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Review Article

# Rectal carcinoid tumor: diagnosis and management

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ABSTRACT

The authors present a case of rectal carcinoid tumor in an asymptomatic patient who sought a coloproctology service with the purpose of colorectal cancer prevention. During colonoscopy, a polyp lesion was found in the rectum, and it was resected with a polypectomy loop. Anatomopathological examination revealed a rectal carcinoid tumor with compromised margins. The lesion site was resected again and pathological exam no longer showed neoplasia. A systematic review of the issue was performed, discussing diagnosis aspects, difficulties in the choice of therapeutic approaches, and prognosis. The conclusion is that the rarity of the disease brings difficulties in the choice of treatment; although it has a good prognosis in most cases, its malignant potential cannot be underestimated.



## Tumor carcinoide de reto: diagnóstico e orientação

*Palavras-chave:*
Tumor carcinóide
Reto
Tumor neuroendócrino

RESUMO

Apresentamos um caso clínico de um tumor carcinóide de reto em um paciente assintomático que procurou um serviço de colo-proctologia com o objetivo de fazer prevenção ao câncer colorretal. Durante a colonoscopia observou-se uma lesão polipóide no reto, a qual foi ressecada com alça de polipectomia. O exame anatomopatológico evidenciou tumor carcinóide de reto com comprometimento de margem. O local foi novamente ressecado e o resultado patológico não mais evidenciou neoplasia. Neste artigo é feita uma revisão bibliográfica do assunto abordando aspectos diagnósticos, dificuldade na escolha da conduta

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terapêutica e prognóstica. O trabalho conclui que a raridade do caso implica em dificuldades na escolha da conduta e que apesar de ter bom prognóstico, em uma parcela dos casos o seu potencial maligno não deve ser desprezado.



## Introduction

Carcinoid tumors were first described in 1867; they were histopathologically defined in 1888 by Lubarsch, who found multiple tumors in the distal ileum of two patients at autopsy.[1] The term *Karzinoide* was used by Oberndorfer in 1907 to describe ileal tumors that presented a more benign behavior than typical adenocarcinomas.[2]

Neuroendocrine tumors grow from Kulchitsky or chromaffin cells, which cover the epithelium of the respiratory and gastrointestinal tract. They originate in the crypts of Lieberkühn.[2] These are rare neoplasms that account for only 0.49% of all malignant tumors.[3] Despite being relatively uncommon when compared with rectal adenocarcinoma, there is evidence that the incidence of rectal carcinoid tumors is increasing, perhaps related to increased diagnosis secondary to greater access to endoscopy.[1] The incidence of colon and rectum carcinoid tumors is approximately 1 per 100,000.[4]

Rectal carcinoids were first described in 1912 and account for 1–2% of all rectal tumors. In contrast with carcinoids of the small intestine and colon, which produce more serotonin, rectal carcinoids mainly produce glucagon and glycine peptides. Characteristically, the vast majority are non-functioning. Of all rectal carcinoid tumors, 50% are asymptomatic and are diagnosed incidentally by endoscopies performed due to various indications. Although potentially metastatic, carcinoid syndrome is rare.[2]

Therefore, although rectal carcinoids present relatively indolent behavior, they are malignant and can metastasize, as postulated by the American Joint Committee on Cancer.[1] Despite the various reclassifications of the World Health Organization, the term "carcinoid" is still used as a synonym for "well differentiated neuroendocrine tumor" and the term "malignant carcinoid" is used as a synonym for "well differentiated neuroendocrine carcinoma." Among these tumors, colon and rectal carcinoids are grouped together in the classification of the World Health Organization (WHO), and are distinct from those of the appendix or ileum. In this classification, colorectal carcinoids are described as having "low grade of malignancy," even in the presence of metastases. This classification also defines colorectal carcinoids as "benign" if the tumors are located within the submucosa, measure 20 mm or less, and there is no vascular invasion. Although many colorectal carcinoids are localized at diagnosis and have low malignant potential, rectal carcinoids measuring less than 1 cm still have malignant potential; the incidence of reported metastases ranges from 1.7% to 3.4%.[5] In a large American series, the five-year survival rate for all carcinoids was 67% and for rectal carcinoids, 88%. Therefore, it is clear that this is not a benign condition, and should be appropriately managed and treated to reduce the risk of local and distant metastases.[1,5–7] It is estimated that up to 50% of patients with carcinoid tumors present metastasis at diagnosis.[2]

