Heliyon 11 (2025) e41197

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Construction and evaluation of the prediction model for advanced disease in well-differentiated colorectal neuroendocrine neoplasms less than 2 cm in diameter

Hongda Yin [a,1], Yanan Chen [b,1], Wei Zhao [c], Fuqiang Zhao [c], Zhijun Huang [d], Aimin Yue [a,*], Zhijie Wang [e,**]

[a] *Abdominal Surgical Oncology Ward, Xinxiang Central Hospital, The Forth Clinical College of Xinxiang Medical University, Xinxiang, 453000, China*

[b] *Department of Gastroenterology, Nanchong Central Hospital, The Second Clinical Medical College of North Sichuan Medical College, Nanchong, 637000, China*

[c] *Department of Colorectal Surgery, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China*

[d] *Outpatient Department, Strategic Support Force Medical Center, Beijing, 100101, China*

[e] *Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Gastrointestinal Cancer Center, Peking University Cancer Hospital & Institute, Beijing, 100142, China*

ARTICLE INFO

Keywords:
Colon
Rectum
Neuroendocrine
Neoplasm
Nomogram

ABSTRACT

Objective: Advanced lesions are often ignored in well-differentiated colorectal neuroendocrine neoplasms (NENs) smaller than 2 cm, and we aimed to develop an effective nomogram for these lesions.

Methods: We extracted data from the Surveillance, Epidemiology, and End Results (SEER) database and used a logistic regression model to identify independent risk factors for advanced disease. All these identified factors were included to construct the prediction model, and the receiver operating characteristic (ROC) curve, calibration plot and DCA curve were utilized to assess the predictive value. The data obtained from the National Cancer Center were utilized for external validation.

Results: In total, 3223 patients were enrolled in the training set, including 2947 (91.4 %) with early disease and 276 (8.6 %) with advanced disease. The logistic analysis showed that age (odds ratio (OR) = 1.486, 95 % confidence interval (CI): 1.102–2.003, P = 0.009), tumor size (OR = 11.071, 95 % CI: 8.229–14.893, P < 0.001), tumor location (OR = 7.882, 95 % CI: 5.784–10.743, P < 0.001) and tumor grade (OR = 1.768, 95 % CI: 1.206–2.593, P = 0.004) were independent variables for advanced disease. All of them were included in the final prediction model. The area under the ROC curve (AUC) was 0.838 (95 % CI: 0.807–0.868). The calibration plot and Hosmer–Lemeshow test (P = 0.108) indicated favorable consistency between the predicted probabilities and actual probabilities of advanced disease. The Brier score was 0.108, indicating acceptable overall performance. The DCA curve presented a significant clinical net benefit. In the validation

* Corresponding author. No.56 Jinsui Avenue, Weibin District, Xinxiang City, Henan Province, China.

** Corresponding author. No.52, Fucheng Road, Haidian District, Beijing, China.

E-mail addresses: yueaimin_a123@163.com (A. Yue), 1459046932@qq.com (Z. Wang).

[1] Hongda Yin and Yanan Chen contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.heliyon.2024.e41197

Received 9 March 2024; Received in revised form 30 June 2024; Accepted 12 December 2024

Available online 13 December 2024

set, both the ROC curve and calibration plot exhibited an acceptable discrimination ability (AUC = 0.807 (95 % CI 0.702–0.913) and calibration (Hosmer Lemeshow P = 0.997), respectively.
Conclusions: The prediction model had good value for identifying advanced disease from well-differentiated colorectal NENs smaller than 2 cm.

1. Introduction

Colorectal neuroendocrine neoplasms (NENs) are a group of rare diseases and constitute less than 1 % of all colorectal neoplasms [1]. However, epidemiological investigation based on the Surveillance, Epidemiology, and End Results (SEER) database indicated that their incidence has been rapidly increasing over the years and has become the second most common NENs in the whole body after the lung [2–4]. The most recent data from Kentucky (USA) showed that their incidence has reached 10.3 per 100000 [5]. Owing to their rarity, high-level evidence-based medical studies have not been fully performed thus far, and numerous clinical problems cannot be explored and elucidated [6].

Colorectal NENs are categorized into G1, G2 and G3 NENs based on the 2019 WHO classification of tumors of the digestive system [7]. G1 and G2 NENs are more common than G3 NENs and account for 74.0%–78.6 % of all colorectal NENs [8,9]. Compared to G3 NENs, G1 and G2 NENs are a group of indolent and well-differentiated diseases with a low proliferation index and low malignant potential. Most of them are diagnosed as diminutive lesions confined only in the mucosa and submucosa and need only local excision [10]. Considering their low risks of regional lymph node metastasis and distant metastasis, the previous European Neuroendocrine Tumor Society (ENETS) recommended that colorectal NENs less than 1 cm in diameter needed no imaging examinations and post-operative surveillance, and local excision was the mainstay for colorectal NENs below 2 cm[11].

However, clinical practice has shown that some well-differentiated colorectal NENs below 2 cm can still invade the muscularis propria, involve regional lymph nodes and even present distant metastasis [12–14]. Previous reports showed that 3.4%–14.6 % of these patients can present metastatic disease [15,16]. However, these patients may be misdiagnosed following previous ENENS guidelines. Considering the potential malignancy and aggressiveness, the latest 2023 ENETS consensus demonstrated a more cautious approach, updating its guidelines for the management of well-differentiated colorectal NENs below 2 cm [17]. It recommended a systematic evaluation of NENs measuring 1–2 cm and suggested a multidisciplinary discussion about either endoscopic or surgical therapy. Regular follow-up within 5 years postoperatively was also recommended. However, the identification of patients who require radical resection for these NENs remains challenging. Previous studies have suggested that conventional imaging techniques have difficulty detecting metastatic lesions in colorectal G1 and G2 NENs. Researches indicated that the size of metastatic lymph nodes was much smaller than that of adenocarcinoma metastatic lymph nodes, with over half of metastatic lymph nodes having a maximum diameter of less than 5 mm, averaging at 4.3 mm, and some having a maximum diameter of only 2–3 mm [18,19]. Therefore, the

