

## COLON AND RECTUM NEUROENDOCRINE TUMORS: EXPERIENCE OF THE NATIONAL CANCER INSTITUTE IN BRAZIL

*Tumores neuroendócrinos do cólon e reto: experiência do Instituto Nacional do Câncer no Brasil*

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**ABSTRACT - Background** - Neuroendocrine tumors (NETs) are rare, comprising nearly 0.49% of all malignancies. The majority occurs in the gastrointestinal tract. **Aim** - To analyze the demographic factors, clinicopathologic features, treatment employed, prognostic factors and the oncologic results related to colorectal NETs. **Methods** - Between the period from 1996 to 2010 174 patients were treated. From these, 34 were localized in the colon and rectum. Demographic factors, stage, therapeutics and its results were analyzed. All patients were followed for more than three years with image exams, urinary 5-hydroxyindolacetic acid (5-HIAA), serum chromogranin A and prostatic acid phosphatase. **Results** - The median age was 54,4 years (22-76), the majority was female (64,7%). Out of the 12 patients with colon NETs, one (8,3%) patient was classified as Stage IA; one (8,3%) as Stage IB; three (25%) as Stage IIIB and seven (58,4%) as Stage IV. Out of the 22 patients with rectum NETs, six (27,3%) were classified as Stage IA; four (18,2%) as IB; three (13,6%) as IIIA; one (4,5%) as IIIB and eight (36,4%) as IV. Of rectal NETs, nine (41%) were treated with endoscopic resection, six (27,2%) underwent conventional surgical treatment and six (27,2%) were treated with chemotherapy. Eleven patients with colon NETs (91,6%) were surgically treated, seven of them with palliative surgery, one (8,4%) was treated with endoscopic resection and no patient was submitted to chemotherapy. After an average follow-up of 55 months, 19 (55%) patients were alive. Analyzing the overall survival was obtained an average overall survival of 29 months in Stage IA, 62 months in IB, 12 months in IIIA, 31 months in IIIB and 39 months in IV. **Conclusion** - The treatment of colon and rectal NETs is complex, because it depends of the individuality of each patient. With adequate management, the prognosis can be favorable with long survival, but it is related to the tumor differentiation degree, efficacy of the chosen treatment and to the patient adhesion to the follow-up after treatment.

**HEADINGS** - Neuroendocrine tumors.  
Colon. Rectum. Prognosis. Treatment.

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**RESUMO - Racional** - Os tumores neuroendócrinos (TNEs) são raros e compreendem apenas 0,49% de todas as neoplasias malignas. A maioria acomete o trato gastrointestinal. **Objetivo** - Analisar os fatores demográficos, características clinicopatológicas, tratamento empregado, fatores prognósticos e resultados oncológicos relacionados aos TNEs colorretais. **Métodos** - No período compreendido entre 1996 e 2010 foram tratados 174 pacientes. Destes, 34 localizavam-se no cólon e reto. Foram analisados fatores demográficos, estadiamento, os procedimentos terapêuticos aplicados e seus resultados. No seguimento todos os pacientes foram acompanhados acima de três anos com exames de imagem, dosagem de 5-HIAA urinário, cromogranina-A sérica e fosfatase ácida prostática. **Resultados** - A média de idade no diagnóstico foi de 54,5 anos (22-76), com predominância do sexo feminino (64,7%). Dos 12 com TNEs de cólon, um (8,3%) foi classificado como estágio IA; um (8,3%) em IB; três (25%) em IIIB e sete (58,4%) em IV. Dos 22 pacientes com TNEs de reto, seis (27,3%) foram classificados como estágio IA; quatro (18,2%) em IB; três (13,6%) em IIIA; um (4,5%) em IIIB e oito (36,4%) em IV. Dos TNEs de reto, nove (41%) foram tratados com ressecção endoscópica, seis (27,2%) com procedimento cirúrgico e seis (27,2%) somente com quimioterapia. Onze pacientes com TNEs de cólon (91,6%), foram tratados cirurgicamente, sendo sete paliativamente, um (8,4%) com ressecção endoscópica e nenhum foi submetido à quimioterapia no primeiro momento. Após seguimento médio de 55 meses, 19 (55%) pacientes estavam vivos. Analisando a sobrevida global obteve-se média de 29 meses no estágio IA, 62 meses no IB, 12 meses no IIIA, 31 meses no IIIB e 39 meses no IV. **Conclusão** - O tratamento dos TNEs de cólon e reto é complexo, pois depende de variáveis que são individuais a cada paciente. Com adequado manuseio, o prognóstico pode ser favorável e a sobrevida longa, mas ela está relacionada ao grau de diferenciação tumoral, tamanho, localização do tumor, estadiamento no momento do diagnóstico, eficácia da terapêutica adotada e à aderência do paciente ao seguimento após o tratamento.

