Original Article
Analysis of the factors affecting lymph node metastasis and the prognosis of rectal neuroendocrine tumors

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Abstract: Objective: To analyze the factors affecting lymph node metastasis and the prognosis of rectal neuroendocrine tumors after surgical treatment. Methods: A retrospective analysis was conducted using the clinical data from 156 cases of rectal neuroendocrine tumors during the period of January 1999 to December 2013. The Kaplan-Meier method was used to calculate the survival time, Cox regression analysis was performed for statistical analysis of clinicopathological factors that may be associated with lymph node metastasis and prognosis, and correlation analysis was carried out using binary logistic regression. Results: The overall 5-year survival rate of the entire group was 95.7%. Multivariate analysis showed that the depth of invasion was an independent prognostic factor ($P < 0.001$). The incidence of lymph node metastasis was 7.7% (12/156), and logistic regression analysis showed that lymph node metastasis was related to the depth of invasion ($P = 0.003$) and tumor diameter ($P = 0.006$). Conclusion: The surgical approach of rectal neuroendocrine tumors should be selected based on a comprehensive consideration of factors such as tumor size, depth of invasion and lymph node metastasis.

Keywords: Neuroendocrine tumors, rectal neuroendocrine, lymph node metastasis

Introduction

Originating from chromaffin-like cells, neuroendocrine tumors (NENs) are a type of tumor with neuroendocrine functions and malignant potential. The clinical manifestations of NENs are significantly heterogeneous depending on the disease site and endocrine function [1, 2]. According to the US Surveillance, Epidemiology, and End Results (SEER) database, NEN incidence rose from 1.09/100,000 population per year in 1973 to 5.25/100,000 population per year in 2004 [3], and the incidence rate has increased annually [2]. Several large-scale epidemiological surveys have confirmed that NENs primarily occur in the digestive tract [4-6]. Differing from the European and American populations, studies based on populations in Taiwan and Japan revealed that the rectum is the most likely site of the digestive tract affected by NENs in Asian populations [7, 8]. Similar to colorectal cancer, surgical resection is the standard treatment of NENs, but lymph node metastasis is an important factor affecting the

choice between radical resection and local excision. Therefore, the investigation of factors related to lymph node metastasis and prognosis has a great clinical significance for rectal NENs. The purposes of this study were to analyze the factors affecting lymph node metastasis and the prognosis of rectal neuroendocrine tumors after surgical treatment.

