ORIGINAL ARTICLE

Risk factors of lymph node metastasis in rectal neuroendocrine tumors*

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Abstract

Objective The aim of this study was to investigate the risk factors of lymph node metastasis in rectal neuroendocrine neoplasms (RNENs).

Methods We enrolled 168 patients with RNENs as the research object, and their clinicopathological and survival data were collected. The risk factors affecting lymph node metastasis were analyzed retrospectively, and independent risk factors affecting prognosis were evaluated.

Results Analysis showed that age, tumor diameter, tumor function, grade, and T stage were correlated with lymph node metastasis ($P < 0.05$). Multiple logistic regression analysis showed that tumor size, grade, and T stage were independent risk factors for lymph node metastasis in patients with RNENs. Kaplan–Meier analysis showed that the 5-year overall survival (OS) of patients with lymph node metastasis was 40.0% (10/25), and that of patients without lymph node metastasis was 93.0% (133/143). The prognosis of RNENs patients with lymph node metastasis along with patients with large tumor diameter and high grade was poor. Cox multivariate analysis showed that tumor diameter (HR = 1.985, $P = 0.008$), grade (HR = 3.416, $P = 0.004$), T stage (HR = 2.413, $P = 0.014$), and lymph node metastasis (HR = 3.119, $P = 0.000$) were independent risk factors affecting the prognosis of patients with RNENs.

Conclusion Tumor size, grade, and T stage are the main risk factors for lymph node metastasis and prognosis in patients with RNENs. These risk factors should be fully evaluated before surgery.

Key words: rectal neuroendocrine tumor; lymph node metastasis; risk factors

Neuroendocrine neoplasms (NENS) are heterogeneous tumors of peptidergic neurons that originate from neuroendocrine cells and exert a neuroendocrine function. They can produce a variety of different hormones resulting in different symptoms [1]. In recent years, the incidence of NENS originating from the gastroenteric pancreas system and lungs is increasing [2]. The incidence rate of rectal neuroendocrine neoplasm (RNENs) is the highest in the gastrointestinal tract. As diagnostic technology continues to improve, the incidence rate of RNENs has increased by nearly ten-fold [3] in the past 30 years. Many factors affect the prognosis of patients with RNENs, among which lymph node metastasis is an important risk factor. Therefore, the determination of lymph node metastasis or related high-risk factors in patients is of utmost importance in the selection of clinical treatment strategy [4]. However, the relevant factors related to lymph node metastasis of RNENs have not been fully understood.

Therefore, this study retrospectively analyzed the clinical data of 168 patients with RNENs. This study explored the risk factors affecting lymph node metastasis, in order to provide a strong basis for the treatment and prognosis of such patients.

Materials and methods

Research object

Overall, 168 patients with NENS who were treated in our hospital from January 2002 to January 2019 were selected as the research objects. The inclusion criteria were: (1) Patients who underwent pathological as well as immunohistochemical examination and were histologically diagnosed with RNENS. (2) Patients who underwent radical resection. (3) Patients with initial diagnosis and treatment. The exclusion criteria were: (1) Endoscopic treatment or local anal resection. (2)

Concurrent severe liver, kidney, and lung damage or serious mental illness. (3) Concurrent benign and malignant tumors of the rectum. (4) Incomplete clinical or follow-up data. The demographic data, clinicopathological characteristics, and treatment plans of patients were collected through the electronic medical record system. Patient survival data was obtained from outpatient examination and follow-up via telephone. The median age of 168 patients with RNENs was 48 years, with a range of 20 to 78 years. There were 67 patients over 50 years old, 101 patients under 50 years old, 108 male patients (%), and 60 male patients (%). Excluding two patients on different treatment plans, all other patients received radical rectal surgery, endoscopic resection, anal resection and somatostatin analogs. All patients received surgical treatment, and all patients had negative margins. According to the proliferative activity of the tumor, gastrointestinal, and pancreatic neuroendocrine tumors were classified as G1 (low-grade, mitotic image number 1/10, high-power field or Ki-67 index ≤ 2%), G2 (medium-grade, mitotic image number 2–20/10, high-power field or Ki-67 index 3%–20%), G3 (high-grade, mitotic image number > 20/10, high-power field or Ki-67 index > 20%).

