



Research Article

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# Digestive Neuroendocrine Tumors about 44 Cases and Review of the Literature Experience of CHU Hassan II, Fez

O Siyouri<sup>1\*</sup>, J Chouef<sup>1</sup>, H Medyouni<sup>1</sup>, L Amaadour<sup>1</sup>, K Oualla<sup>1</sup>, Z Benbrahim<sup>1</sup>, S Arifi<sup>1</sup> and N Mellas<sup>2</sup>

<sup>1</sup>Department of Medical Oncology, Hassan II University Hospital, Morocco

<sup>2</sup>Faculty of Medicine, Dentistry and Pharmacy of Fez

\*Corresponding author: O Siyouri, Department of Medical Oncology, Hassan II University Hospital, Morocco.

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## Abstract

Neuroendocrine tumors of the digestive system account for 1% of all digestive tumors. These are a group of clinically and biologically heterogeneous neoplasms. The objective of this article is to report the epidemiological, clinical, paraclinical, histological, therapeutic, and progressive characteristics of digestive NETs in our context. Through a study of files over the period from January 2010 to September 2023, 44 cases of NET been collected in the medical oncology department of CHU HASSAN II in Fez. Clinical, paraclinical, therapeutic and evolutionary data were collected. The average age found was 50.42 years. A slight female predominance was noted with a sex ratio of 0.66. The clinical presentation was dominated by non-specific digestive symptoms. Carcinoid syndrome was found in 12.5% of patients. According to the WHO classification: 65% of patients presented well-differentiated NETs versus 30% of poorly differentiated CNE, 5% are undifferentiated NETs. The highest frequency of these tumors was observed in the D-P block (22.5%) and the small intestine (22.5%), followed by NET of unknown origin 15%. The majority of patients presented at an advanced stage (stage 4 in 65%), and the extension assessment already revealed distant metastases, particularly in the liver, and 57.5% of patients received chemotherapy.

## Introduction

NETs are rare. They represent about 1% of digestive tumors. refer to any tumor developed from cells of the diffuse neuroendocrine system which is a network of cells scattered throughout the body, whose structure resembles that of nerve cells, and which produce hormones such as endocrine cells, regardless of their location and their embryonic origin (endoderm or neuroectoderm) [1]. Significant recent progress has been recorded in the diagnosis (molecular imaging, end sonography with puncture) and the treatment of digestive NETs. The diagnostic process depends on the initial presentation. Given the multitude of therapeutic means available, a multidisciplinary approach is desirable in the management of these patients.

## Materials and Methods

This is a retrospective study in the medical oncology department of the Fez University Hospital Center over a period from January 2010 to September 2023 including all patients with digestive NET.

## Results

Epidemiological Profile 44 patients with digestive neuroendocrine tumors were treated by the medical oncology service. With an average of 4.44 patients/year, the age of the patients at the time of diagnosis varied between 16 years and 77 years. The average age was 50.42 years with a standard deviation of 14.72 (years) and a peak between 50 and 60 years. A slight female predominance was



noted since the female sex represents 60% of the patients and the sex ratio M/F is 0.66 (Figure 1).

Clinical Data 39 cases presented a clinical manifestation (i.e. 80%), the time between these first clinical manifestations and the discovery of digestive NETs was variable. Thus, we found that only 5 patients consulted within less than a month while the majority con-

sulted within a variable period of 1 month to more than 6 months. In our series, 3 cases (7.5%) were discovered fortuitously, one of which was incidental to imaging (2.5%) and two of which were incidental surgical (5%). In addition, 32 cases presented symptoms of tumor compression (80%) with 5 cases of carcinoid syndromes (12.5%) (Figure 2).

