Risk Factors for Development of Rectal Neuroendocrine Tumors Longer Than 9 mm: Retrospective Cohort

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ABSTRACT

Background: *Rectal neuroendocrine tumors (R-NET) represent the most frequent of gastroenteropancreatic neuroendocrine neoplasms (NEN-GEP) according to the United States Surveillance, Epidemiology, and End Results database. With an annual percentage of occurrence increasing to 8.2% of all rectal neoplasms, R-NET affect less than 2% and are reported in only 0.05% to 0.07% of patients undergoing colorectal cancer (CRC) screening. The primary objective of this study was to assess the risk factors associated with R-NET greater than 10 mm. As a secondary objective, it was also aimed to evaluate the response to endoscopic treatment.*

Methods: *This was a retrospective study, using data collected through the analysis of medical records of colonoscopies performed from January 2008 to December 2014. Records of polypectomies were identified, and the results were searched for pathological findings of R-NET. We also gathered epidemiological data and outcomes as risk factors for lesions greater than or equal to 10 mm, with local and distant recurrence.*

Results: *During the study period, 18 218 colonoscopies were performed and 10 865 polypoid lesions were detected and removed, 20 with R-NET anatomopathology. The detection rate was 0.1%. The risk factors associated with major lesions were Japanese ethnicity, the lack of previous cancer diagnosis, and a Ki67 index > 2%. The mean follow-up was 56.6 months, and there was no local lymph node recurrence or distant relapse.*

Conclusion: *This study concludes that endoscopic resection is a good and effective method for treatment of Grade 1 rectal NET smaller than 11 mm, with high cure rates and low rates of local or distant relapse.*

Keywords: *Neuroendocrine tumors, colorectal neoplasms, follow-up studies, endoscopic mucosal resection, cohort studies.*

INTRODUCTION

Rectal neuroendocrine tumors (R-NET) have shown an increased incidence in recent years, and this is thought to be due to the increased awareness of the disease process, in conjunction with increased CRC screening.[1-3] Of all rectal neoplasms, NET affect less than 2% and are reported in only 0.05% to 0.07% of patients undergoing CRC screening.[1,4] The racial distribution R-NET occurrence in the United States differs significantly from other sites, with a higher rate observed in blacks and Asians compared to whites.[1,5,6] There is a slight predominance in males over females, by a factor of approximately 1.1. R-NET are commonly diagnosed in the sixth decade of life, with a mean age at diagnosis of 56 years.[5,6]

Approximately half of all R-NET are diagnosed in the low endoscopic routine and also during CRC or symptom investigation.[5,6,7] The TNM 2010 World Health Organization (WHO) staging system and the Ki67-based classification determined a better prognostic assessment of these tumors.[5,6]

The risk of malignant behavior is related to tumor size and invasion depth.[1,3,8] With increasing early detection, minimally invasive endoscopic methods for resection have emerged, and the guidelines suggest endoscopic treatment for R-NET smaller than one centimeter.[3]

Objective

The primary endpoint of this study was to assess risk factors associated with R-NET greater than 10 mm. The secondary endpoint was to evaluate the response to endoscopic treatment.

MATERIALS AND METHODS

This study was a retrospective analysis, with data collected by reviewing the medical records of patients

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undergoing colonoscopies performed from January 2008 to December 2014 at the A.C. Camargo Cancer Center, São Paulo (SP), Brazil. We identified patients who had endoscopic resection of lesions, and we selected the anatomopathological results of R-NET. We collected epidemiological data such as age, gender, race, previous cancer diagnosis, indication and findings on colonoscopy, the Ki67 index, and outcomes such as local and distant recurrence. In order to obtain a more reliable measurement of the size of the lesion, we used the piece measurement sent to the pathology. The exclusion criteria for the study were the presence of NET from 2 concurrent intestinal sites other than the rectum, age younger than 18 years, or the presence of other lesions such as adenoma, hyperplastic polyp, inflammatory and serrated adenoma, in the absence of NET.

Statistical Analysis

For the statistical analysis, the relative risk calculation was performed considering a 95% confidence interval and an alpha value of 0.05. An adjusted linear regression calculation was also performed to verify the association between the independent variables such as age, gender, presence of diverticula, previous cancer diagnosis, Ki67 index, and Asian origin and the dependent variables, for lesions greater than or equal to 10 mm. The calculations were made using the program BioEstat 5.3 (ONG Mamiraua, Belém, PA, Brazil).