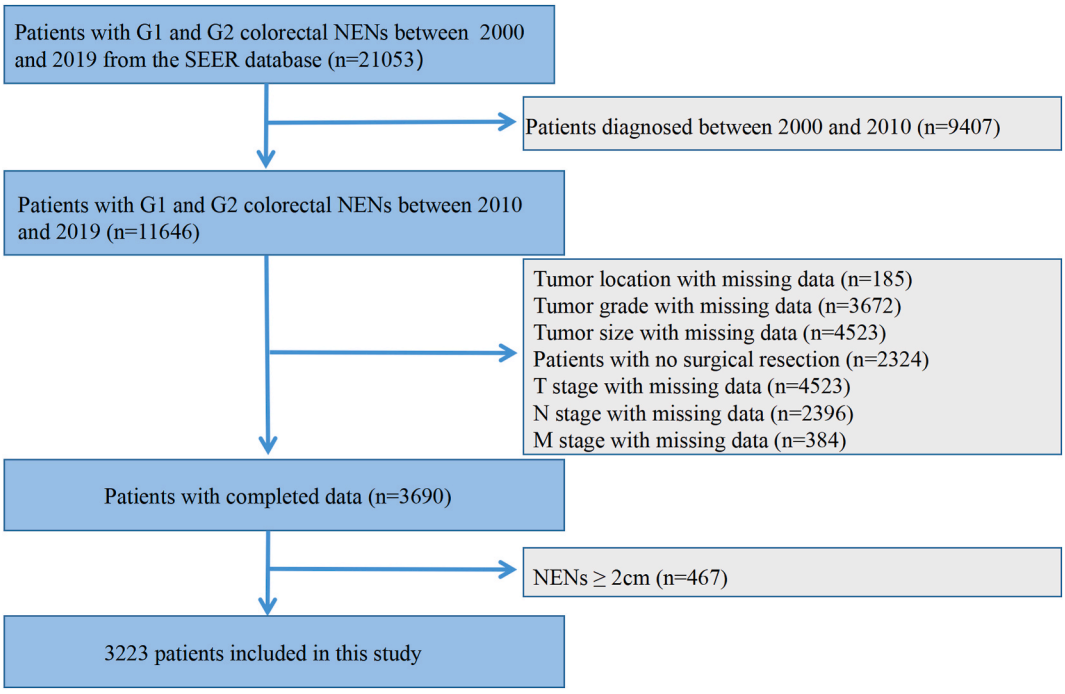

Fig. 1. Flow chart presenting the patients' enrollment in our study.

difficulty of detecting tumor metastasis using conventional imaging methods is significant, with a sensitivity of only 66.7 % [20]. Therefore, we planned to construct an effective and simple prediction model to identify advanced diseases for well-differentiated colorectal NENs below 2 cm.

2. Methods

2.1. Patients and data collection

Our study was approved by the Ethics Committee of National Cancer Center and was conducted in accordance with the principles outlined in the Declaration of Helsinki. We used SEER*Stat (8.4.0.1) and downloaded the dataset "incidence SEER Research Data, 17 Registries, Nov 2021 Sub (2000–2019)" from the SEER database. In addition, we retrieved data from the electronic medical system of National Cancer Center, including patients diagnosed between January 2010 and June 2023. The inclusion criteria were as follows: (1) all neoplasms were pathologically diagnosed as well-differentiated NENs; (2) all NENs were located in the colon and rectum; (3) all patients had primary NENs less than 2 cm in diameter; (4) all NENs were diagnosed between 2010 and 2019; and (5) all patients received surgical resection. The exclusion criteria were as follows: (1) poorly-differentiated NENs and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs); (2) patients who underwent no surgical resection; and (3) patients with incomplete clinicopathological data and survival data.

In total, we obtained 21053 patients with well-differentiated colorectal NENs from the SEER database, and 3223 patients were finally included in our study as the training set following the inclusion and exclusion criteria (Fig. 1). The variables downloaded from the SEER database included age of diagnosis, year of diagnosis, sex, race, tumor size, tumor location, tumor grade, T stage, N stage, M stage, TNM stage, treatment, survival outcome, survival time and cause of death. In addition, 131 patients from the National Cancer Center were obtained as the validation set. All patients from the National Cancer Center have signed an informed consent form before the study. We defined NENs of T1N0M0 as early disease and NENs invading the muscularis propria, with nodal or distant metastasis as

Table 1
The clinicopathological features of patients.

Variables	Training set (n = 3223)	Validation set (n = 131)
Age		
<60	2137 (66.3 %)	96 (73.3 %)
≥60	1086 (33.7 %)	35 (26.7 %)
Gender		
Male	1580 (49.0 %)	77 (58.8 %)
Female	1643 (51.0 %)	54 (41.2 %)
Race		
White	1782 (55.3 %)	0
Black	730 (22.6 %)	0
Asian and the Pacific islander	589 (18.3 %)	131 (100 %)
American Indian and Alaska native	19 (0.6 %)	0
Unknown	103 (3.2 %)	0
Tumor location		
Rectum	2773 (86.0 %)	129 (98.5 %)
Colon	450 (14.0 %)	2 (1.5 %)
Tumor size (cm)		
<1	2685 (83.3 %)	68 (51.9 %)
1-2	538 (16.7 %)	63 (48.1 %)
Tumor Grade		
G1	2840 (88.1 %)	116 (88.5 %)
G2	383 (11.9 %)	15 (11.5 %)
T stage		
T1	3003 (93.2 %)	119 (90.8 %)
T2	123 (3.8 %)	10 (7.6 %)
T3	76 (2.4 %)	1 (0.8 %)
T4	21 (0.7 %)	1 (0.8 %)
N stage		
N0	3073 (95.3 %)	125 (95.4 %)
N1	150 (4.7 %)	6 (4.6 %)
M stage		
M0	3189 (98.9 %)	130 (99.2 %)
M1	34 (1.1 %)	1 (0.8 %)
TNM stage		
I	2947 (91.4 %)	115 (87.8 %)
II	109 (3.4 %)	8 (6.1 %)
III	133 (4.1 %)	7 (5.3 %)
IV	34 (1.1 %)	1 (0.8 %)
Extent of disease		
Early disease	2947 (91.4 %)	115 (87.8 %)
Advanced disease	276 (8.6 %)	16 (12.2 %)

advanced disease.