Patients and methods

The subjects were rectal NEN cases that received surgical treatment at the Chinese Academy of Medical Sciences Cancer Hospital during the period of January 1999 to December 2013. The study content included the clinical data of patients (including age, gender, tumor size, tumor stage and grade, and location), factors related to lymph node metastasis, and long-term survival and its related factors. A rectal NEN is defined as a NEN with the lower edge of the mass located within 15 cm from the anus. The tumor locations were determined preoperatively via examination using fingers or
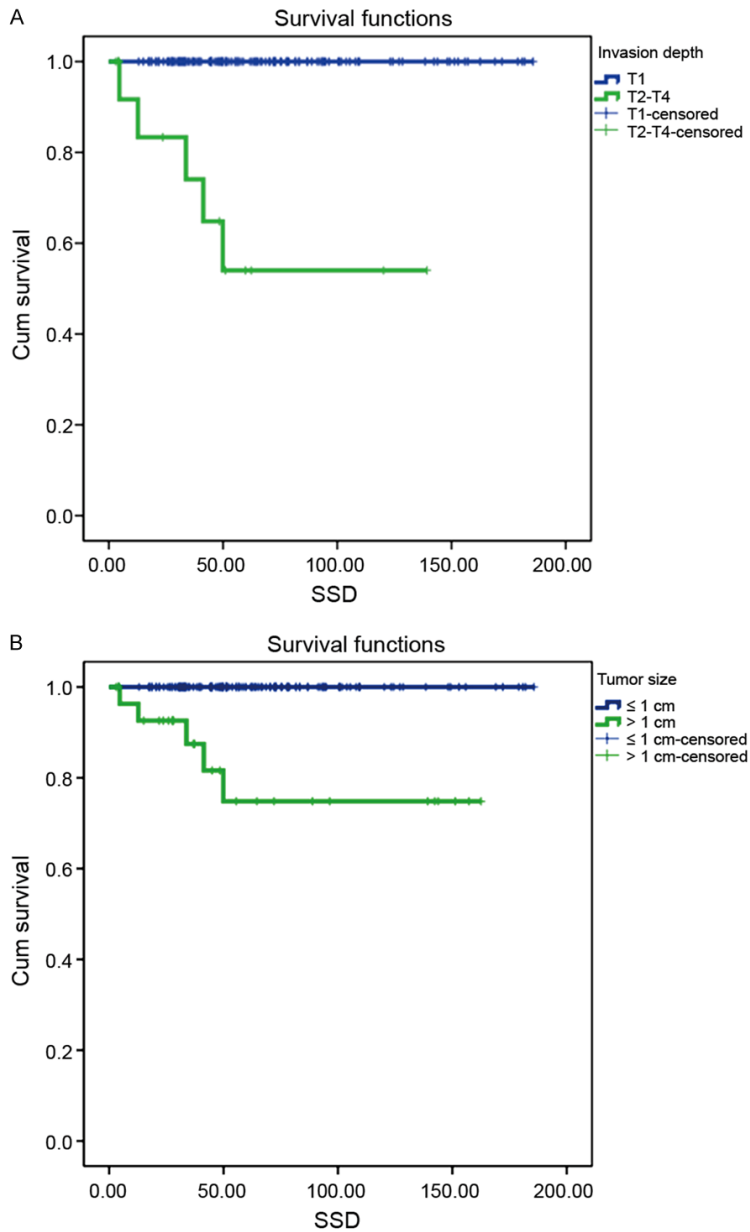
Figure 1. Survival curves stratified by tumor invasion depth (A. *P* < 0.001) and tumor size (B. *P* < 0.001).

graded the lesions. The study was conducted with the approval of the institutional ethics board of our institute.

Surgical approaches were divided into two categories, local excision and radical surgery. Local tumor excision included transanal excision (TAE) and endoscopic resection [endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)]. Radical surgery included low anterior resection (LAR), abdominoperineal resection (APR), and transsacral resection (TSR). Follow-up studies were conducted based on outpatient re-examination and telephone follow-up.

This study used SPSS 21.0 software for statistical analysis. All of the continuous variables were expressed as means ± standard deviation and were compared using independent sample t-test. Count data were expressed as percentages. The Kaplan-Meier method was used to plot survival curves, and the log-rank test and Cox regression were conducted for univariate survival analysis. Cox regression was used for multivariate analysis of prognosis. Correlation analysis was conducted using binary logistic regression. *P* value less than 0.05 was considered to be statistically significant.

colonoscopy, and pathological confirmation was also obtained. The clinical and pathological data were obtained through medical records and databases. Pathological sections underwent immunohistochemical staining, and the Ki-67 index and mitotic images under high-power fields were also recorded. According to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual and pathological grading system of the World Health Organization 2010 criteria of tumors of the digestive system [9, 10], we re-staged and

Results

Clinical and pathological characteristics

This study collected 181 rectal NEN cases that received treatment at the Chinese Academy of Medical Sciences Cancer Hospital during the period of January 1999 to December 2013. Of these cases, 25 were not included in the study, including 15 cases associated with a second primary cancer, 5 cases that received palliative surgery and 5 cases that did not receive surgery. The final analysis included 156 cases.