RESULTS

During the study period, 18 218 colonoscopies were performed and 10 865 lesions were detected and removed. We identified 20 R-NET (Table 1). The incidence of R-NET was 0.10%. The survey of the epidemiological data revealed that of the 20 patients with R-NET, 3 (15%) were of Asian ethnicity and 17 (85%) were westerners, 11 (55%) were females and 9 (45%) males. The mean age of patients was 55.4 years (30 to 71 years). In patients with lesions greater than or equal to 10 mm, the average age was 51.50 years, and the average age of patients with lesions less than 9 mm was 56.38 years. The main indication for colonoscopy was CRC screening in 9 (45%), followed by bleeding (2), altered bowel habits (2), and primary tumor screening in patients with metastasis (2), a family history of CRC in 1 (5%), and abdominal pain (1); colonoscopy was also performed during the review in patients treated for CRC (1), for polyp removal (1), and to investigate weight loss (1). In the study, 11 (55%) had no history of cancer, 2 (10%) had breast cancer; and of for the other patients, NET from other sites 2 (10%), CRC 1 (5%), prostate cancer 1 (5%), retroperitoneal tumor 1 (5%), malignant melanoma 1 (5%), and unknown primary cancer site 1 (5%) were found.

Table 1. Patient Characteristics

N	20
Age (SD), years, median (range)	55.4 (45 ± 9) (30-71)
Asian/Western	3/17
Colonoscopy indication	
Screening CRC	9
Hematochezia	2
Alteration of bowel habits	2
Primary tumor site search CRC	2
CRC family history	1
Abdominal pain	1
Follow-up after CRC treatment	1
Weight loss	1
Polyp removal	1
Previous oncological disease	
Absent	11
Breast cancer	2
Neuroendocrine tumor from other sites	2
Colorectal cancer	1
Prostate cancer	1
Retroperitoneum tumor	1
Melanoma	1
Primary cancer site unknown	1
Presence of diverticula on colonoscopy (n)	4
R-NET size (mm). median (range)	7.05 (4-11)
Polypectomy/mucosectomy	18/2
Grade 1 (n)	20
Submucosa infiltration	6
Ki67 index (<1%/> 2%)	13/6

CRC, colorectal cancer; R-NET, rectal neuroendocrine tumor; SD, standard deviation.

During colonoscopy, 15 (75%) patients were found to have only R-NET. The other findings in the colonoscopy that were revealed in 5 (25%) patients, besides the R-NET were: 2 patients with 1 adenoma each, 1 patient with a hyperplastic polyp, 1 with an inflammatory polyp, and 1patient with 3 adenomas. Diverticula were found in 25% (5) of the patients, and the examination was complete in 95% (19) of the cases; and, 1 patient in

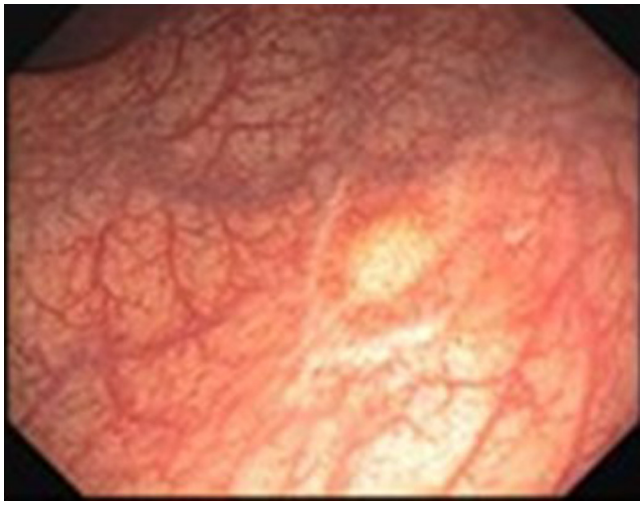

Figure 1. Macroscopic aspect of rectal neuroendocrine tumor.

whom the cecum examination was not possible, underwent virtual colonoscopy with no findings other than the R-NET. The endoscopic aspects of all R-NET were subepithelial lesions, yellowish in color, and without surface ulceration (Figure 1). The resection method used was loop polypectomy in 18 patients and mucosectomy with elevation of the submucosa in 2 patients. The average size of the lesions was 7.05 mm (4 mm to 11 mm), and all material was sent for anatomopathological study. All were of differentiation degree one, and six had submucosal infiltration. The Ki67 index was 1% or less in 13 patients, while it was 2% or more in 6 patients. Two lesions had compromised margins and 8 had free margins. Lesions measuring 10 mm or more were identified in 4 patients, and in 16 patients, the lesions measured 9 mm or less.