2.2. Statistical analysis

The data are presented as frequencies with percentages. Univariate and multivariate logistic regression analyses were performed in the training set to identify the independent risk factors for advanced disease. Odds ratios (ORs) were also reported with 95 % confidence intervals (CIs). The identified independent risk factors were subsequently included in the final logistic regression analysis to construct a prediction model for advanced disease. The nomogram was drawn based on the final regression model. Each variable was assigned a score based on its regression coefficient, with higher regression coefficient values receiving higher scores. The optimal cutoff value of the total score was obtained at the highest Youden index (sensitivity + specificity − 1). The receiver operating characteristic (ROC) curve and area under the curve (AUC) value were used to evaluate the discriminability, and the calibration curve and Hosmer–Lemeshow goodness-of-fit test were used to assess the calibration. The Brier score was calculated to measure the overall performance of the model. Finally, the clinical net benefit was assessed by decision curve analysis (DCA).

The external validation was performed using the validation set. Each patient in the validation set was assigned a score according the scoring system developed using the training set and received their probability of advanced disease based on the nomogram. Patients with scores below the cutoff value were considered to have early NENs, while patients with scores equal to or higher than the cutoff value were considered to have advanced NENs. ROC curve and calibration plot were generated to evaluate the discriminability and calibration of the nomogram.

The Kaplan–Meier curves were used to calculate the overall survival (OS) rates. Log-rank tests were utilized to compare differences between the groups. Univariate and multivariate Cox regression analyses were used to identify the independent risk factors affecting prognosis. Hazard ratios (HRs) were also reported with 95 % confidence intervals (CIs). Statistical significance was set at a two-sided P value < 0.05. All statistical analyses were performed using R software version 4.1.2 (https://www.r-project. org/).

3. Results

3.1. The clinicopathological features of patients

In total, we included 3223 and 131 patients with well-differentiated colorectal NENs <2 cm in size in the training set and validation set, respectively (Table 1). We defined patients with T1N0M0 as having early disease, and the remaining patients were defined as having advanced disease. Therefore, 276 (8.6 %) and 16 (12.2 %) patients had advanced disease in the training set and validation set, respectively. In the training set, 2137 (66.3 %) patients were below 60 years old, and 1580 (49.0 %) were male. More than half (55.3 %) of the patients were white, black patients constituted 22.6 %, and Asian and Pacific islanders accounted for 18.3 % of all individuals. Most patients (86.0 %) had their NENs located in the rectum, and only 14.0 % of them had colonic NENs. In terms of tumor size, 2685 (83.3 %) had NENs smaller than 1 cm in size, and the other 538 (16.7 %) had NENs between 1 and 2 cm. Regarding tumor grade, 2840 (88.1 %) and 383 (11.9 %) had G1 and G2 NENs, respectively. Regarding the depth of tumor invasion, 93.2 %, 3.8 %, 2.4 % and 0.7 % of them had T1, T2, T3 and T4 disease, respectively. One hundred and fifty (4.7 %) and 34 (1.1 %) patients had regional

Table 2
Univariate and multivairate logistic regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P	OR (95 % CI)	P
Age				
<60	1		1	
≥60	2.042 (1.593–2.618)	<0.001	1.486 (1.102–2.003)	0.009
Gender				
Male	1			
Female	0.809 (0.631–1.037)	0.094		
Race				
White	1		1	
Black	0.627 (0.453–0.868)	0.005	0.834 (0.571–1.218)	0.347
Asian and the Pacific islander	0.588 (0.410–0.845)	0.004	0.940 (0.621–1.424)	0.771
American Indian and Alaska native	0.474 (0.063–3.570)	0.469	0.722 (0.088–5.906)	0.761
Unknown	NA	0.996	NA	0.996
Tumor location				
Rectum	1		1	
Colon	10.897 (8.354–14.213)	<0.001	7.882 (5.784–10.743)	<0.001
Tumor size (cm)				
<1	1		1	
1-2	14.650 (11.141–19.264)	<0.001	11.071 (8.229–14.893)	<0.001
Tumor Grade				
G1	1		1	
G2	2.370 (1.746–3.217)	<0.001	1.768 (1.206–2.593)	0.004

NA: not available.

nodal metastasis and distant metastasis, respectively.

A higher proportion of patients in the validation set were younger than 60 years old, male, of Asian and Pacific islander descent, with tumors located in the rectum, larger than 1 cm in size, compared to the training set.

3.2. Univariate and multivariate analyses

In the training set, the univariate analysis revealed several significant associations. Patients who were over 60 years old (OR = 2.042, 95 % CI: 1.593–2.618, P < 0.001), had colon neuroendocrine neoplasms (OR = 10.897, 95 % CI: 8.354–14.213, P < 0.001), G2 neuroendocrine neoplasms (OR = 2.370, 95 % CI: 1.746–3.217, P < 0.001), or tumors larger than 1 cm (OR = 14.650, 95 % CI: 11.141–19.264, P < 0.001), were more likely to have advanced disease. On the other hand, black patients (OR = 0.627, 95 % CI: 0.453–0.868, P = 0.005) and Asian and Pacific Islander patients (OR = 0.588, 95 % CI: 0.410–0.845, P = 0.004) had a lower likelihood of advanced disease compared to white individuals (Table 2). All these variables were subsequently included in the multivariate logistic regression analysis (Table 2). Ultimately, age (OR = 1.486, 95 % CI: 1.102–2.003, P = 0.009), tumor location (OR = 7.882, 95 % CI: 5.784–10.743, P < 0.001), tumor size (OR = 11.071, 95 % CI: 8.229–14.893, P < 0.001) and tumor grade (OR = 1.768, 95 % CI: 1.206–2.593, P = 0.004) were independent risk factors for advanced disease.