The WHO also divides neuroendocrine tumors into three categories: neuroendocrine, neuroendocrine carcinomas, and adenoneuroendocrine carcinomas. These are then graded into three groups based on proliferation rate, mitotic indices, and Ki-67 antigen-positive dye ratio. Minor tumors with no adverse findings, which are eligible for local excision, are probably relatively benign carcinoids, which would be graded as 1 or 2 in the WHO classification. Small tumors with adverse findings or large and aggressive tumors that may present with pain receive the highest grade among neuroendocrine tumors and thus require more aggressive treatment.[8]

Rectal carcinoid tumors are usually small, circumscribed, yellowish, submucosal, and of 1 cm or less in diameter. In a review by Mani et al., the most common finding was the tumor being described as non-specific.[7] The most common complaint was anorectal discomfort, and rectal bleeding was the second most common finding. Other complaints included constipation, weight loss, change in bowel habits, rectal obstruction, hemorrhoids, diarrhea, and the presence of an abdominal mass. Endoscopic ultrasonography is used to determine the depth of the invasion, which is a very important variable in the case of a local resection.[9] The invasion or non-invasion of the muscular mucosa determines whether endoscopic excision is sufficient or if surgery is necessary in cases of endoscopically resected rectal carcinoids. It is generally indicated that lesions smaller than 1 cm in diameter can be adequately treated by endoscopic resection in case of negative margins after histological evaluation.[2,9,10] Another approach is transanal local excision, as 75% of rectal tumors are located in the mid- and lower thirds of the rectum. Anterior abdominal resection or abdomino-perineal amputation of the rectum have also been indicated in lesions larger than 2 cm in diameter.[2,9,10] Treatment and prognosis depend on tumor size, staging, degree, resectability, and distant metastases. In the case of localized tumors, surgical resection should be performed if the tumor is resectable. For tumors at a more advanced stage, control of carcinoid syndrome symptoms and prudent use of anti-tumor therapy are essential.[11]

## Clinical case

The authors present the case of an asymptomatic 57-year-old male patient who presented to the office aiming to undergo a colonoscopy for intestinal cancer prevention He used antihypertensive medication, and had no other comorbidities. Regarding surgical history, he had undergone meniscus surgery. His mother and a sister had a history of breast cancer.