**DESCRITORES** - Tumores neuroendócrinos.  
Cólon. Reto. Prognóstico. Tratamento.

## INTRODUCTION

Neuroendocrine tumors (NETs) arise from Kulchitsky or chromaffins cells, which cover the epithelium of the respiratory and digestive tracts. These are rare neoplasias<sup>5</sup>, comprising only 0.49% of all malignant tumors<sup>12</sup>. Historically, the term "carcinoid" was employed to designate the intestine epithelial tumors that presented a relatively similar structure and behavior less aggressive than carcinomas<sup>14</sup>. Due to the morphological and biological heterogeneity of this disease, the World Health Organization (WHO) in 2000, adopted a new classification, and it forthwith called such neoplasm as Neuroendocrine Tumors and Neuroendocrine Carcinomas<sup>19</sup>. The distinction was made between well-differentiated neuroendocrine tumors, which showed: 1) benign behavior or an uncertain malign potential (WHO classification 1a); 2) benign behavior with low malignant potential (WHO classification 1b); 3) and well differentiated neuroendocrine carcinomas with low malign potential (WHO classification 2); 4) poor differentiated neuroendocrine carcinomas with high malign potential (WHO classification 3)<sup>9</sup>.

Despite the considerable advances made in recent decades in relation to the cell origin, cell proliferation markers, diagnosis and treatment of colon and rectum NETs, some aspects remain open.

The objective of this study is to analyze the demographic factors, clinicopathologic features, treatment employed, prognostic factors and the oncologic results related to colorectal NETs.

## METHODS

Between the years 1996 and 2010, 174 patients with neuroendocrine tumors of the gastrointestinal tract were treated at Cancer National Institute – INCA, Rio de Janeiro, RJ, Brazil. Out of these, 34 were located in the colon and rectum.

To analyze the demographic factors the median age at diagnosis and gender of the colon and rectal tumors were observed separately. To staging, the ENETS (European Neuroendocrine Tumor Society) 2006 stage system was used<sup>15</sup>. Considering the treatment employed the endoscopic, laparoscopic, conventional surgical procedures and adjuvant chemotherapy were studied.

In the follow-up period, all patients had medical consults with three, six, nine and twelve months in the first year, biannually during the first three years and annually thereafter. The following exams were used during this period: abdominal USG or CT, chest radiography, urinary 5-HIAA, serum chromogranin A and prostatic acid phosphatase in all medical consults.

For prognosis the recurrence was defined as the emergence of regional or distant disease after three months of initial treatment.

## RESULTS

The average age at diagnosis was 54.5 years (22-76), predominantly female (64.7%). Out of the patients studied, 12 (35.3%) had colon NETs and 22 (64.7%) rectum. When analyzed separately, the average age for rectum NETs was 50 years (22-74), predominantly female (72.7%), while the average age for colon NETs was 59 years (46-76), with identical distribution between genders.

The 34 patients were analyzed according to the proposed staging system by ENETS<sup>15</sup>. Out of the 12 patients with colon NETs, one (8.3%) patient was classified as stage IA; one (8.3%) as IB; three (25%) as IIIB and seven (58.4%) as IV. Out of the 22 patients with rectum NETs, six (27.3%) patients were classified as stage IA; four (18.2%) as IB; three (13.6%) as IIIA; one (4.5%) as IIIB and eight (36.4%) as stage IV.

When the therapeutic approach of rectum NETs was analyzed, nine (41%) were treated with endoscopic resection, six (27.2%) with surgical treatment and six (27.2%) treated with chemotherapy, because they presented distant or locally advanced disease at diagnosis. Eleven patients with colon NETs (91.6%) were surgically treated, seven of them with palliative surgery since they had advanced disease (stage IV), one (8.4%) was treated with endoscopic resection and no patient was submitted to chemotherapy early in the process.