Table 1. Analysis of prognostic factors of overall survival

Clinicopathological factors	No.	5-Year survival (%)	P Value of univariate analysis	Multivariate analysis		
				HR	95% CI	P value
Gender			0.093			
Male	104	93.3				
Female	52	100				
Age			0.342			
< 60 years	121	96.1				
≥ 60 years	35	94.1				
Tumor size			< 0.001			
0-10 mm	126	100				
11-20 mm	19	92.3				
> 20 mm	11	40				
Invasion depth			< 0.001	5.460	2.607-11.437	< 0.001
T1	140	100				
T2-4	16	54				
Pathological grading			< 0.001			
G1	137	100				
G2	10	75				
G3	9	47.6				
Symptoms			0.089			
Yes	102	93.3				
No	54	100				
TNM Staging			< 0.001			
I	140	99				
II	4	50				
III	12	60				
1-cm stratification			< 0.001			
≤ 1 cm	126	100				
> 1 cm	30	74.8				
Lymph node metastasis			< 0.001			
N0	144	98.4				
N1	12	60.0				
Surgical approach			< 0.001			
Endoscopic surgery	61	100				
Transanal resection	72	98.4				
Radical surgery	23	77.5				

There were a total of 104 males and 52 females, with a median age of 50.82 ± 11.566 years. Approximately 34% (n = 54) of the patients had no clinical symptoms, and the disease was identified during routine physical examination. Changes in bowel movement habits (n = 43) and hematochezia (n = 44) were the most common clinical manifestations. None of the patients showed symptoms associated with carcinoid syndrome. Tumor location was determined by preoperative colonoscopy, and the pathological diagnosis was also obtained. The median distance between the lower edge of the tumor and anus was 5.798 ± 4.044 cm. The median lesion diameter was 9.79 ± 11.34 mm. Among the 156 cases, 126 had a lesion diameter ≤ 1 cm, 19 cases had a lesion diameter between 1-2 cm, and 11 cases had a lesion diameter > 2 cm.

Lesions in 140 cases were confined to the submucosa, of which lesions in 4 cases were accompanied by lymph node metastasis. Lesions in five cases invaded the muscular

layer, including one case that also had lymph node metastasis; lesions in seven cases involved the subserosa, of which four cases had intestinal lymph node or distant metastases; lesions in four cases invaded the outer serosa, of which three cases had lymph node metastasis. According to the seventh edition of the AJCC staging manual, the cases were categorized as 140 stage I cases (89.7%), 4 stage II cases (2.56%), and 12 stage III cases (7.69%). According to pathological grading, there were 87.8% of grade 1 (G1) lesions (n = 137), 6.4% of G2 lesions (n = 10) and 5.8% of G3 lesions (n = 9).

Surgical approaches included local excision and radical surgery. A total of 85.3% of patients underwent local excision, including TAE (n = 72) and endoscopic resection (n = 61). Radical resection included LAR (n = 15), TSR (n = 2), APR (n = 5), and Hartmann's operation (n = 1). There were no postoperative complications and postoperative mortality (≤ 30 days).

Overall survival

As of December 2014, the average follow-up time was 65 ± 43.31 months (range, 3-185 months). The overall 5-year survival rate was 95.7%. The 5-year survival rates for tumors at different stages were 99.0% for stage I tumors, 50.0% for stage II tumors, and 60.0% for stage III tumors. The 5-year survival rates for tumors of different pathological grades were 100% for G1 tumors, 75% for G2 tumors, and 47.6% for G3 tumors. After the tumors were grouped according to the tumor diameter of 0-10 mm, 11-20 mm, or > 20 mm, there were significant differences (P < 0.001) in the prognosis between the groups. There were also significant differences in prognosis between different surgical procedures (P < 0.001). Lymph node metastasis was a prognostic factor (P < 0.001).

Univariate analysis showed that factors associated with prognosis of overall survival included TNM stage (P < 0.001), grade (P < 0.001), depth of invasion (P<0.001), tumor size (P < 0.001) (**Figure 1**), surgical approach (P < 0.001), and lymph node metastasis (P < 0.001). Multivariate analysis via Cox regression showed that the depth of invasion was an independent prognostic factor (P < 0.001; **Table 1**). The 133 cases with local excision were all G1-G2 grade lesions, and the lesion diameter was less than 2 cm. The 5-year survival rates of patients in the TRG and ECG groups were 98.4% and 100%, and there was no significant difference between the two groups (P = 0.452).

Lymph node metastasis and influencing factors

There were 12 cases in this group with lymph node metastasis, and the metastasis rate was 7.69%. Logistic binary regression analysis showed that a tumor size larger than 1 cm in diameter (*P* = 0.006) and depth of invasion (*P* = 0.003) were independent factors associated with lymph node metastasis (**Table 2**).