Follow-up

All patients received regular follow-up, including physical examination. Tests were conducted to check whole blood cell count, and serum carcinoembryonic antigen (CEA) levels. When necessary, the patients underwent imaging examinations such as abdominal ultrasound and chest radiography. When recurrence was suspected, CT or MRI was performed.

statistical analysis

All data were analyzed using the SPSS20.0 software. The counting data were expressed as the frequency (example), and chi square test was used. A logistic multivariate model was used to analyze the risk factors of lymph node metastasis. Kaplan–Meier and log rank survival curves were used to compare the survival rates. Multivariate Cox regression analysis was used for survival analysis. Differences were considered significant at $P < 0.05$.

Results

Clinicopathological features of patients

Among the 168 patients, 115, 18, 16, and 19 had stage I, II, III and IV RNENs, respectively. Tumor invasion reached the mucosa and submucosa (T1) in 128 patients. Tumors invaded the muscularis propria in 18 cases (T2), and the external muscularis in 22 cases. Grade G1, G2, and G3 was found in 124, 34, and 10 cases, respectively. The average tumor size was 1.28 ± 0.60 cm, of which

132 cases were < 1 cm and 36 cases were greater than 2 cm. Approximately 29 patients with functional tumors developed intermittent flushing and diarrhea, and 25 patients had lymph node metastasis. The rate of lymph node metastasis was 14.9%. All patients received regular follow-ups. The average follow-up time was 38 months. The longest follow-up time was 138 months, and the shortest follow-up time was 3 months. 20 patients died, which accounted for 11.9% of all patients.

Single factor analysis of lymph node metastasis

Univariate analysis showed that age, tumor diameter, tumor function, grade, and T stage were correlated with lymph node metastasis ($P < 0.05$). Higher age, larger tumor diameter, higher functional tumor, grade, and T stage, were associated with higher risk of lymph node metastasis in patients with RNENs (Table 1).

Multivariate analysis of lymph node metastasis

Multiple logistic regression analysis revealed that tumor size, grade, and T stage were independent risk factors for lymph node metastasis in patients with RNENs (Table 2).

Prognostic analysis of patients with different clinical characteristics
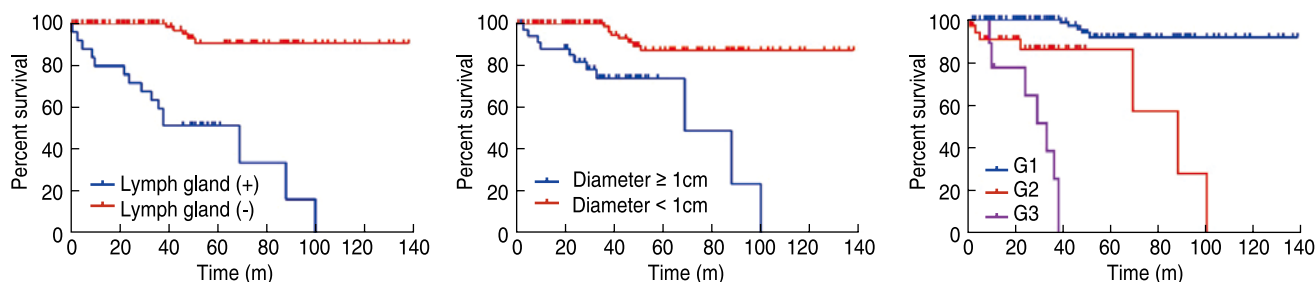
Among 168 patients, 25 succumbed to the disease. The overall survival rate was 85.1% (143/168). Kaplan–

Table 1 A univariate analysis of the affected lymph node metastasis

| Index | n | Lymphatic metastasis | | χ^2 | P |
		Positive (n=25)	Negative (n=143)		
Gender				0.176	0.674
Female	108	17	91		
Male	60	8	52		
Age (years)				19.717	0.000
≤ 50	101	5	96		
> 50	67	20	47		
Tumor diameter (cm)				77.309	0.000
< 1	132	3	129		
≥ 1	36	22	14		
Functional tumor				4.467	0.035
Yes	29	8	21		
No	139	17	122		
WHO Grade				56.505	0.000
G1	124	7	117		
G2	34	9	25		
G3	10	9	1		
T stage				85.859	0.000
T1	128	3	125		
T2	18	5	13		
> T2	22	17	5		