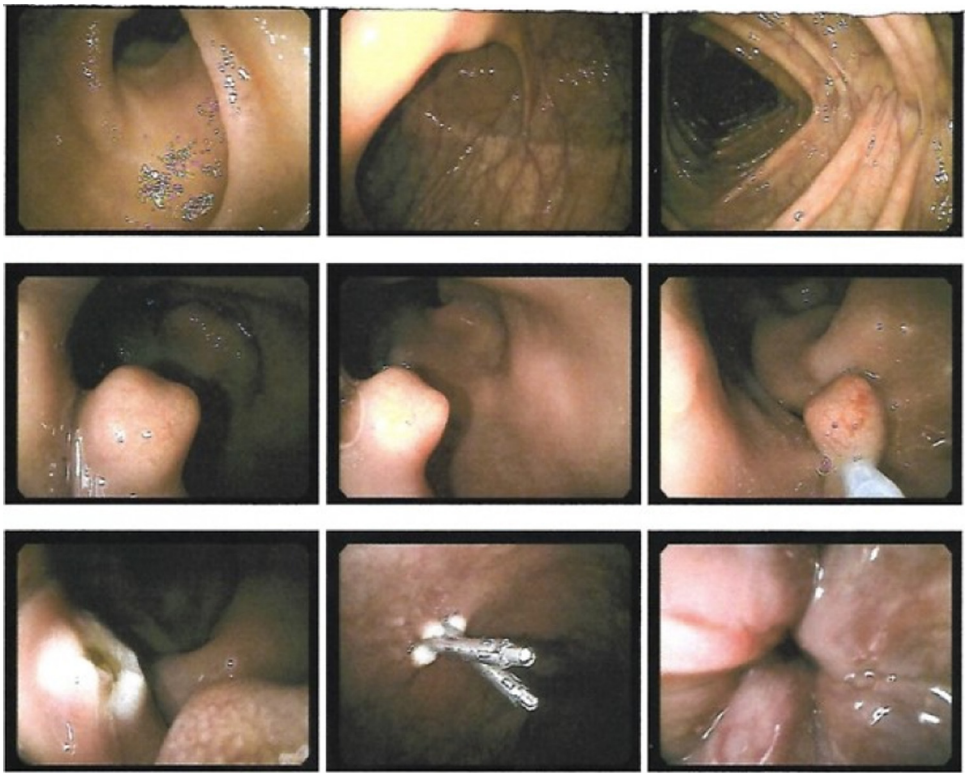

**Fig. 1 – Colonoscopy. Polypoid, yellowish lesion, approximately 1 cm in diameter, resected with a polypectomy loop.**

At colonoscopy, a yellowish polypoid lesion of approximately 1 cm in diameter was observed, which was resected with a polypectomy loop (Fig. 1).

During the examination, no other abnormalities were observed. The anatomopathological result demonstrated a typical carcinoid tumor infiltrating the rectal mucosa, with compromised surgical margins. Immunohistochemical examination confirmed the diagnosis.

Two weeks later, the patient underwent a new endoscopic examination, which evidenced a small scar area in the rectum, subsequently elevated with solution of 0.9% saline solution and adrenaline, followed by a mucosectomy and enlargement of the biopsy in the submucosal layer (Fig. 2).

The anatomopathological evaluation did not evidence a carcinoid tumor. Computed tomography of the abdomen, pelvis, and chest indicated no metastasis or other primary tumor. The patient remains asymptomatic.

## Discussion

The diagnosis and treatment of rectal carcinoid tumors are challenging. They continue to be a condition with unclear protocols and therapeutic modalities that still need better evaluation, even regarding the nomenclature of neuroendocrine tumors.[1] Their incidence in the gastrointestinal tract increases from the duodenum toward the ileum; over 80% are located in the small intestine. They arise most commonly in the cecal appendix, and are found in 0.26% of the appendectomies. The second most common site is the small intestine, followed by the rectum and stomach. Colonic involvement is uncommon, accounting for 2.5% of gastrointestinal carcinoids.[7]

There is a misconception that rectal carcinoids are benign. While many will have an indolent course, there is a clear risk of local or distant metastasis, with associated mortality. Although the results of patients with localized disease are excellent, there is a dramatic decline in outcomes for those with lymph node involvement and distant metastasis.[2]

Carcinoid tumors, regardless of their site of origin, are associated with an increase in the incidence of other malignancies; the rates of a second primary malignancy are up to 55%.[7] A possible reason for the increased incidence of other cancers is the carcinogenic properties of the peptides secreted by neuroendocrine cells.[2]

A permanent dilemma is how to manage a condition in which most patients will have a good prognosis, but a certain proportion will require radical surgery to prevent distant dissemination. How can this subpopulation be stratified? The most commonly used tool is tumor size. Measures of 10 mm, 10–20 mm, and >20 mm have been traditionally used to classify the predictive risk of generating metastasis and to guide management and treatment. Risk factors for metastasis include tumors greater than 10 mm; atypical surface; patients older than 60 years; and invasion of the muscular, perineural, or lymphovascular layer.[1,3,5] This has been reaffirmed by a meta-analysis of three articles, which demonstrated that tumor size greater than 10 mm, pT stage, and lymphovascular invasion were independently associated with an increased risk of metastatic disease.[1,5] Factors associated with survival were