Discussion

Rectal NENs account for 60-89% of all NENs of the entire digestive tract [11], and the NEN incidence shows a gradual upward trend due to the wide application of endoscopic examination. NENs of the rectum show no specific clinical symptoms. Additionally, 89% of the newly diagnosed patients in this group were accidentally discovered in colonoscopy. Weinstock et al. showed that the prognosis of asymptomatic patients was significantly better than that of symptomatic patients [12]. In this study, asymptomatic patients accounted for 33.9% of the patients, and there were no significant difference in the prognosis between the asymptomatic and symptomatic groups (P = 0.119). We found that 81.7% of the symptomatic patients had stage I disease, and the early-disease stage is the main cause of the lack of difference in the survival between the symptomatic and asymptomatic groups. Therefore, improving the early detection of rectal NENs by colonoscopy is an important factor to improve prognosis.

Lymph node status before treatment is an important factor in deciding radical surgery or local excision. However, the preoperative evaluation of lymph node status remains a difficult problem in clinical practice. Gleeson et al. [13] found that rectal NENs with a diameter of 11-19 mm had a higher metastatic potential. Currently, there are only limited numbers of studies on the patterns of lymph node metastasis in rectal NENs. This study analyzed factors associated with rectal NEN prognosis and lymph node metastasis, and provided an impor-

Table 2. Analysis of factors associated with lymph node metastasis

Clinicopathological factors	NO	Lymph node metastasis (%)	P Value of univariate analysis	Multivariate analysis		
				HR	95% CI	P Value
Gender			1.000			
Male	104	8 (7.69)				
Female	52	4 (7.69)				
Age			0.352			
< 60 years	121	8 (6.61)				
≥ 60 years	35	4 (11.43)				
Tumor size			< 0.001			
0-10 mm	126	2 (1.59)				
11-20 mm	19	2 (10.53)				
> 20 mm	11	8 (72.73)				
Invasion depth			< 0.001	3.295	1.508-7.200	0.003
T1	140	4 (2.86)				
T2-4	16	8 (50.00)				
Pathological grading			< 0.001			
G1	137	4 (2.92)				
G2	10	2 (20.00)				
G3	9	6 (66.67)				
Symptoms			0.997			
Yes	102	12 (11.76)				
No	54	0 (0)				
Staging			0.991			
I	140	0 (0)				
II	4	0 (0)				
III	12	12 (100)				
1-cm stratification			< 0.001	13.124	2.068-71.073	0.006
≤ 1 cm	126	2 (1.59)				
> 1 cm	30	10 (33.33)				

tant reference for the selection of clinical treatment methods.

Due to the low incidence of rectal NENs, statistical analyses with large sample sizes are lacking. There remain many inconsistent reports on the prognostic factors of rectal NENs. For example, multiple retrospective studies have suggested that factors such as tumor stage, tumor grade, tumor size, lymph node metastasis, depth of invasion, and surgical methods are associated with prognosis. Garcia-Carbonero et al. [14] found that only pathological stage (P = 0.0001, hazard ratio (HR) = 3.96, 95% CI: 1.97-7.96) and Ki-67 index (P = 0.008, HR = 6.69, 95% CI: 1.96-22.88) were independent prognostic factors. Chi et al. [15] found that tumor grade was an independent factor associated with prognosis (HR = 2.797, 95% CI:

1.676-4.668, P = 0.004). Chagpar et al. [16] found that the depth of invasion, tumor size, lymph node metastasis, and distant metastasis were all independent prognostic factors (P < 0.001). The 5-year survival rate of this study group was 92.6%, a value that is similar to that reported in the literature. Univariate prognostic factor analysis focusing on this group of 156 NEN cases revealed that the prognostic factors included tumor stage, grade, depth of invasion, tumor size, surgical approach, and lymph node metastasis. However, multivariate analysis showed that only the depth of invasion was an independent prognostic factor. Wang et al. [17] conducted a retrospective analysis of 106 cases of rectal NEN and obtained conclusions similar to this study. Therefore, based on the above studies, preoperative staging and lymph node status have

decisive significance on the selection of rectum NEN treatment methods.