After an average follow-up of 55 months (2-178 months), 19 (55%) patients with colorectal NETs were alive. Analyzing the overall survival with respect to clinical stage, was obtained a median overall survival of 29 months in stage IA, 62 months in IB, 12 months in IIIA, 31 months in IIIB and 39 months in IV

## DISCUSSION

In 2003, Modlin et al.<sup>12</sup> analyzed 13,715 NETs collected between 1973 and 1999, the highest incidence of NETs occurred in the gastrointestinal tract (67.5%) followed by the bronchopulmonary NETs (25.3%). When only the gastrointestinal tract NETs were analyzed, most of them occurred in the small intestine (41.8%), followed by the rectum (27.4%) and stomach (8.7%). In this study was identified incidence of 19,5% of colon and rectum NETs, therefore different of the percentiles referred by the authors.

Median age relatively lower for NETs than to adenocarcinomas was described before by Godwin in 1975<sup>5</sup>. The same was observed in this series.

The NETs present morphological characteristics and their own staining pattern. Their cells have slightly pink granular cytoplasm and rounded nucleus with few

mitoses<sup>18</sup>. These cells were called enterochromaffins because they are stained by potassium chromate. They absorb and reduce the silver, and are also called argentaffins. Some of them absorb the silver, but are not able to reduce it, receiving the designation of arginophytic<sup>2</sup>.

Argentaffin and angiophytic cells have the ability to absorb and decarboxylate precursor amines. Both cells from the neural crest and NETs are capable to synthesize very similar amines and the ability of NETs to synthesize 5-hydroxytryptophan (5-HTP) from food tryptophan is pathognomonic of these neoplasms. The by-product of 5-HTP metabolism is 5-hydroxyindolacetic acid (5-HIAA), a marker used in clinical evaluation for NETs.

Numerous studies have been made in cell proliferation markers, Ki-67, mitotic rate and tumor suppressor protein (p53) as predictors of malignant behavior in NETs. The basic immunohistochemistry in the evaluation and histological classification include Ki-67, chromogranin and synaptophysin. Of these, the chromogranin was used in this study and showed to be an adequate prognosis marker.

There is no doubt that the main biochemical markers used in the clinical practice for NETs are the urinary 5-HIAA and the serum chromogranin A. The elevation of the degree of the urinary 5-HIAA is correlated with the severity of the carcinoid syndrome. But in the colorectal NETs this exam is often negative<sup>4</sup>. Although the serum chromogranin A is not a specific marker it is very useful in the follow-up, in the evaluation of response after treatment and disease progression<sup>20</sup>. High serum concentrations are found in patients with advanced disease<sup>7</sup>, being, therefore, considered a prognosis marker. In NETs of the rectum, pancreatic polypeptide, enteroglucagon and  $\beta$ -hCG may be useful tools in the monitoring of this neoplasia<sup>13</sup>. The prostatic acid phosphatase is present in 80-100% of rectal NETs<sup>3</sup>; this marker should always be requested once the diagnosis is made for purposes of evaluating the response to the treatment and follow-up after surgery.

The clinical presentation varies, depending on the size, the primary site and the type of substance produced by the tumor. There is an association between inflammatory bowel diseases and colon NETs<sup>6</sup>. But in the majority of the cases they are not associated with this condition and are usually incidentally found during endoscopies, because they are often small and asymptomatic. When they become larger, they may have bleeding, intestinal obstruction and tenesmus. Although varying in frequency this clinical features were observed in this study.

The carcinoid syndrome manifests itself in approximately 10% of patients, and occurs when the metabolites of 5-HTP, neurohormones and prostaglandins released by the tumor to systemic circulation, bypassing hepatic metabolism. Carcinoid syndrome occurs in the presence of metastatic liver

disease, extensive retroperitoneal disease or when primary site is extraintestinal (bronchi, ovaries, testicles). It is characterized by flush, diarrhea, bronchospasm, heart valve disease and pellagra<sup>1</sup>. Rarely rectum NETs present carcinoid syndrome, and when the symptoms occurs, they are similar to those ones of the carcinoid syndrome of ileum tumors, due to similarities of the products secreted by both tumors. Distant metastases may be present at diagnosis (1.7% - 8.1%), but in most cases the disease is localized (75% - 85%)<sup>12</sup>.

Most colorectal NETs are diagnosed by endoscopy. Transrectal ultrasound is an imaging method useful for staging rectal tumors. The tumor size, depth of invasion and lymphadenopathies can be studied with good accuracy<sup>11</sup>. It can guide the treatment. Small tumors (<10mm), limited to the mucosa and with out nodal disease can be managed by endoscopic resection or local resection with safety<sup>14</sup>.