3.3. Development of the prediction model

All the independent risk factors were included in the final logistic regression analysis to construct the prediction model. Each variable was scored based on the results of the logistic model. Patients <60 years old, ≥60 years old; tumor size of <1 cm, 1–2 cm; tumor location of the rectum and colon; grade of G1 and G2 were assigned a score of 0, 17, 0, 100, 0, 86, 0 and 24, respectively. The total score ranged from 0 to 227, and the possibility of advanced disease could be obtained based on the scores that patients received (Fig. 2). According to the maximal Youden index, the optimal cutoff value was set at 93, and patients with scores of 93 or more were identified as having a high risk of advanced disease, while patients with scores below 93 were regarded as having a low risk of advanced disease. At a score of 93, the sensitivity and specificity were 72.8 % and 84.5 %, respectively.

Based on the prediction model, patients with G1 and G2 neuroendocrine neoplasms (NENs) smaller than 2 cm were stratified into different risk groups (Fig. 3). Rectal NENs measuring below 1 cm were categorized as low-risk of advanced disease. Furthermore, patients with colonic NENs smaller than 1 cm, aged younger than 60 years, and with a tumor grading of G1 were also classified as low-risk of advanced disease. Conversely, patients with colonic NENs smaller than 1 cm, aged 60 years or older, or with a tumor grading of G2, were categorized as high-risk of advanced disease. Additionally, all NENs larger than 1 cm were classified as high-risk of advanced disease.

3.4. Evaluation of the prediction model

The ROC curve was drawn based on the prediction model (Fig. 4A). The AUC value was 0.838 (95 % CI: 0.807–0.868), which indicated acceptable discriminability of this model. The calibration curve is also presented (Fig. 4B). Both the calibration curve and the Hosmer–Lemeshow test (P = 0.108) showed a favorable consistency between the predicted possibilities and actual possibilities of patients with advanced disease. The Brier score was 0.052, which indicated a good overall performance of the prediction model. The DCA curve indicated that the model provided a significant net benefit over "treat-all" or "treat-none" strategies at high-risk threshold probabilities between 0.03 and 0.80 (Fig. 5).

The external validation was performed using the validation set. The ROC curve (AUC = 0.807 (95 % CI 0.702–0.913) indicated that the nomogram had acceptable predictive ability for advanced disease (Fig. 6A). The calibration plot (Fig. 6B) and Hosmer–Lemeshow test (P = 0.997) demonstrated satisfactory model calibration.

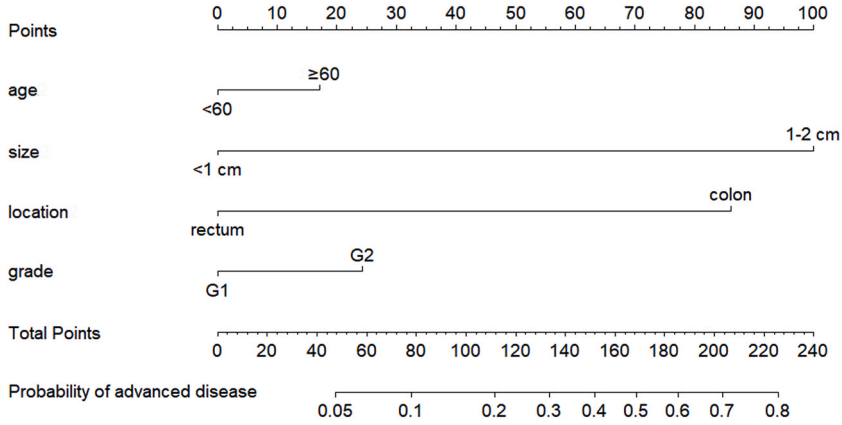

Fig. 2. Nomogram for advanced disease in well-differentiated colorectal NENs measuring smaller than 2 cm.

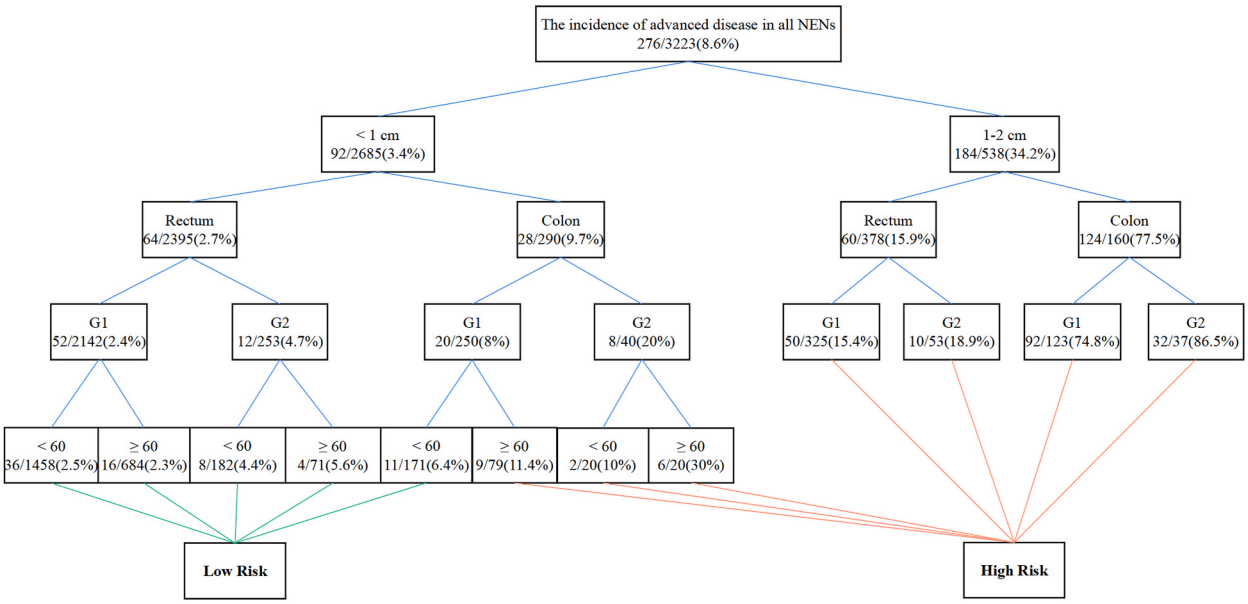

Fig. 3. Classification tree identifying the groups at high and low risk for advanced disease.