Previous literature has suggested that the metastasis rate of T1 lesions with a diameter < 1 cm was less than 3%. When the tumor diameter was greater than 1 cm, the metastasis rate may increase to 10-15% [18]. Gleeson et al. [13] found that the metastasis rates of tumors with a diameter ≤ 10 mm, between 11 and 19 mm, and ≥ 20 mm were 3%, 66%, and 73%, respectively. In this study, 12 patients exhibited lymph node metastasis. Among them, two had a diameter < 1 cm, of which 1 was a case of G1 mucosal lesion and 1 was a case of a G2 lesion invading the muscular layer. There were two cases with a diameter of 1-2 cm; both were confined to the mucosa: one case was a G3 lesion, and the other was a G1 lesion. Logistic bivariate analysis showed that a tumor diameter greater than 1 cm and depth of invasion are independent factors associated with lymph node metastasis. Currently, endoscopic ultrasonography (EUS) has a high accuracy for evaluating per-intestinal lymph node status. It has been reported that EUS has an accuracy of 74.6% in the preoperative assessment of rectal adenocarcinoma lymph node metastasis, a value that dropped to 43.3% after postoperative pathological correction [19]. Chen et al. reported that the accuracy rate of ultrasonography in rectal NENs was approximately 94.4% [20]. Therefore, paying attention to the preoperative evaluation of lymph node metastasis in rectal NEN patients and improving EUS are of important guiding significance, particularly for tumors greater than 1 cm in diameter and those suspected of deep invasion.

Surgical resection is the primary treatment approach for rectal NENs, and the surgical methods primarily include endoscopic surgical resection, local excision and radical resection. The determination of the surgical approach is based on the evaluation of lymph node metastasis, while tumor size and depth of invasion are also important determinants of the surgical approach. The present study separated the cases into different groups based on the invaded muscular layers and then conducted bivariate logistic regression. We found that histological grade (P = 0.002, HR = 9.429, 95% CI: 2.243-39.632) and a tumor diameter greater than 2 cm (P = 0.004, HR = 49.999, 95% CI: 3.609-692.687) are independent factors associated with muscular layer invasion. For rectal NENs less than 1 cm in diameter, because the probability of metastasis is less than 5% [21-24], local excision is sufficient [25]. There has been no international consensus on the treatment of lesions with a diameter of 11-20 mm. The European Neuroendocrine Tumor Society (ENETS) guidelines recommend endoscopic ultrasound assessment of lymph nodes and depth of invasion, and G1 lesions of stage T1N0 can be treated by local excision [21]. The National Comprehensive Cancer Network (NCCN) guidelines recommend local excision for tumors with a diameter less than 2 cm, while tumors 1-2 cm in diameter require the removal of external muscular layer invasion and lymph node metastasis. Tsukamoto et al. [26] suggested that tumors with a diameter greater than 10 mm had a significantly increased rate of lymph node metastasis and should be recommended to receive radical treatment in accordance with the principle of radical treatment for colorectal cancer. In this study, 19 cases corresponded to a tumor diameter in the range of 11-20 mm, 16 cases received local excision, and 1 case received salvage radiation due to a positive surgical margin after TAE, but the patient died due to cancer 3 years after the surgery. There were no significant differences in long-term survival between radical resection and local excision (P = 0.670), and between endoscopic resection (n = 6) and TAE (n = 10) (P = 0.752). These results suggest that, for tumors less than 2 cm in diameter, local excision can be conducted after the removal of lymph node metastasis and muscular invasion, and these tumors can also be treated with the less invasive endoscopic treatment. However, this study had limited data, and further research is required to confirm and clarify the above observations.

In conclusion, a rectal NEN is a relatively rare type of tumor, with a good prognosis after surgical treatment. Fully assessing and comprehensively considering the tumor size, depth of invasion, lymph node status and other factors can help select the appropriate treatment approach, and therefore improve the prognosis of patients.

Disclosure of conflict of interest

None.

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