The relative risks (RR) were calculated for factors of age, gender, race, previous oncological diagnosis, presence of diverticulum on colonoscopy, and the Ki67 index (Table 2).

The Asian population, all of Japanese descent, tended to have larger lesions. Of the 3 subjects, 2 (66.7%) had lesions > 10 mm, with a RR of 6.0 (CI: 3.38-10.66; *P* = .0001). There was no difference in lesion size between males and females (CI, 0.7-2.14; *P* = .29).

In patients older than 50 years 7.1% had tumors > 10 mm, whereas in those younger than 50 years the frequency was 50%, with RR: 0.31 (CI, 0.25-0.81; *P* = .05). Among patients with previous cancer diagnosis, 11.1% had tumors > 10 mm, while in those without cancer diagnosis, the corresponding rate was 27.3%, RR: 2.45 (CI, 1.29-4.67; *P* = .003). The presence of diverticula was not associated with lesions > 10 mm, RR: 2.45 (CI: 0.57-1.74 *P* = .42). In patients with Ki67 > 1%, 50% had lesions > 10 mm, while in those with Ki67 <1% the corresponding rate was 7.7%, RR: 7.14 (CI: 3.41-14.98 *P* = .0001).

Table 2. Risk Factors Associated With Lesions Greater Than or Equal to 10 mm

Risk Factor	*N*	%	Relative Risk	CI	*P*
Age (<50 years)	3	50	0.31	0.25-0.81	.056
Male	2	22.2	1.22	0.70-2.14	.297
Lack of previous cancer diagnosis	3	27.3	2.45	1.29-4.67	.003
Diverticulum finding in colonoscopy	2	20	1.00	0.57-1.74	.429
Ki67 index > 2%	3	50	7.14	3.41-14.98	.0001
Asian (Japanese)	2	66.7	6.00	3.38-10.66	.0001

Sixteen patients maintained follow-up at the service, and 4 patients were lost to follow-up (all with lesions smaller than 10 mm). The duration of follow-up ranged from 14 months to 114 months, with an average of 56.6 months. There was no evidence of local, lymph node, or distant disease recurrence during the follow-up period.

DISCUSSION

Rectum NET are commonly small, of low or intermediate degree of differentiation (G1 and G2), and have become increasingly common in relation to other sites, including the small intestine, since the 2000s.[9] Rectal NNE (neoplasia neuroendocrine) tumors are classified according to WHO 2010 and are recognized in the following categories: NET, neuroendocrine carcinoma (NEC), and mixed adenoneuroendocrine carcinoma (MANEC).

Neuroendocrine tumors are well-differentiated neuroendocrine neoplasms with low cell atypia and low proliferative activity, and comprise degrees of differentiation 1 and 2. NEC are poorly differentiated neuroendocrine neoplasms, showing marked cellular atypia with high proliferative activity. They are the so-called Grade 3 tumors, and 2 categories are recognized: large-cell NEC and small-cell NEC. Rectal NNE are graded at 3 levels, based on tumor cell proliferation, as shown in Table 3. When the degree assessed by mitotic count and Ki67 differ, the higher degree is assumed. The WHO classification implies

Table 3. Criteria for Differentiation of the Degree of R-NET

Mitotic Index (MI) and Ki67	
Low grade (G1)	MI <2 /10 hpf AND <3% Ki67 index
Intermediate grade (G2)	MI 2-20 /10 hpf OR 3%-20% Ki67 index
High grade (G3)	MI >20 /10 hpf OR >20% Ki67 index

R-NET, rectal neuroendocrine tumors; G1, Grade 1; G2, Grade 2; G3, Grade 3; hpf, high-power fields.

that the colorectal NNE category is malignant, and therefore should be staged according to a site-specific staging system (TNM)[1,5] (Table 4).