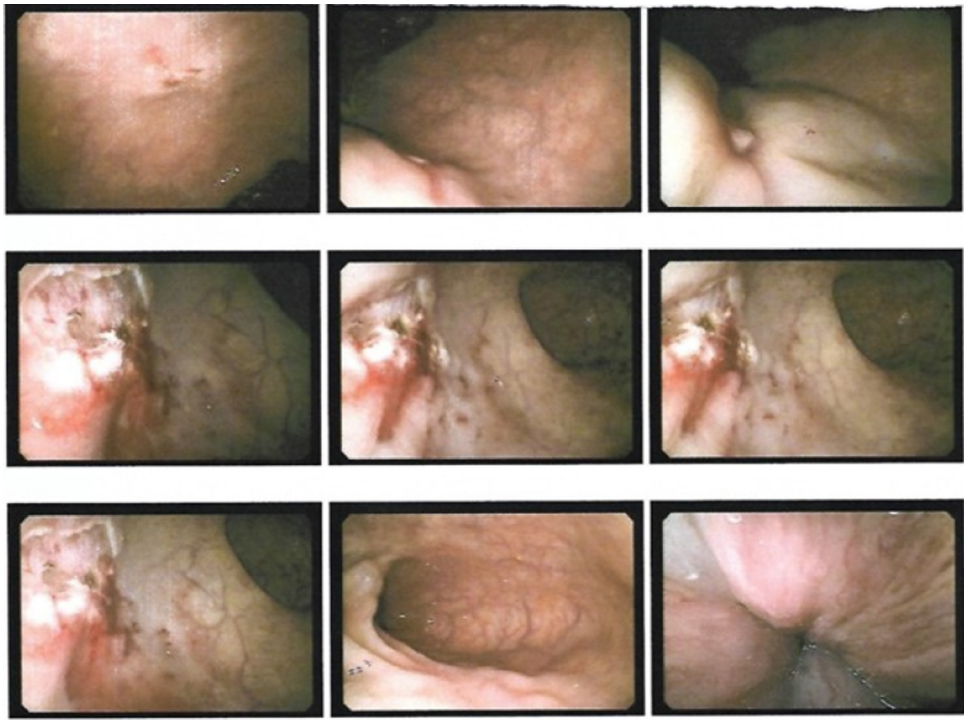

**Fig. 2 – Control colonoscopy. A small scar area is observed in the rectum; a mucosectomy and enlargement of the biopsy in the submucosal layer were performed.**

tumor size, muscle invasion, and presence of metastases. Distant metastases were observed in less than 5% of patients with tumors smaller than 10 mm.[1,5,9,10]

Most carcinoid tumors can be macroscopically distinguished by colonoscopy, and biopsy may inhibit complete resection. Unresected lesions may require frequent endoscopic follow-up and/or subsequent treatments. As a result, they can increase medical costs and cause unnecessary suffering. Biopsy is not currently indicated.[11]

The shape of rectal carcinoids resemble that of sessile polyps. Many endoscopists may misidentify carcinoids smaller than 0.5 cm as hyperplastic polyps and ignore them, thus delaying treatment. One study assessed the use of colonoscopy in the diagnosis and treatment of rectal carcinoids less than 1 cm in 21 patients. Endoscopic ultrasonography was performed in 16 patients, and the lesions were treated with endoscopic mucosal resection. The study concluded that the use of colonoscopy combined with endoscopic ultrasonography was very effective.[9]

In a retrospective study, 106 patients with rectal carcinoid tumors underwent transanal excision (66%) and transabdominal surgery (34%). The five-year survival rate was 87%. Carcinoid invasion of the muscular layer was the only independent prognostic factor to assess five-year survival; tumor size was significantly associated with invasion of the muscular layer ($p = 0.00003$). That study concluded that patients with rectal carcinoid have a good prognosis.[12] A 2016 Japanese study assessed how the country's pathology laboratories reported cases, routines, and types of dye used. Many laboratories reported depth of the invasion, size, lympho-vascular invasion, Ki-67 index, and mitotic count. Only 32.2% reported tumor stage. Chromogranin A and synaptophysin were the most commonly used neuroendocrine markers. D2-40 and elastin dye were frequently used to confirm lymphovascular invasion. That study concluded that there is still a lack of standardization in the description of the anatomopathological findings.[13]

