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Research Article

Neuroendocrine Tumors of the Digestive System: Topographic Distribution and Multidisciplinary Management

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Abstract

Introduction: The new methods of pathological detection have made it possible to determine with greater certainty the diagnosis of neuroendocrine tumors (NET). SOLCA, an institution from Ecuador specialized in oncology, considers it necessary to identify the frequency of this type of pathology in the digestive tract, as well as to describe the clinical and surgical management in a multidisciplinary environment.

Objective: To describe the topographic distribution, multidisciplinary management and pathological diagnosis according to WHO classification for neuroendocrine tumors of the digestive tract.

Materials and Methods: A descriptive study of the cases with confirmed anatomopathological diagnosis of neuroendocrine tumor located in the digestive tract between 2011 and 2018 at the National Institute of Oncology - SOLCA from Guayaquil-Ecuador.

Results: In the study period, 45 patients diagnosed with NET exclusively located in the digestive tract were treated at the institute, of which 21 cases met the inclusion criteria. According to the topographic distribution of neuroendocrine tumors in the gastrointestinal tract, the most frequent location in our series was the cecal appendix (n = 8, 38%). The pathological diagnosis according to the WHO classification in our series was in stage G1 (65%). The first line of treatment was surgery with curative intent (n = 19, 90.47%) and endoscopic treatment (n = 2, 9.53%). Patients undergoing surgery (n = 16, 84%) obtained resection levels 0 (R0) and remained under clinical observation, the other subjects in the study received adjuvant treatment with somatostatin alone (n = 1, 4.76%) or combination of somatostatin and radiotherapy (n = 2, 9.53%).

Conclusions: Neuroendocrine tumor of the digestive tract is a rare oncological condition. Surgical treatment should be focused as a curative action depending on the anatomopathological features of the tumor; and the global management of the disease must involve a multidisciplinary team.

Keywords: *Neuroendocrine Neoplasm; Digestive System; Multidisciplinary; Treatment; Surgery*

Introduction

Neuroendocrine tumors (NET) are a group of neoplasms that originate from enterochromaffin cells; the same ones that are distributed throughout the body, but especially in the submucosa of the intestine and the lung. They were identified for the first time as a specific type

of growth different from the mid-1800s. Langhans was the first to describe a carcinoid tumor (CT) in 1867, and in 1888 it was Lubarsch who registered it for the first time as a new tumor, so two years later Ransom gave the first explanation of the classic picture of carcinoid syndrome symptoms [1]. Currently in the term of neuroendocrine tumors the broad spectrum of these neoplasms is included, from the classic presentation of the carcinoid tumor in one extreme to the anaplastic variety in the other. According to the new guidelines, the term NET should be used as a synonym for carcinoid tumor. These include from well-differentiated neoplasms with slow growth and low potential for metastasis (CT), to poorly differentiated neoplasms with rapid growth and high potential for metastasis (NET). The incidence has increased significantly, according to the international literature, apparently based on the new diagnostic studies performed [2]. The overall survival of these tumors can vary significantly from 40 to 60% at 50 years depending on their distribution and different prognostic factors; being one of the most important: location of the tumor, stage of the disease and histological differentiation, and mitotic index; those that compromise the pancreas followed by those that affect the colon, represent the worse prognosis. It is estimated that carcinoid tumors usually originate from malignant transformations of pluripotent neuroendocrine cells, this mechanism being largely unknown; it is postulated that the early damage of the pluripotent neuroendocrine cells originates poorly differentiated or high grade tumors; while the G1 and G2, known as well differentiated, originate from later stages [3,4].

In the Republic of Ecuador, there are no studies that establish the incidence of neuroendocrine tumor in the digestive tract, and there are few specialized centers that allow to establish the management of this pathology in a multidisciplinary set.

Materials and Methods

This is a retrospective study of all cases of neuroendocrine tumors of the digestive tract confirmed by histopathological diagnosis of surgical and endoscopic resections; collected from 2011 to 2018 at the National Oncology Institute of Ecuador- SOLCA from Guayaquil city. The following variables were considered: tumor localization in the digestive tract, clinical symptoms, surgical and endoscopic treatment, histopathological diagnosis according to WHO (Ki67 and mitotic count), and adjuvant treatment, all of them were available in the hospital records.