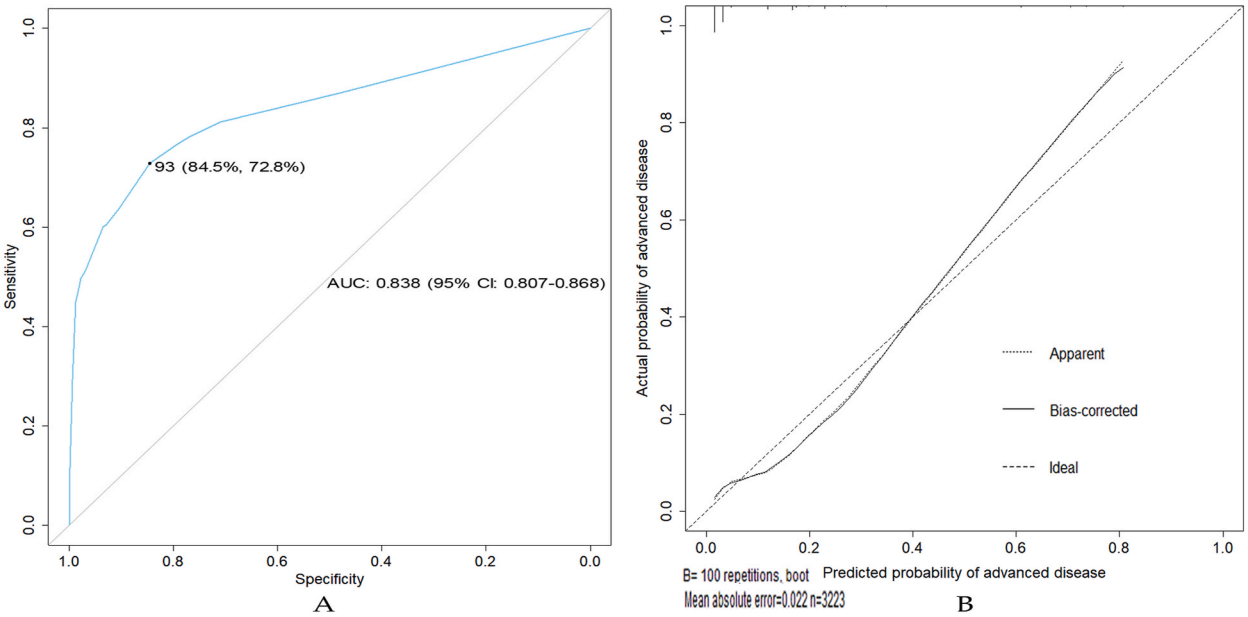

Fig. 4. Evaluations of the predictive value of the nomogram for advanced disease. A: ROC curve. B: calibration plot. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

3.5. Oncological outcomes

The survival analysis was performed using the data from the SEER database. The 3-year, 5-year and 10-year OS rates were 97.2 %, 95.0 % and 90.4 % for patients with low score (total score <93), respectively. For patients with high score (total score ≥93), the 3-year, 5-year and 10-year OS rates were 93.2 %, 88.0 % and 77.9 %, respectively. The scoring system could help identify patients with shorter OS, and patients with high score had significantly worse OS than patients with low score (Fig. 7). The univariate Cox regression analysis demonstrated that age, sex, race, tumor size, tumor grade, tumor location and tumor stage were all significantly associated with OS. The multivariate Cox regression analysis showed that age ≥60 (HR = 5.147, 95 % CI: 3.677–7.204, P < 0.001), female sex (HR = 0.654, 95 % CI: 0.484–0.883, P = 0.006), black individuals (HR = 1.485, 95 % CI: 1.057–2.085, P = 0.022), G2 NEN (HR = 1.562, 95 % CI: 1.084–2.250, P = 0.017) and advanced disease (HR = 2.182, 95 % CI: 1.361–3.497, P = 0.001) were risk factors for

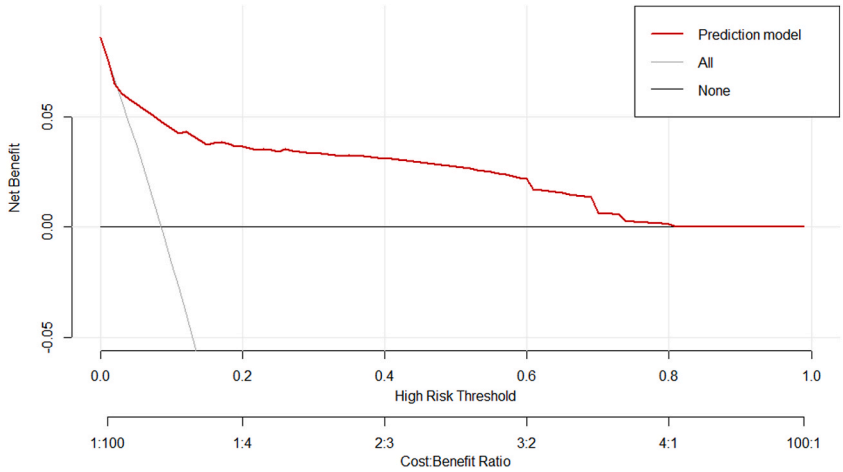

Fig. 5. The DCA curve evaluating the net benefit of the nomogram. DCA: decision curve analysis.