Regarding treatment, there are no definitive protocols to date, but previous studies suggest that local excision is safe if the tumor meets the following criteria: smaller than 10 mm, without invasion of the muscle itself and without ulceration, or smaller than 10 mm with adequate endoscopic surveillance.[1] The literature indicates that tumors larger than 10 mm with lymphovascular invasion are significantly associated with lymph node involvement, requiring mesorectal excision. Smaller tumors can safely be removed with a local excision. T1a lesions (<1 cm and confined to the lamina propria/submucosa) can be safely treated by local excision, as long as resection is complete and the depth of invasion, size, and lymphovascular invasion are known.[1]

The most common treatment is endoscopic, in approximately 78% of all cases. Some studies have demonstrated that endoscopic submucosal resection with a ligature apparatus was superior to endoscopic mucosal resection, with a higher free margin index in the case of small tumors (<10 mm).[1] Chao et al. specifically addressed the comparison between polypectomy and endoscopic submucosal resection using ligature apparatus, indicating the latter as better. The rate of compromised margins was significantly lower in the submucosal resection group (2/33, 6.1%) when compared with the polypectomy group (19/55, 34.5%; $p = 0.002$). The rate of vertical involvement was markedly lower in the submucosal

resection group (1/33, 3.0%) when compared with the polypectomy group (19/55, 34.5%; $p < 0.001$).[14] Another study compared endoscopic resection of the mucosa with submucosal dissection, assessing different endoscopic techniques for colorectal tumors, using cases from 1966 to 2014. In this wide evaluation, endoscopic submucosal dissection was better than endoscopic mucosal resection, presenting a higher rate of complete histological resection, a lower rate of recurrence, and a similar rate of bleeding, despite the longer procedure time. The perforation rate was higher in endoscopic submucosal dissection.[15]

Some studies have reported that tumors larger than 20 mm should be referred to radical surgery. The literature does not report details of endoscopic treatment of tumors larger than this size.[1]

Considering the data presented in this study, the patient who inspired this bibliographic review meets several aspects regarding the diagnosis and therapeutic management of rectal carcinoid tumors. The patient was 57 years old, *i.e.*, in the characteristic age group at the time of diagnosis. The fact that the patient is asymptomatic and was diagnosed in a non-suspicious manner is in agreement with the literature. The fact that this is not a common case is also a challenge for coloproctologists, who should analyze the lesion with due suspicion, since an incomplete resection may hinder the prognosis. In the case of this patient, it was observed that, macroscopically, the lesion appeared to have been completely resected by the polypectomy loop. As it was a hardened and thick lesion, the force used in the polypectomy loop was slightly higher than that used to remove an adenomatous polyp. This may have microscopic implications when evaluating the pathological specimen. In the present case, the fact that the margin was compromised stimulated a second colonoscopy, which showed a small scar of approximately 1 cm that was elevated and subsequently resected. Posterior pathological examination did not reveal a carcinoid tumor. The literature review indicates that some services have devices that facilitate resection with safer margins. Endoscopists should always require the hospital unit manager to invest more in improving the equipment, since for most well-trained specialists with adequate equipment, a safer approach can be performed with a single surgery. In the present patient, imaging exams did not show local involvement or distant metastases, nor a second primary neoplasm. However, because this was a rare case that surprised the patient and tested the diagnostic accuracy of the attending physician, an individualized approach, with endoscopic follow-up and imaging (computed tomography and endorectal ultrasound) should be made available. According to the literature, carcinoid tumors of up to 10 mm without adverse findings can be treated with local/endoscopic excision. There is no consensus regarding the treatment of carcinoid tumors between 10 and 20 mm, but those greater than 16 mm without adverse findings are eligible for local endoscopic excision, followed by careful histopathological evaluation. Patients with tumors larger than 16 mm, or those with any size tumors along with adverse findings, should undergo radical surgery due to the high rate of lymph node involvement. Rectal carcinoid tumors should not be disregarded; rather, they should be treated in a center that utilizes a multidisciplinary approach for neuroendocrine tumors.[1,5,9,10,14,15]

Therefore, treatment of the rectal carcinoid tumors is complex, as it depends on the individual characteristics of each patient. With an appropriate approach, the prognosis can be favorable, with a high survival rate. A literature review and data comparison may provide the necessary safety to better treat the patient, especially considering the rarity of these cases in colorectal practice.

## Conflicts of interest

The authors declare no conflicts of interest.

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