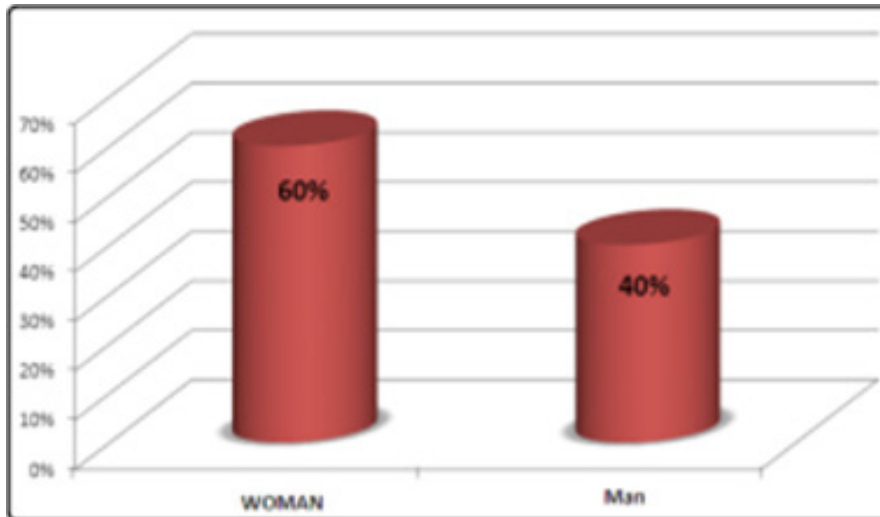


Figure 1: Percentage distribution by sex.

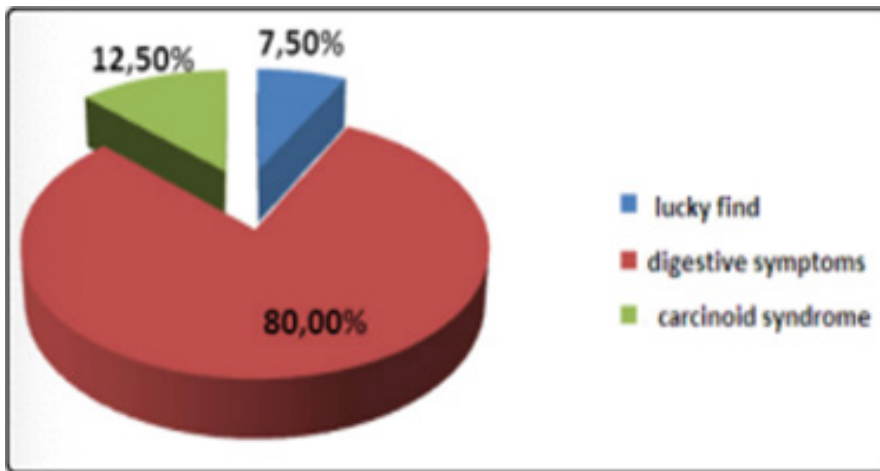


Figure 2: Distribution of discovery modes.

-Abdominal pain was the most common symptom; it was reported by 65% of patients. -Five patients (12.5%) developed jaundice. -Sub occlusive syndrome was reported in two patients (5%). -In addition, two patients had a digestive hemorrhage (5%), the first of which was a patient’s melena from a small NET and the second had a hematemesis secondary to gastric NET. -Five patients experienced vomiting (12.50%) (Figure 3).

Carcinoid syndrome is made of: -Facial skin flush reported in two patients (5% of cases), -Diarrhea reported in 4 patients (10% of cases), -Carcinoid heart disease was noted in 2 patients (5% of cases). Paraclinical Data Chromogranin A was performed in 5 patients (12.5% of cases) and returned high in 4 patients: Abdomi-

nal CT was performed in 13 patients (32.5%) and was in favor of: -Small tumor process in 2 patients, Carcinoid tumor in 2 patients, Tumor liver in 3 patients, Gastric tumor in a patient, Mesenteric mass in a single case, Ileal process with retractable mesenteritis in one case, Mass of the tail of the pancreas in one case and tumor of the duodenopancreatic crossroads in a single case. All our patients underwent a Thoraco abdomino pelvic CT scan. Liver metastases were present in 12 patients, a percentage of 30%. Lymphadenopathy was present in 6 patients (15% of cases). Peritoneal metastases were present in 5 patients (12.5% of cases), and pulmonary and bone metastases were present in 2 and 1 patients respectively (5% and 2.5% of cases). Other metastatic locations have been reported in 3 patients (7.5% of cases) (Figure 4)(Table 1).