Table 2 Multivariate analysis affecting lymph node metastasis

Index	β	SE	Wald	df	P	95%CI
Gender	0.241	0.262	0.829	1	0.551	0.542–1.98
Tumor diameter	0.524	0.485	5.141	1	0.000	1.146–4.632
Functional tumor	0.498	0.362	1.256	1	0.412	1.035–3.791
Grade	0.320	0.208	14.965	1	0.000	1.369–2.216
T stage	0.265	0.277	14.846	1	0.000	1.965–2.470

Fig. 1 Analysis of the prognosis of patients with different clinical characteristics

Meier analysis showed that the 5-year OS of patients with lymph node metastasis and without lymph node metastasis was 40.0% (10/25) and 93.0% (133/143) respectively. The difference between the two groups was statistically significant ($\chi^2 = 29.64$, $P = 0.00$), and the prognosis of RNEN patients with lymph node metastasis was significantly worse. Nevertheless, when the tumor diameter was large ($\chi^2 = 22.75$, $P = 0.000$), the grade was higher ($\chi^2 = 121.70$, $P = 0.000$; Fig. 1).

Cox univariate and multivariate analysis affecting the prognosis of patients

Cox univariate and multivariate analysis revealed that tumor diameter (HR = 1.985, $P = 0.008$), grade (HR = 3.416, $P = 0.004$), T stage (HR = 2.413, $P = 0.014$), and lymph node metastasis (HR = 3.119, $P = 0.000$) were independent risk factors affecting the prognosis of patients with RNEN (Table 3).

Discussion

According to the surveillance, epidemiology, and end results (SEER) data, the incidence rate of RNENs increased from 1.09/10 million in 1973 to 5.25/10 million in 2004, with an incidence rate that increased every year. Studies in Taiwan and Japan show that the highest incidence of RNENs in Asian people is in the digestive tract. The incidence rate of [5] is the highest. Surgery, which includes radical resection, endoscopic resection, or transanal resection, is the most important treatment for RNENs. It is believed that G1 grade early RNENs can be treated by endoscopic resection; however, once lymph node metastasis occurs, radical surgical resection should be performed [6]. Therefore, understanding the high-risk factors of lymph node metastasis will help clinicians to choose the best surgical method.

In this study, 25 of 168 patients had lymph node

Table 3 Cox univariate and multivariate analysis affecting patient outcomes

Items	Univariate analysis			Multiplicity analysis		
	HR	95%CI	P	HR	95%CI	P
Gender	1.036	0.897–1.320	0.326	-	-	-
Age	1.130	0.964–1.254	0.489	-	-	-
Tumor diameter	2.512	1.820–3.336	0.013	1.985	1.316–2.765	0.008
functional tumor	1.236	0.874–1.521	0.117	-	-	-
Grade	3.154	2.870–3.461	0.005	3.416	2.794–3.852	0.004
T stage	2.203	1.754–2.965	0.032	2.413	1.978–3.021	0.014
Lymphatic metastasis	3.846	2.143–5.089	0.001	3.119	2.541–5.135	0.000

metastasis, where the lymph node metastasis rate was 14.9%. The 5-year survival rate with lymph node metastasis and without lymph node metastasis was 40.0% (10/25) and 93.0% (133/143) respectively. The survival rate indicated that the prognosis of patients with RNENs complicated with lymph node metastasis was significantly poor. Hence, there is a necessity of preoperative lymph node metastasis status evaluation in treatment selection. The lymph node metastasis rates of G1, G2, and G3 tumors were 5.6%, 26.4%, and 90.0% respectively. Li *et al*. [7] found that the lymph node metastasis rates of G1, G2 and G3 patients were 2.92%, 20.0%, and 66.67% respectively, which was similar to that in our results. In multivariate analysis, grade was an independent risk factor for lymph node metastasis. In addition, there was a significant difference in the rate of lymph node metastasis between G1 and G2 patients, which suggested that patients above G2 are more likely to have regional lymph node metastasis. The 5-year survival rates of patients with grade G1, G2, and G3 were 94.4%, 79.9%, and 19%, respectively. The 5-year survival rate of patients with grade G2 or above was significantly lower than patients with grade G1. The survival rate indicated that the prognosis of patients with grade G2 or above is worse than patients with grade G1. The prognosis may be related to the higher risk of lymph node metastasis in patients with grade G2 or above.