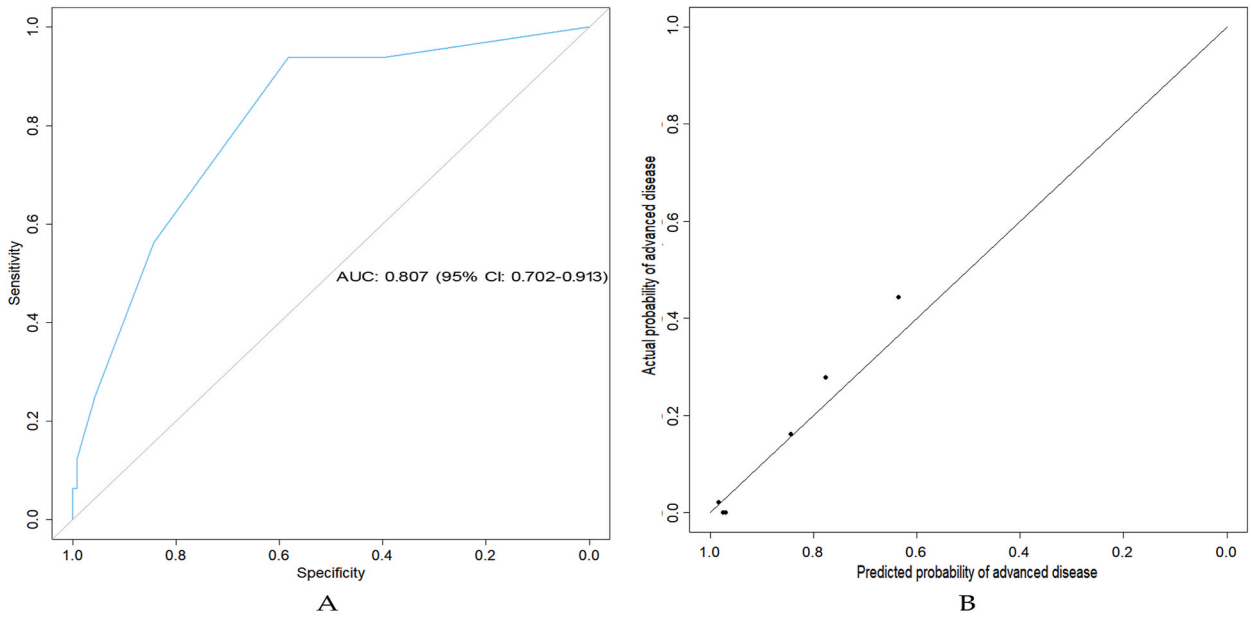

Fig. 6. The external validation of the predictive value of the nomogram for advanced disease. A: ROC curve. B: calibration plot. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

worse OS, while Asian and Pacific Islander individuals (HR = 0.608, 95 % CI: 0.374–0.989, P = 0.001) had better OS than white patients (Table 3).

4. Discussion

Well-differentiated NENs below 2 cm are the most common colorectal NENs and are regarded as a group of benign diseases by many physicians and patients. Therefore, local excision has been the main choice for this type of disease, and a favorable prognosis has been confirmed before [21]. However, owing to the increase in their incidence in recent years, NENs invading the muscularis propria or with tumor metastasis have indeed been reported in numerous studies [13,22,23].

The European Neuroendocrine Tumor Society (ENETS) guidelines and the North American Neuroendocrine Tumor Society (NANETS) guidelines were the mainstay of the management of colorectal NENs. However, they were divided for the management of well-differentiated colorectal NENs smaller than 2 cm. The ENETS guidelines recommended local excision for these patients. For well-differentiated colorectal NENs smaller than 1 cm, the ENETS guidelines do not recommend preoperative systematic examinations and postoperative surveillance [11]. The NANETS guidelines recommended local excision only for rectum NENs. For cecal NENs, they recommended radical resection. For the rest of colonic NENs, the NANETS guidelines present an ambiguous attitude. Regarding

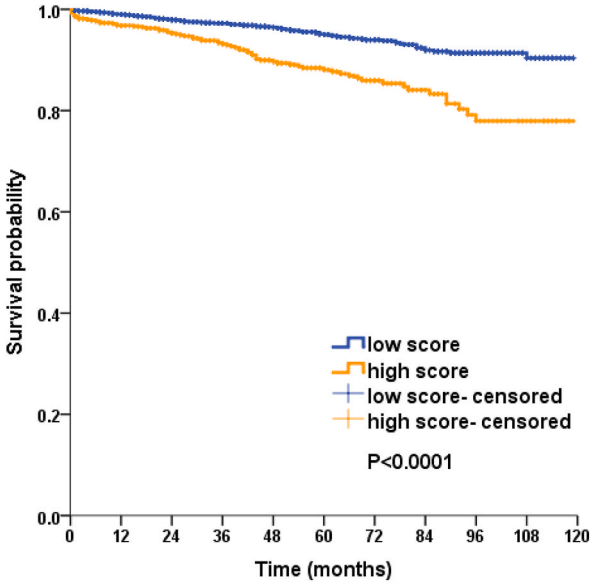

Fig. 7. The Kaplan-Meier curve of overall survival.

Table 3
Univariate and multivairate cox regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P	HR (95 % CI)	P
Age				
<60	1		1	
≥60	5.461 (3.911–7.623)	<0.001	5.147 (3.677–7.204)	<0.001
Gender				
Male	1		1	
Female	0.725 (0.538–0.976)	0.034	0.654 (0.484–0.883)	0.006
Race				
White	1		1	
Black	1.220 (0.874–1.704)	0.242	1.485 (1.057–2.085)	0.022
Asian and the Pacific islander	0.564 (0.349–0.910)	0.019	0.608 (0.374–0.989)	0.045
American Indian and Alaska native	2.539 (0.805–8.005)	0.112	2.689 (0.847–8.534)	0.093
Unknown	NA	NA	NA	NA
Tumor location				
Rectum	1		1	
Colon	2.266 (1.630–3.151)	<0.001	1.354 (0.914–2.005)	0.131
Tumor size (cm)				
<1	1		1	
1-2	1.912 (1.378–2.652)	<0.001	1.056 (0.707–1.577)	0.791
Tumor Grade				
G1	1		1	
G2	1.743 (1.217–2.496)	0.002	1.562 (1.084–2.250)	0.017
Extent of disease				
Early disease	1		1	
Advanced disease	3.301 (2.328–4.681)	<0.001	2.182 (1.361–3.497)	0.001

NA: not available.

preoperative and postoperative management strategies, they recommended no need for preoperative systematic examinations and postoperative surveillance for well-differentiated rectal NENs smaller than 2 cm. For well-differentiated colonic NENs, the NANETS guidelines presented a more prudent attitude [24,25].