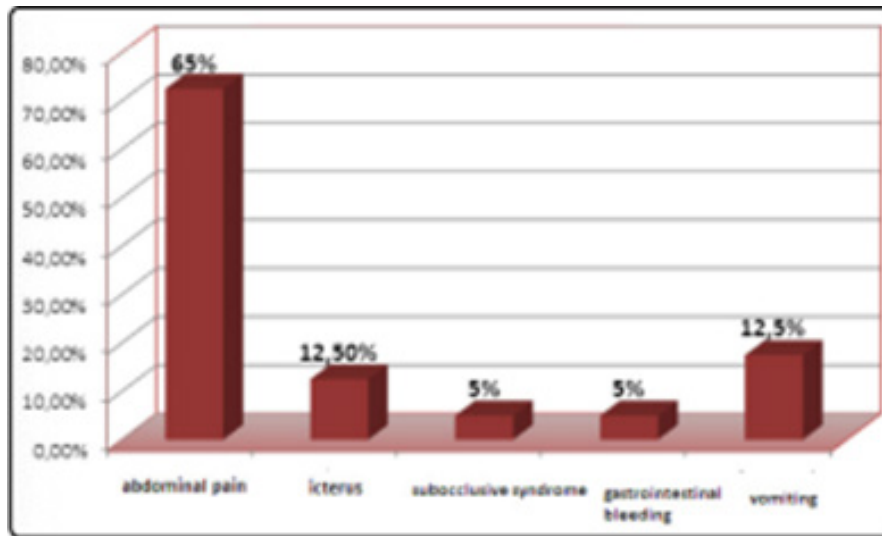


Figure 3: Distribution of clinical presentations.

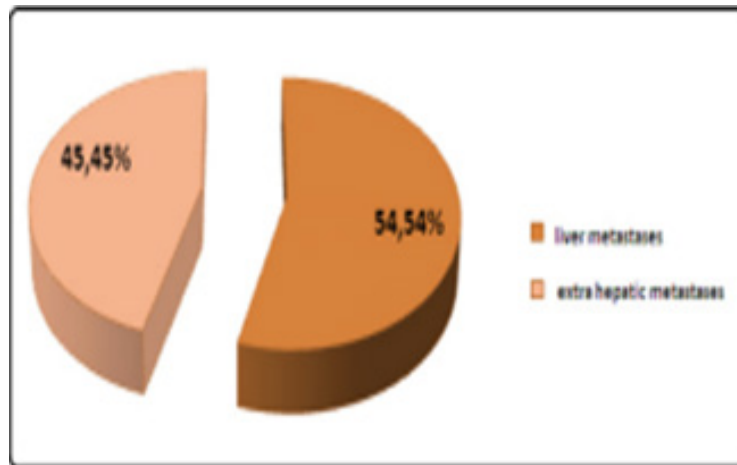


Figure 4: Distribution of metastatic locations (hepatic and non-hepatic).

Table 1: The results of the chromogranin assay in our series.

Cases	Results	Primitive Site
First Patient	105	small intestine
Second Patient	657	unknown
Third Patient	280	small intestine
Fourth	153	Pancreas
Fifth Patient	Normal	small intestine

### Anatomopathological

Data The anatomopathological study was carried out in all the patients in our series on biopsies in 23 cases (or 57.5%) or on operating pieces in 16 cases (or 40%) with one case diagnosed on the anatomopathological study of ascites cytology (2.5%). In our series, 9 patients had a NET in in small ingest (22.5%), 9 cases of pancreatic NET (22.5%), 6 cases of unknown NET (15%), 3 cases stomach NET (7.5%), 3 cases of appendicular NET (7.5%), 3 cases of NET gall bladder (7.5%), 2 cases of colonic NET (5%), 2 cases of hepatic

NET (5%) and 2 cases involving the Vater's vial (5%) and 1 case of caeca NET (2.5%).