A neuroendocrine tumor is a well-differentiated neuroendocrine neoplasm, composed of tumor cells that express neuroendocrine markers such as chromogranin A, synaptophysin, and hormones. Cell atypia and proliferative activity are low. They are, by definition, Grade 1 or Grade 2. The rectum and colon NET are of enterochromaffin or L-cell type. The first ones occur mainly in the right colon, and are characterized by the production of serotonin.[5] Approximately half of R-NET are diagnosed during a screening program for investigation of unrelated symptoms, and about 82% are diagnosed as localized diseases.[5,6] Comparing to other primary sites, rectal NET are associated with higher 5-year survival rates, reaching

Table 4. Staging of the Neuroendocrine Tumor of the Rectum

	AJCC				ENETS			
Stage	Primary Tumor CD				T-Primary Tumor			
Tx	Primary tumor cannot be assessed				Primary tumor cannot be assessed			
T0	No evidence of primary tumor				No evidence of primary tumor			
T1	Tumor invades lamina propria or submucosa and size <2 cm				Tumor invades mucosa or submucosa			
T1a	Tumor size <1 cm in greatest dimension				Size <1 cm			
T1b	Tumor size 1-2 cm in greatest dimension				Size 1-2 cm			
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa				Tumor invades muscularis propria or size >2 cm			
T3	Tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissue				Tumor invades subserosa pericolic perirectal fat			
T4	Tumor invades peritoneum or other organs				Tumor directly invades other organ structures and or perforates visceral peritoneum			
	Regional Lymph Nodes (N)				N-Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed				Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastases				No regional lymph node metastases			
N1	Regional lymph node metastases				Regional lymph node metastases			
	Distant Metastases (M)				M-Distant .Metastases (Sub-specifications as in Small Bowel)			
M0	No Distant Metastases				No Distant Metastases			
M1	Distant Metastases				Distant Metastases			
	Stage	T	N	M	Stage	T	N	M
	I	T1	N0	M0	LA	T1a	N0	M0
					IB	T1b	N0	M0
	IIA	T2	N0	M0	HA	T2	N0	M0
	IIB	T3	N0	M0	IIB	T3	N0	M0
	IIIA	T4	N0	M0	II1A	T4	N0	M0
	IIIB	Any T	N1	M0	1IIB	Any T	N1	M0
	IV	Any T	Any N	Ml	IV	Any T	Any N	M1

NETs, neuroendocrine tumors; AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; T, primary tumor; N, regional lymph nodes; M, distant metastases. (Source: Anthony LB, Strosberg JR, Klimstra DS, 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. Pâncreas 2015; 22:213-20.)

88%. The tumor size, depth of invasion, and lymph node involvement predict malignant behavior in localized R-NET. According to Concors et al.,[10] in their retrospective cohort study involving 4893 participants, 3880 (79.3%) had well-differentiated R-NET. The increased size was associated with a higher likelihood of lymph node involvement, and both the size and degree of differentiation were independent factors associated with a greater likelihood of distant metastatic disease. For the well-differentiated, the cutoff point was 1.15 cm (sensitivity: 88% and specificity: 88%).[1,10]

The present study included 20 patients extracted from a retrospective cohort of patients undergoing colonoscopy performed at the A.C. Camargo Cancer Center in São Paulo (SP), Brazil, from January 2008 to December 2014, who had rectal lesions resected by colonoscopy and confirmed by the pathology as NET. The detection rate of R-NET in patients who underwent colonoscopy in this study was 0.10%, about twice higher than that described by Gleeson et al.[4] (0.05% to 0.07%). The mean age was similar to that reported by the American Society of Neuroendocrine Tumor (NANETS), at 56 years versus 55.4 years, and the predominance was female, at 55%; unlike NANETS, it was slightly higher for males by a factor of 1.1.[1] Almost 85% were Western, and 15% were Asian. The average size of the lesions was 7.05 mm (between 4 mm and 11 mm). All tumors were Grade 1 differentiated, and 6 had submucosal infiltration. The invasion of the submucosa and not of the proper muscle was suggested by the small dimensions of the lesions. The Ki67 index <1% in 13 patients and > 2% in the others. Two lesions had compromised margins, and colonoscopy surveillance was chosen for all patients. The risk factors associated with lesions > 10 mm were: absence of previous cancer diagnosis, Ki67 index > 2%, and Asian descent.

