Basel) 2020; 12: 1402.

[5] Wei J, Zhang Y, Liu Y, Wang A, Fan B, Fu T, Jia Z, He L, Ji K, Ji X, Wu X, Zhang J, Li Z, Zhang L, Bu Z and Ji J. Construction and validation of a risk-scoring model that preoperatively predicts lymph node metastasis in early gastric cancer patients. Ann Surg Oncol 2021; 28: 6665-6672.

[6] Mu J, Jia Z, Yao W, Song J, Cao X, Jiang J and Wang Q. Predicting lymph node metastasis in early gastric cancer patients: development and validation of a model. Future Oncol 2019; 15: 3609-3617.

[7] Zhang M, Ding C, Xu L, Feng S, Ling Y, Guo J, Liang Y, Zhou Z, Chen Y and Qiu H. A nomo-

gram to predict risk of lymph node metastasis in early gastric cancer. Sci Rep 2021; 11: 22873.
[8] Wang Z, Liu J, Luo Y, Xu Y, Liu X, Wei L and Zhu Q. Establishment and verification of a nomogram for predicting the risk of lymph node metastasis in early gastric cancer. Rev Esp Enferm Dig 2021; 113: 411-417.
[9] Kim SM, Lee H, Min BH, Kim JJ, An JY, Choi MG, Bae JM, Kim S, Sohn TS and Lee JH. A prediction model for lymph node metastasis in early-stage gastric cancer: toward tailored lymphadenectomy. J Surg Oncol 2019; 120: 670-675.
[10] Chen D, Chen G, Jiang W, Fu M, Liu W, Sui J, Xu S, Liu Z, Zheng X, Chi L, Lin D, Li K, Chen W, Zuo N, Lu J, Chen J, Li G, Zhuo S and Yan J. Association of the collagen signature in the tumor microenvironment with lymph node metastasis in early gastric cancer. JAMA Surg 2019; 154: e185249.
[11] Schmitz R, Madesta F, Nielsen M, Krause J, Steurer S, Werner R and Rösch T. Multi-scale fully convolutional neural networks for histopathology image segmentation: from nuclear aberrations to the global tissue architecture. Med Image Anal 2021; 70: 101996.
[12] Caradu C, Spampinato B, Bérard X, Ducasse E and Stenson K. Artificial intelligence for fully automatic segmentation of abdominal aortic aneurysm using convolutional neural networks. J Vasc Surg 2021; 74: 348.
[13] Kawahara J, Brown CJ, Miller SP, Booth BG, Chau V, Grunau RE, Zwicker JG and Hamarneh G. BrainNetCNN: convolutional neural networks for brain networks; towards predicting neurodevelopment. Neuroimage 2017; 146: 1038-1049.
[14] Shelhamer E, Long J and Darrell T. Fully convolutional networks for semantic segmentation. IEEE Trans Pattern Anal Mach Intell 2017; 39: 640-651.
[15] Milhomem LM, Milhomem-Cardoso DM, da Mota OM, Mota ED, Kagan A and Filho JBS. Risk of lymph node metastasis in early gastric cancer and indications for endoscopic resection: is it worth applying the east rules to the west? Surg Endosc 2021; 35: 4380-4388.
[16] Oh YJ, Kim DH, Han WH, Eom BW, Kim YI, Yoon HM, Lee JY, Kim CG, Kook MC, Choi IJ, Kim YW and Ryu KW. Risk factors for lymph node metastasis in early gastric cancer without lymphatic invasion after endoscopic submucosal dissection. Eur J Surg Oncol 2021; 47: 3059-3063.
[17] Min BH, Kim SM, Ahn JH, Jung SH, An JY, Choi MG, Sohn TS, Bae JM, Kim S, Lee H, Lee JH, Kim YW, Ryu KW, Kim JJ and Lee JH. Nomogram to predict lymph node metastasis in patients with early gastric cancer: a useful clinical tool to reduce gastrectomy after endoscopic resection. Endoscopy 2020; 52: 435-443.
[18] Wada T, Yoshikawa T, Kamiya A, Date K, Hayashi T, Otsuki S, Yamagata Y, Katai H and Nishida T. A nodal diagnosis by computed tomography is unreliable for patients who need additional gastrectomy after endoscopic submucosal dissection. Surg Today 2020; 50: 1032-1038.
[19] Koide N, Takeuchi D, Suzuki A, Ishizone S and Miyagawa S. Additional gastrectomy after endoscopic submucosal dissection for early gastric cancer patients with comorbidities. Int J Surg Oncol 2012; 2012: 379210.
[20] Aoyama J, Sakuramoto S, Miyawaki Y, Ito M, Ito S, Watanabe K, Oya S, Fujiwara N, Sugita H, Nonaka K, Sato H, Yasuda M and Yamaguchi S. Impact of endoscopic resection on the choice of surgical procedure in patients with additional laparoscopic gastrectomy. Gastric Cancer 2020; 23: 913-921.
[21] Tian YT, Ma FH, Wang GQ, Zhang YM, Dou LZ, Xie YB, Zhong YX, Chen YT, Xu Q and Zhao DB. Additional laparoscopic gastrectomy after noncurative endoscopic submucosal dissection for early gastric cancer: a single-center experience. World J Gastroenterol 2019; 25: 3996-4006.
[22] Lorenzo D, Ochoa M, Piulats JM, Gutiérrez C, Arias L, Català J, Grau M, Peñafiel J, Cobos E, Garcia-Bru P, Rubio MJ, Padrón-Pérez N, Dias B, Pera J and Caminal JM. Prognostic factors and decision tree for long-term survival in metastatic uveal melanoma. Cancer Res Treat 2018; 50: 1130-1139.
[23] Romero MP, Chang YM, Brunton LA, Parry J, Prosser A, Upton P, Rees E, Tearne O, Arnold M, Stevens K and Drewe JA. Decision tree machine learning applied to bovine tuberculosis risk factors to aid disease control decision making. Prev Vet Med 2020; 175: 104860.
[24] Jang Y, Kim S, Kim K and Lee D. Deep learning-based classification with improved time resolution for physical activities of children. PeerJ 2018; 6: e5764.
[25] Zhu H, Wang G, Zheng J, Zhu H, Huang J, Luo E, Hu X, Wei Y, Wang C, Xu A and He X. Preoperative prediction for lymph node metastasis in early gastric cancer by interpretable machine learning models: a multicenter study. Surgery 2022; 171: 1543-1551.
[26] Gao X, Ma T, Cui J, Zhang Y, Wang L, Li H and Ye Z. A CT-based radiomics model for prediction of lymph node metastasis in early stage gastric cancer. Acad Radiol 2021; 28: e155-e164.
[27] Dong D, Fang MJ, Tang L, Shan XH, Gao JB, Giganti F, Wang RP, Chen X, Wang XX, Palumbo D, Fu J, Li WC, Li J, Zhong LZ, De Cobelli F, Ji JF, Liu ZY and Tian J. Deep learning radiomic no-