We note the presence of pathological association in 4 cases (10%)

- i. 3 cases of adenocarcinoma +digestive NET.
- ii. 1 case of tumor with weak cohesive cells +digestive NET.

In our series, 65% of NETs were morphologically well-differentiated tumors and 30% were poorly differentiated while 5% were

undifferentiated NETs. Research on neuroendocrine markers was carried out in 32 patients/40 (80% of cases).

**-AC antichromogranin:** The anti-chromogranin antibody was tested in 31 patients (77.5%). The positivity was 87.09%.

**-AC Antisynaptophysin:** Synaptophysin was sought in 29 pa-

tients (i.e. 72.50%). It was positive in 28 patients (96.55%) and negative in a single patient (3.4%).

**-AC Anti CD56:** CD56 was tested in 11 patients (27.5%) and was positive in 81.81% of cases (9 patients). Other antibodies such as cytokeratins AE1-AE3 were tested in 3 patients and they were positive (Figure 5).

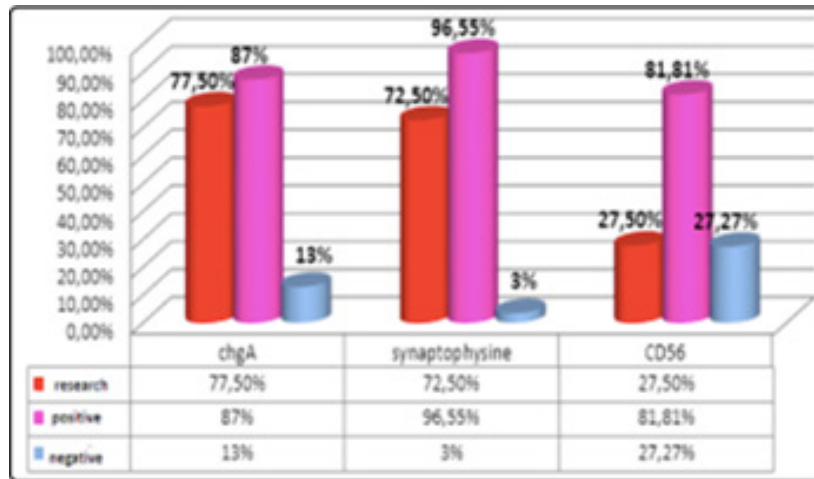


Figure 5: Percentages of antibodies sought in IHC.

The proliferation index Ki-67 was found in the clinical records of 22 patients in our series (55% of cases). And the mitotic index

was found in 16 patients (40%) (Figure 6).

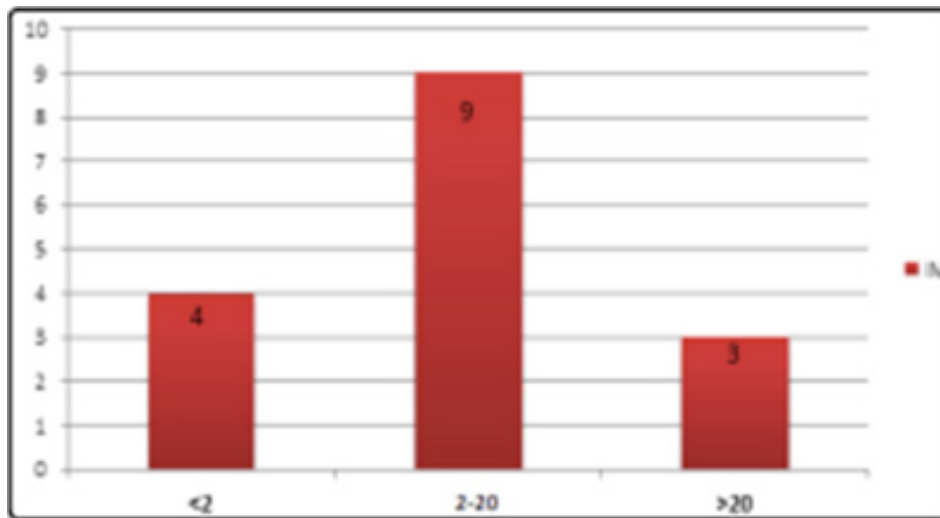


Figure 6: Nombre de patients selon 1 indice mitotique.