The depth of tumor invasion is also a key factor affecting the prognosis of patients with RNEN[8]. Studies have shown that the depth of tumor invasion is a predictor of lymph node metastasis [9]. Shields *et al*. found that the 5-year survival rate of T1 and T2 differed by approximately 10% [10]. At present, it is believed that when the tumor invades the muscularis propria, the risk of lymph node metastasis is significantly increased. Furthermore, the prognosis is far worse than patients where tumor invasion is limited to submucosa. The lymph node metastasis rates of T1, T2, and above T2 were 2.3%, 27.8%, and 77.3% respectively. The depth of tumor invasion is an independent risk factor for lymph node metastasis of RNEN. When the tumor invades greater than T2, the risk of lymph node metastasis increases significantly, radical surgery should be performed in such cases.

This study presented that tumor size is also an important factor affecting the risk factors and prognosis of lymph node metastasis in RNEN. The European neuroendocrine tumor society guidelines suggest that when lymph node metastasis does not occur, endoscopic tumor resection or transanal resection can achieve the effect of radical surgery with good long-term survival [11]. The guidelines of the national comprehensive cancer network also suggest that when the lesion is less than 2 cm in diameter, endoscopic resection or anal resection is sufficient radical treatment [7]. However, Japanese scholars believe that when the tumor diameter is > 1 cm, radical surgery including lymph node dissection must be performed, as research has shown that RNEN with diameter > 1 cm have the same risk of lymph node metastasis as colorectal adenocarcinoma [12]. Further studies have reported that the lymph node metastasis rates of tumors with diameter > 2 cm and 1.0–2.0 cm are 50% and 23.5% respectively. Moreover, the lymph node metastasis rate of tumors with a diameter <1 cm is less than 2% [13], which indicated that the lymph node metastasis rate of tumors with a diameter <1 cm is very low. Hence, for tumors with a diameter <1 cm, endoscopic resection, or anal resection is satisfactory. In addition, tumors with a diameter > 2 cm should undergo radical surgery, such as anterior rectal resection or abdominal resection. Nonetheless, the optimal criteria to decide on the surgical procedure when the tumor diameter is between 1-2 cm remains unclear. In this study, tumor size was an independent risk factor for lymph node metastasis. There was a significant difference in the rate of lymph node metastasis between patients with tumor diameter < 1 cm and patients with tumor diameter of 1–2 cm. Patients with tumor diameter of 1 = 2 cm or > 2 cm are more likely to have regional lymph node metastasis. Thus, taking the research mentioned above into account, we postulate that patients with tumor diameter > 2 cm require radical surgery. Nevertheless, tumors with a diameter of 1–2 cm require careful treatment. Our study showed that 11 patients with lymph node metastasis and tumor diameter of 1–2 cm had tumor infiltration to T2 or deeper or grade G2 or G3. The data from these 11 patients suggested that other high-risk factors, such as tumor infiltration depth or grade, should be considered before surgery. Therefore, according to our results, we suggest that when the tumor diameter is 1–2 cm, has invaded T2 or deeper, or when it is grade G2 or G3 at the same time, radical surgery should be performed.

In conclusion, this study found that tumor size, grade and depth of tumor invasion were independent risk factors for lymph node metastasis of RNENs. When the depth of tumor invasion reaches beyond the muscularis propria, the tumor is classified as grade G2 or G3. Additionally, when the diameter is > 2 cm, the risk of lymph node metastasis increases significantly. In such cases, radical surgery is recommended. However, this study has some limitations which should be considered: (1) this study was a retrospective study, where the timespan for patient selection was large, which inevitably led to a certain sample bias. (2) The sample size is small. (3) This study is a descriptive report where all the patients received surgical treatment. Additionally, there was a lack of control group without surgical intervention.

Author contributions

Not applicable.

Data availability statement

Not applicable.

Ethical approval

Not applicable.

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