Results

A total of 21 cases of NET of the digestive tract were identified; 6 men (29%) and 15 women (71%) with an average age of 47 years, with a range from 19 years to 70 years.

The initial clinical symptomatology corresponded to general symptoms (n = 9, 43%) such as abdominal pain, hair loss, weight loss; followed by specific symptoms (n = 7, 33%) such as diarrhea, flushing and dyspnea; and other symptoms (n = 5, 24%).

The location in descending order was: cecal appendix (n = 8, 38%), stomach (n = 4,19%), small intestine (n = 3, 14%) of which all belonged to the duodenum, colon and rectum (n = 4, 19%), finally, the pancreas (n = 2, 10%) (Figure 1).

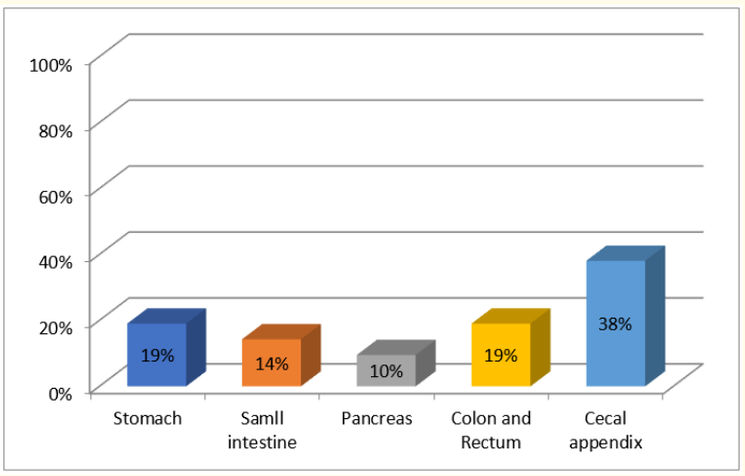

Figure 1: *Topographic distribution of NET in the digestive tract.*
Source: Tumor Registry from SOLCA-Guayaquil (2011-2018).

Surgical interventions with curative intent in patients with non-metastatic neuroendocrine tumor were performed according to their topography, so we can detail that in the stomach were performed, subtotal gastrectomy (n = 3, 14%) and total gastrectomy (n = 1,5%); in pancreas, distal pancreatectomy (n = 1, 5%) and enucleation (n = 1,5%); in small intestine, resection with tumor excision (n = 1, 5%); and cephalic duodenopancreatectomy (n = 2,9%); in cecal appendix, therapeutic appendectomy (n = 6,29%) and prophylactic appendectomy (n = 2,9%); in colon and rectum, low anterior resection (n = 3,14%) and transanal resection (n = 1,5%) (Figure 2).