Computed tomography and magnetic resonance imaging are more sensitive and specific than ultrasonography for diagnosis and follow-up in patients with colorectal NETs<sup>8</sup>. Octreotide scintigraphy (Octreoscan) is very useful in the diagnosis of metastatic disease not visualized on CT or MRI, or for investigation of liver disease where the primary NET is unknown.

In November 2006, the consensus of ENETS (European Neuroendocrine Tumor Society) approved the TNM classification for staging of colon and rectum NETs<sup>15</sup>. This classification should be used in the management of these patients to guide the treatment and prognosis, which is related to tumor differentiation, size, location, stage at diagnosis, effectiveness of therapy and follow-up.

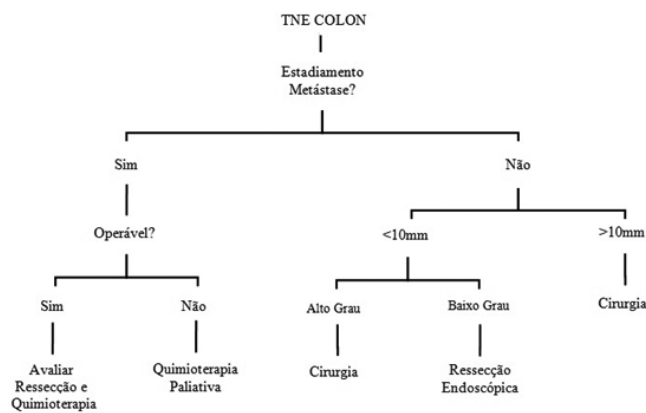
Surgery is the only therapy that can cure colon and rectum NETs<sup>10</sup>. The surgical options are divided into two types: conventional surgery (colectomy, anterior resection of the rectum or abdominoperineal amputation) and local resection (endoscopic resection, transanal excision or TEM [Transanal Endoscopic Microsurgery]). In tumors smaller than 10 mm, local resection is an acceptable therapeutic option, since imaging study does not show lymphadenopathy, the margins obtained are free and the degree of differentiation does not reveal poorly differentiated neuroendocrine carcinoma and/or grade 3<sup>17</sup>. In tumors larger than 20 mm, with invasion of the muscular layer or suspected lymph node disease conventional surgery is indicated<sup>16</sup>. Tumors between 10-20 mm are subject of controversy. In these cases, it is fundamental to differentiate the treatment between the NETs of colon and rectum. In NETs of colon surgical resection of the affected segment is indicated, as well as all regional lymph node chain, either by conventional surgery or laparoscopy. For rectal NETs between 10-20 mm with invasion of the muscular layer, angiolymphatic invasion, or showing symptoms, resection by conventional surgery is indicated. The authors of this paper suggest that tumors larger than 20 mm and with angiolymphatic

invasion have more risk of metastasis, either nodal or distant.

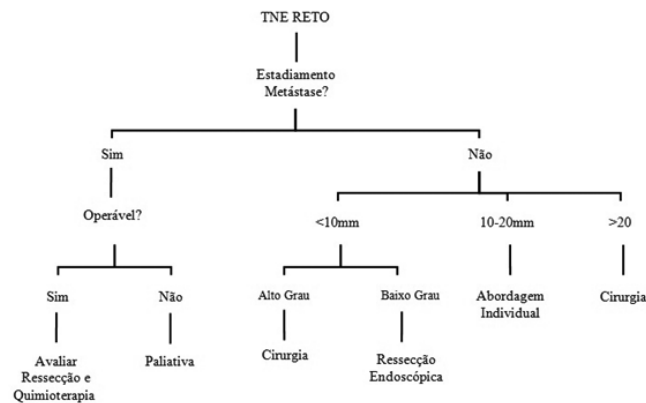
In attempting anal preservation, a diameter of 15 mm can be used as a cutting point for decision between local excision or abdominoperineal amputation, when the tumor does not present lymphatic or vascular invasion in previous biopsy. Therefore, the treatment of rectal NETs larger than 10 mm must be individually tailored, considering age, comorbidity and patient's wishes.

In Figures 1 and 2 are shown algorithms for the management of NETs for the better understanding of the therapeutics options.

## CONCLUSION



**FIGURE 1** – Treatment algorithm for colon NETs



**FIGURE 2** – Treatment algorithm for rectum NETs

The treatment of colon and rectal NETs is complex, because it depends of the individuality of each patient. With adequate management, the prognosis can be favorable with long survival, but it is related to the

tumor differentiation degree, efficacy of the chosen treatment and to the patient adhesion to the follow-up after treatment.

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