mogram can predict the number of lymph node metastasis in locally advanced gastric cancer: an international multicenter study. Ann Oncol 2020; 31: 912-920.

[28] Wang Y, Liu W, Yu Y, Liu JJ, Xue HD, Qi YF, Lei J, Yu JC and Jin ZY. CT radiomics nomogram for the preoperative prediction of lymph node metastasis in gastric cancer. Eur Radiol 2020; 30: 976-986.

[29] Li J, Dong D, Fang M, Wang R, Tian J, Li H and Gao J. Dual-energy CT-based deep learning radiomics can improve lymph node metastasis risk prediction for gastric cancer. Eur Radiol 2020; 30: 2324-2333.

Table S1. Examples of LNM risk prediction using the Decision Tree in patients with early gastric cancer

	Patients 01	Patients 02	Patients 03	Patients 04	Patients 05
Vascular invasion	Yes	No	Yes	No	No
Grade	Poorly	Moderately	Well	Well-moderately	Poorly
pT stage	pT1a	pT1b	pT1a	pT1b	pT1a
Tumor size	4.1 cm	5.8 cm	2.6 cm	2.0 cm	4.4 cm
Gender	Male	Male	Female	Male	Male
Prediction LNM risk (%)	55.13	15.63	16.67	2.94	14.71

Table S2. Model structure of used FCNN

Number	Layer type	Kernel number	Kernel size	Activation
1	Convolution	32	3	ReLU
2	Max-pooling	-	-	-
3	Convolution	16	3	ReLU
4	Fully-connected	1	4	-
5	Fully-connected	1	1	sigmoid

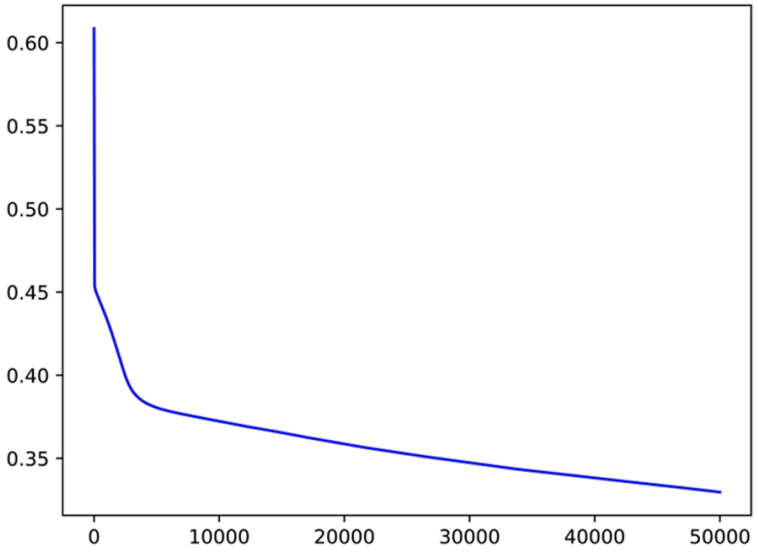

Figure S1. The loss curve of FCNN model for LNM prediction.