The histological grade was established in 28 patients, i.e. 70%, of whom 15% were grade 1 and 27.5% was grade 2 with 27.5% grade 3. In our series, 26 patients or 65% had stage IV, 15% stage III and 20% in stage I get II. Therapeutic Data In our study, the surveillance strategy was proposed in 8 patients (20%). Of the 40 cases studied, 21 patients underwent surgery (52.50%): Primary tumor surgery in 14 cases (35%), with lymph node dissection in 8 cases (57, 14%). Among 40 cases, 5 cases were treated with somatostatin analogs (12.5%). 23 patients benefited from chemotherapy in

our study (57.5%): palliative in 20 patients (86.95%), concomitant with radiotherapy in 1 patient (4.34%), and adjuvant in 2 patients (8.69 %)(Table 2).

Radiation therapy was indicated in 2 patients (5%): a patient with an unknown grade 3 primary (2.5%) benefited from a palliative RTT for bone metastases of multiple dorsolumbar and sacral vertebral bodies. Concomitant adjuvant Radio Chemotherapy (RCC) (2.5%) was indicated for a mixed gastric carcinoma associating CNE with small cells (Table 3).

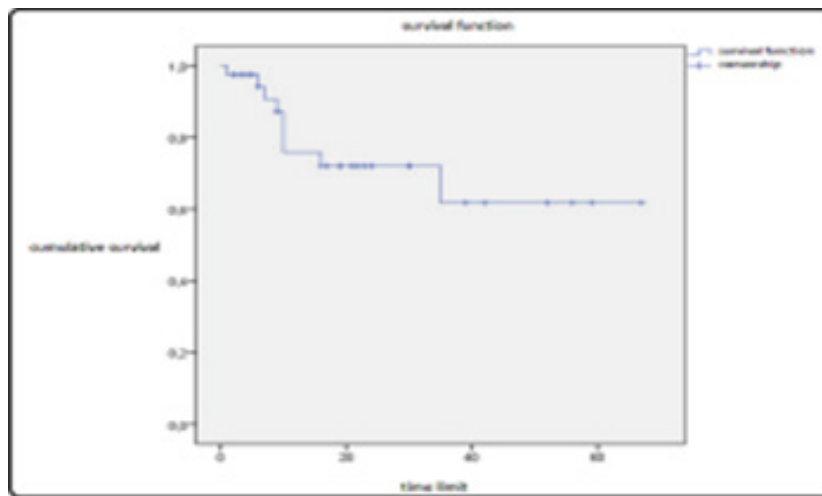
**Table 2:** Radiation therapy was indicated in 2 patients (5%): a patient with an unknown grade 3 primary (2.5%) benefited from a palliative RTT for bone metastases of multiple dorsolumbar and sacral vertebral bodies. Concomitant adjuvant radio chemotherapy (RCC) (2.5%) was indicated for a mixed gastric carcinoma associating CNE with small cells.