However, advanced disease may be ignored by following the current consensus, especially nodal metastasis and distant metastasis. Some researchers use publicly available large clinical databases or small single-center retrospective data to explore the risk factors for colorectal NENs metastasis and attempt to integrate these factors to build clinical prediction models. Although these models demonstrate satisfactory predictive performance, their limitations make them still difficult to apply to address real clinical issues [8,26,27]. First, most models include a large number of variables, making the evaluation system complex, and some variables are difficult to obtain through preoperative routine examinations, making practical implementation difficult and feasibility poor. Second, these

existing models incorporate all colorectal NENs pathological types into model construction, whereas colorectal NENs are a highly heterogeneous tumor type, and a universal model may not fit well with all pathological subtypes. Third, most existing models lack external validation, and the reliability of their predictive results has not been thoroughly verified. Our study included age, tumor grade, tumor location and tumor size and developed a novel and effective model to predict the risks of advanced disease, which might be simpler and more feasible than previous models. Physicians can calculate the total scores each patient obtains before surgical therapy, and patients with scores $\geq$93 have a high possibility of advanced disease.

For NENs smaller than 1 cm and located in the rectum, their scores were below 93 regardless of age and tumor grade, and the probabilities of advanced disease were only 2.7 %. Therefore, systematic examinations can be avoided if endoscopic ultrasonography indicates no signs of tumors invading the muscularis propria or involved regional lymph nodes, and local excision can be performed, which is consistent with the consensus of both ENETS and NANETS [11,24]. For NENS smaller than 1 cm and located in the colon, the clinical decisions depend on age and tumor grade. If the patients are under 60 years old and the tumors are grade G1, their total scores will be 86, and the probabilities of advanced disease will be only 6.4 %, and they should be classified into the low-risk group and try to receive endoscopic resection. However, if the patients are 60 years old and above or have G2 NEN, their score will exceed 93 and they will be classified into the high-risk group, and their probabilities of advanced disease range from 10.0% to 35.0 %. Careful systematic examination should be performed to evaluate the depth of tumor invasion and regional lymph nodes and distant organs. Radical surgery with lymphadenectomy may be performed to avoid residual tumors.

For colorectal NENs of 1–2 cm in size, there has been widespread controversy about their management strategies. Our study indicated that these patients can score over 93 regardless of their age, tumor grade and tumor location, and the overall probability of advanced disease was 34.2 %. For G2 NENs, the probability was 46.7 %. For NENs located in the colon, the probabilities reached 77.5 %. For NENs that were both G2 and located in the colon, the probabilities reached 86.5 %. Given the high risk of advanced disease in colorectal NENs of 1–2 cm in size, we recommended meticulous evaluation of the status of regional lymph nodes and distant organs. Specifically, for rectum NENs, pelvic magnetic resonance imaging should be performed to assess the status of lateral lymph nodes, as lateral lymph node metastasis has been frequently reported in recent reports [28–30]. Octreotide PET-CT can be performed if routine techniques have difficulty distinguishing metastatic disease from benign lesions [31]. With regard to the treatment method, we recommend radical resection with lymphadenectomy instead of local excision after excluding widespread metastatic disease.

Our study has the following limitations. First, we used public data to construct the prediction model, but the available variables used to construct the nomogram were limited. Variables such as macroscopic features of tumors also had value in predicting advanced disease but were not included in the nomogram, as they were not available in SEER data [26,32]. Furthermore, due to limited variables that could be collected, we were unable to conduct in-depth stratified analysis based on regional disparities, dietary habits, and lifestyle factors to reveal more detailed insights and enhance the precision of the model. Second, the retrospective nature of our study made the bias from patient selection and data collection difficult to avoid. Conducting prospective clinical studies may effectively reduce selection bias and information bias. Third, we were limited to utilizing a single external validation dataset for validation purposes. Given the scarcity of colorectal NENs, this validation dataset had a constrained sample size. To enhance the robustness of our model and ensure its applicability across diverse populations, it is imperative that we seek additional external validation datasets from regions beyond Asia in future endeavors.

5. Conclusion

In summary, we developed a feasible and effective prediction model to identify advanced disease for well-differentiated colorectal NENs smaller than 2 cm. The model showed an acceptable capacity for both discriminability and calibration. For clinical questions that are controversial in the current consensus, our model can provide a clear recommendation after comprehensive consideration of age, tumor location, tumor size and tumor grade. Our model shows that colonic NENs have a significantly higher risk of advanced disease than rectal NENs, even when their size is less than 1 cm. In the future, we can explore the molecular biological differences between colonic and rectal NENs and investigate through clinical cohorts whether colonic NENs are suitable for endoscopic resection.

CRediT authorship contribution statement

Hongda Yin: Writing – original draft, Data curation. **Yanan Chen:** Formal analysis. **Wei Zhao:** Data curation. **Fuqiang Zhao:** Data curation. **Zhijun Huang:** Data curation. **Aimin Yue:** Writing – review & editing, Conceptualization. **Zhijie Wang:** Writing – review & editing, Conceptualization.

Data availability statement

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

Ethics approval statement

This study was approved by the Ethics Committee of National Cancer Center.