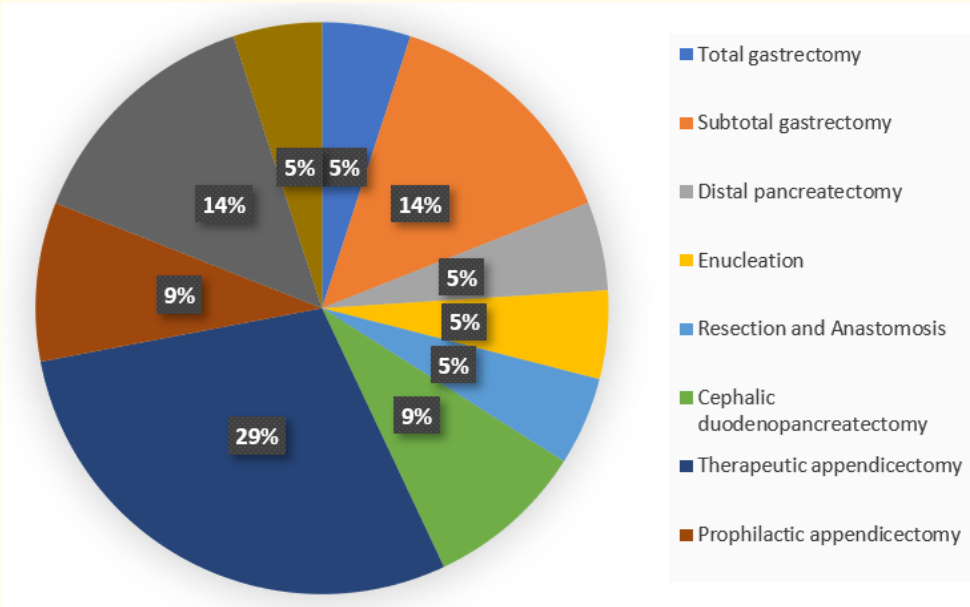

Figure 2: *Surgical treatment of NET in the digestive tract.*
Source: Tumor Registry from SOLCA-Guayaquil (2011-2018).

The level of surgical resection and postoperative treatment indicated by the multidisciplinary team for the study patients included those with resection level R0 (n = 16, 84%), whose postoperative management was clinical observation; while in patients with surgical resection level R1 (n = 3.16%), 1 case received chemotherapy alone, and the others received chemotherapy with somatostatin analogues and complementary radiotherapy.

The histopathology results were established in the total cases of NET of the digestive tract and were based on the stage according to the World Health Organization (WHO, 2010); stage G1 (n = 14, 67%); stage G2 (n = 5,24%) and stage G3 (n = 2, 9%) (Table 1).

Grading of NETs	Mitotic Index	Ki-67 LI
Grade 1 (G1)	Mitotic count < 2 per 10 HPF	≤ 2%
Grade 2 (G2)	Mitotic count 2 - 20 per HPF	3 - 20%
Grade 3 (G3)	Mitotic count > 20 HPF	> 20%

Table 1: *World health organization (WHO) 2010 classification for digestive neuroendocrine neoplasms.*
NETs: Neuroendocrine Tumors; HPF: High Power Fields; LI: labelling Index.
Source: WHO Classification of Tumors of the Digestive System. Fourth Edition (2010).

Discussion

In international reports, the incidence of neuroendocrine tumors represents is around 2% of neoplasms that affect the digestive tract [5,6]. This study demonstrates our experience between 2011 and 2018 at the National Oncology Institute of Ecuador- SOLCA of Guayaquil.

We have compared our study with international studies such as the Surveillance Epidemiology End Results (SEER) [3], in which the small intestine (38%) is evidenced as the topography of the neuroendocrine digestive tumor of greater incidence, contrasting with our study where the tumors neuroendocrines of the cecal appendix occupied the first place (n = 8, 38%) and the pancreas (n = 2,10%).

The age ranged from 19 years to 70 years, with an average of 47 years; with a difference of 10 years compared to other studies [7,8]. Women were the most affected (n = 15, 71%) unlike the ERG, TNCS and SEER studies in which the male/female sex ratio was 2/0.92, respectively [9-11].

Surgical treatment, as well as comparative studies, was indicated based on its topography, tumor size, presentation at the time of diagnosis, whether it was localized, regional or metastatic. With respect to the management of the 4 cases of neuroendocrine tumor of the stomach; subtotal gastrectomy was performed in 75% of the cases in those with tumor lesions smaller than 1 cm, while in the remaining total gastrectomy it was submitted to that lesion larger than 1 cm, while the studies determined that minor lesions of 1 cm and up to 1.5 cm endoscopic mucosectomy type treatment is suggested. Despite the controversy, many groups still perform surgical treatment starting at 1 cm of the tumor size, or in less than 1 cm in case of multiple lesions [12,13].

The treatment chosen in the cases of NET of cecal appendix contrasts with the norms that are used for the most conservative treatments in 50% of the patients, which based on the degree of infiltration and the tumor size should have been complemented with their treatment deferred surgery with a right hemicolectomy, although it should be remembered that the survival until the completion of the study was 100% without signs of tumor recurrence [4,14].

It was demonstrated that surgical treatment is the main component of neuroendocrine tumor management, as we observe our experience regarding the postoperative opted treatment, since only those patients with R1 surgical resection level were beneficiaries of complementary treatment with chemotherapy and radiotherapy [15,16].

Conclusion

In the management of NET of the digestive tract must be within a multidisciplinary team, considering that surgical treatment is the one with the greatest potential for healing, always considering the anatomical location and factors of the tumor; and define the need for adjuvant treatment.

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