The authors chose to use the conventional polypectomy, due to the small dimensions of the lesions. R-NET < 10 mm are usually confined to the submucosa, without lymphovascular invasion, and rarely metastasize.[11] Endoscopic treatment is considered as appropriate therapy in these lesions.[5]

In lesions between 10 mm and 20 mm without muscle, lymphatic, and G1 invasion, endoscopic treatment is recommended.[5] However the suggested procedure is an endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), to achieve a greater complete resection rate (R0).[12]

In a recent meta-analysis, Jianmer Pan et al.[11] evaluated the techniques of ESD and EMR with suction, reaching high rates of R0, at 93.6% and 84%, respectively.

R-NET has a higher incidence in the Asian population[13] and the Ki67 index is associated with a worse prognosis,[1] but there is no reference regarding the absence of previous cancer being associated with larger lesions, as the authors evaluated in this study. In this study, lesions > 10 mm were not associated with the presence of other tumors.

Lesions removed by colonoscopy had an excellent prognosis. The mean follow-up of the patients was 56.6 months (14-114 months), and none of them reported local or distant recurrence. The worst prognosis could not be correlated with relapse or metastasis, as these events did not occur at diagnosis or throughout follow-up.

CONCLUSION

The authors present a series of cases in which endoscopic resection was a good treatment method for patients with differentiation Grade 1 NET, with lesions <11 mm. The risk factors associated with lesions > 10 mm were: the absence of a previous cancer diagnosis, a Ki67 index > 2% and Asian descent. It was not possible to correlate the worst prognosis with relapse or metastasis, as these events did not occur at diagnosis or throughout follow-up.

Ethics Committee Approval: This study was approved by the Research Ethics Comittee of Ethics of A.C. Camargo Cancer Center.

Informed Consent: All subjects signed the written consent forms.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.S.L.C., E.A.V.R., V.A.V.; Design - P.M., F.S.C.K., E.T.; Supervision - W.T.N.; Resource - J.S.L.C., W.T.N.; Materials - J.S.L.C., E.C.V.R, V.A.V.; Data Collection and/or Processing - J.S.L.C., P.M.; Analysis and/or Interpretation - W.T.N; Literature Search - O.W.M.J., C.A.M.C.F.; Writing - J.SL.C., W.T.N.; Critical Reviews - W.T.N., E.T.

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REFERENCES

1. Anthony LB, Strosberg JR, Klimstra DS, 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. Pâncreas. 2015;22:213-220.
2. Bertani E, Ravizza D, Milione M, et al. Neuroendocrine neoplasms of rectum: a management update. Cancer Treat Rev. 2018;66:45-55. [CrossRef]
3. Chablaney S, Zator ZA, Kumta NA. Diagnosis and management of rectal neuroendocrine tumors. Clin Endocr. 2015;22:213-220.
4. Gleeson FC, Levy MJ, Dozois EJ, et al. Endoscopically identified well-differentiated rectal carcinoid tumors: impact of tumor size on the natural history and outcomes. Gastrointest Endosc. 2014;80(1):144-151. [CrossRef]
5. Caplin M, Sundin A, Nillson O, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology. 2012;95(2):88-97. [CrossRef]
6. Mandair D, Caplin ME. Colonic and rectal NET's. Best Pract Res Clin Gastroenterol. 2012;26(6):775-789. [CrossRef]
7. Basuroy R, Haji A, Ramage JK, Quaglia A, Srirajaskanthan R. Review article: the investigation and management of rectal neuroendocrine tumors. Aliment Pharmacol Ther. 2016;44(4):332-345. [CrossRef]
8. Rodrigues Â, Castro-Poças F, Pedroto I. Neuroendocrine rectal tumors: main features and management. GE Port J Gastroenterol. 2015;22(5):213-220. [CrossRef]
9. Ramage JK, De Herder WW, Delle Fave G, et al. ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):139-143. [CrossRef]
10. Concors SJ, Sinnamon AJ, Folkert IW, et al. Predictors of metastases in rectal neuroendocrine tumors: results of a National Cohort Study. Dis Colon Rectum. 2018;61(12):1372-1379. [CrossRef]
11. Pan J., Zhang X., Shi Y., Pei Q. Endoscopic mucosal resection with suction vs. endoscopic submucosal dissection for small rectal neuroendocrine tumors: a meta-analysis. Scand J Gastroenterol. 2018;53(9):1139-1145. [CrossRef]
12. Lee D. S., Jeon S. W., Park S. Y., et al. The feasibility of endoscopic submucosal dissection for rectal carcinoid tumors: comparison with endoscopic mucosal resection. Endoscopy. 2010;42(8):647-651. [CrossRef]
13. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934 -959. [CrossRef]