Funding statement

This work was funded by the following grants: Joint Construction Project of Health Science and Technology R&D Program in Henan Province (No.LHGJ20230884), Joint Construction Project of Henan Province Medical Science and Technology Tackling Key Problems Program (No. LHGJ20210913) and Joint Construction Project of Henan Province Medical Science and Technology Tackling Key Problems Program (No. LHG20220998).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H. Shafqat, S. Ali, M. Salhab, A.J. Olszewski, Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis, Dis. Colon Rectum 58 (3) (2015) 294–303.
[2] J.C. Yao, M. Hassan, A. Phan, et al., One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States, J. Clin. Oncol. 26 (18) (2008) 3063–3072.
[3] V.L. Tsikitis, B.C. Wertheim, M.A. Guerrero, Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis, J. Cancer 3 (2012) 292–302.
[4] A. Dasari, C. Shen, D. Halperin, et al., Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States, JAMA Oncol. 3 (10) (2017) 1335–1342.
[5] A. Chauhan, Q. Yu, N. Ray, et al., Global burden of neuroendocrine tumors and changing incidence in Kentucky, Oncotarget 9 (27) (2018) 19245–19254.
[6] A. Chauhan, E. Kohn, J. Del Rivero, Neuroendocrine tumors-less well known, often misunderstood, and rapidly growing in incidence, JAMA Oncol. 6 (1) (2020) 21–22.
[7] I.D. Nagtegaal, R.D. Odze, D. Klimstra, et al., The 2019 WHO classification of tumours of the digestive system, Histopathology 76 (2) (2020) 182–188.
[8] X. Ding, S. Tian, J. Hu, et al., Risk and prognostic nomograms for colorectal neuroendocrine neoplasm with liver metastasis: a population-based study, Int. J. Colorectal Dis. 36 (9) (2021) 1915–1927.
[9] K. Xiao, Y. Zhao, Y. Cai, et al., The effect of marital status on the survival of patients with colorectal neuroendocrine neoplasms: an analysis of the SEER database, Rev. Esp. Enferm. Dig. 112 (2) (2020) 109–117.
[10] R.H. Al Natour, M.S. Saund, V.M. Sanchez, et al., Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection, J. Gastrointest. Surg. 16 (3) (2012) 595–602.
[11] M. Caplin, A. Sundin, O. Nillson, et al., ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms, Neuroendocrinology 95 (2) (2012) 88–97.
[12] T. Saito, M. Ikenaga, M. Yasui, et al., [A case of 7 mm rectal carcinoid with lymph node metastasis], Gan To Kagaku Ryoho 36 (12) (2009) 2251–2253.
[13] S. Ngamruengphong, A. Kamal, V. Akshintala, et al., Prevalence of metastasis and survival of 788 patients with T1 rectal carcinoid tumors, Gastrointest. Endosc. 89 (3) (2019) 602–606.
[14] A.C. Gamboa, Y. Liu, R.M. Lee, et al., A novel preoperative risk score to predict lymph node positivity for rectal neuroendocrine tumors: an NCDB analysis to guide operative technique, J. Surg. Oncol. 120 (6) (2019) 932–939.
[15] I.W. Folkert, A.J. Sinnamon, S.J. Concors, et al., Grade is a dominant risk factor for metastasis in patients with rectal neuroendocrine tumors, Ann. Surg Oncol. 27 (3) (2020) 855–863.
[16] T. Yamaguchi, K. Takahashi, K. Yamada, et al., A nationwide, multi-institutional collaborative retrospective study of colorectal neuroendocrine tumors in Japan, Ann Gastroenterol Surg 5 (2) (2021) 215–220.
[17] A. Rinke, V. Ambrosini, C. Dromain, et al., European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for colorectal neuroendocrine tumours, J. Neuroendocrinol. 35 (6) (2023) e13309.
[18] B.C. Kim, Y.E. Kim, H.J. Chang, et al., Lymph node size is not a reliable criterion for predicting nodal metastasis in rectal neuroendocrine tumours, Colorectal Dis. 18 (7) (2016) O243–O251.
[19] H. Ushigome, Y. Fukunaga, T. Nagasaki, et al., Difficulty of predicting lymph node metastasis on CT in patients with rectal neuroendocrine tumors, PLoS One 14 (2) (2019) e0211675.
[20] T. Tanaka, H. Nozawa, K. Kawai, et al., Lymph node size on computed tomography images is a predictive indicator for lymph node metastasis in patients with colorectal neuroendocrine tumors, In Vivo 31 (5) (2017) 1011–1017.
[21] H. Zhu, S. Zhao, C. Zhang, et al., Endoscopic and surgical treatment of T1N0M0 colorectal neuroendocrine tumors: a population-based comparative study, Surg. Endosc. (2021).
[22] R. Sappenfield, I.A. Gonzalez, D. Cao, D. Chatterjee, Well-differentiated rectal neuroendocrine tumors: analysis of histology, including insulinoma-associated protein 1 expression, and biologic behavior, involving a large cohort of 94 cases, Hum. Pathol. 104 (2020) 66–72.
[23] C.J. Shields, E. Tiret, D.C. Winter, G. International Rectal Carcinoid Study, Carcinoid tumors of the rectum: a multi-institutional international collaboration, Ann. Surg. 252 (5) (2010) 750–755.
[24] L.B. Anthony, J.R. Strosberg, D.S. Klimstra, et al., The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum, Pancreas 39 (6) (2010) 767–774.
[25] J.P. Boudreaux, D.S. Klimstra, M.M. Hassan, et al., The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum, Pancreas 39 (6) (2010) 753–766.
[26] L. Chen, Y. Guo, Y. Zhang, et al., Development of a novel scoring system based on endoscopic appearance for management of rectal neuroendocrine tumors, Endoscopy 53 (7) (2021) 702–709.
[27] Q. Chen, J. Chen, Y. Deng, et al., Nomogram for the prediction of lymph node metastasis and survival outcomes in rectal neuroendocrine tumour patients undergoing resection, J. Gastrointest. Oncol. 13 (1) (2022) 171–184.
[28] Y. Takatsu, Y. Fukunaga, T. Nagasaki, et al., Short- and long-term outcomes of laparoscopic total mesenteric excision for neuroendocrine tumors of the rectum, Dis. Colon Rectum 60 (3) (2017) 284–289.
[29] Y. Tokumaru, N. Matsuhashi, T. Takahashi, et al., Rectal neuroendocrine tumor developing lateral lymph node metastasis after curative resection: a case report, World J. Surg. Oncol. 18 (1) (2020) 74.
[30] S. Shin, Y.I. Maeng, S. Jung, C.S. Yang, A small, low-grade rectal neuroendocrine tumor with lateral pelvic lymph node metastasis: a case report, Ann Coloproctol 38 (4) (2022) 327–331.
[31] Z. Zhou, Z. Wang, B. Zhang, Y. Wu, G. Li, Z. Wang, Comparison of 68Ga-dotanoc and 18F-FDG PET-CT Scans in the evaluation of primary tumors and lymph node metastasis in patients with rectal neuroendocrine tumors, Front. Endocrinol. 12 (2021) 727327.
[32] Z. Wang, K. An, R. Li, Q. Liu, Tumor macroscopic morphology is an important prognostic factor in predicting chemotherapeutic efficacy and clinical outcomes of patients with colorectal neuroendocrine neoplasms, one multicenter retrospective cohort study, Front. Endocrinol. 12 (2021) 801741.