Lines	Protocols	Effective	Stability	Response	Progress	Average Number of Cures
First Ligne	2 cases	2 cases	50%	-	50%	3,5 cures
	Folfox	2 cases	50%	-	50%	6,5 cures
	Gemcitabine	2 cases	50%	-	50%	2 cures
	5FU	lease	Not rated			1cure
	5FU+doxo	lease	100%	-	-	4cures
	Adria+ CDDP	lease	100%	-	-	6cures
Second Line	Folfox	lease	100%	-	-	10cures
	Déticenne	lease	Not rated			-
Third Line	Xeloda	lease	during monitoring			-

**Table 3:**

Evolution	Number of Cases	Percentage
Lost	10	0.25
Death	9	22,5%
Living	21	52,5%

In our study, 2 patients (5%) benefited from sunitib in the first line for well-differentiated pancreatic NET and in the second line for metastatic undifferentiated liver NET. No patient received chemoembolization treatment. The evolution was marked as follows: Median survival was not achieved in our population. Overall survival at 5 years is estimated at 58% (Figure 7).



**Figure 7:** Overall survival curve according to Kaplan Meier.

### Discussion

Digestive NETs represent 1% of all digestive tumors with a current increase in incidence according to several studies [2]. Similarly in our study, there was an increase in the frequency of digestive NETs over the years between 2010 and 2018 from 1 case in 2010 to 4 cases in 2018. Several factors can be mentioned to explain this increase in the incidence of NETs: the improvement of the knowledge of clinicians, radiologists and pathologists and the generalization of the use of advanced diagnostic means (such as somatostatin receptor scintigraphy, CT, endoscopy and specific markers in IHC), increased the number of patients diagnosed by chance [3]. In our study, the average age at diagnosis was 50.42 years with a standard deviation of 14.72 years. The age of our patients varied between 16

years and 77 years. Our results approximate those of the studies of Hemminki, Zhang, as well as those of Garcia Carbonero [4-6]. In our study, the sex ratio was 0.66 with a female predominance. This result is close to that found in the Italian studies by Faggiano and the Japanese studies in Ito, unlike other studies, which have shown a predominance of men [7,8]. In the literature, small intestine is found to be the most frequent regarding gastrointestinal NETs, so studies by Ellis, et al., in the United Kingdom have shown that jejun-ileal NETs are the most frequent (21-43%) followed by NETs of the duodeno-pancreatic block, gastric NETs (6-11%), colonic and rectal NETs then the NETs of the appendix [9].

In the Spanish study by Garcia carbonero, et al., and the Italian study by Faggiano, et al., the symptomatology of tumor compres-

sion was observed in 53% and 46% respectively [6,7]. The percentage of patients diagnosed with a tumor syndrome is very large in our population (80%) who, for lack of means, often only consults after a noisy tragic symptomatology. Hormonal hypersecretion syndrome is only found in 12.5% in our series compared to the European series (Spanish: 25%, Italian: 23%). Two hypotheses could explain this difference: Ignorance or neglect of hormonal symptoms by our doctors and low hormonal secretion in our population. However, given the absence of a genetic polymorphism study of NETs in our population, we retain the first hypothesis. In a French PRONET study (carcinoid syndrome was reported in 25% of cases contrasting with our study where only 12.5% was reported [10]. Note that in our study, 2 cases of carcinoid heart disease (50%) of patients with carcinoid syndrome were reported, which agrees with the data in the literature. About 40% of patients with carcinoid syndrome had heart disease. Carcinoid, 5-10% of all NET patients [11]. Synaptophysin is less specific than chromogranin A and can be expressed by other endocrine tumors. Most recent recommendations consider that the positivity of the expression of at least two markers is necessary and sufficient to confirm the diagnosis of Gastroentero pancreatic neuroendocrine tumor.

These markers include Chromogranin A (CgA), and synaptophysin [12-14]. NETs are characterized by a very wide variety of evolutionary profiles, which significantly complicates the clinical management of patients, and particularly the therapeutic orientation. Somatostatin has demonstrated its ability to inhibit endocrine secretions from the digestive tract in a paracrine mode allowing control of carcinoid syndrome. In our series, only 5 cases (12.5%) were treated with somatostatin analogs. This use remains reduced compared to other cancer centers (in the study by Garcia-Carbonero and Lombard Bohas: 29% and 44% use of somatostatin analogs respectively) [15,16]. This is largely due to the high price of this therapy and the limited availability in our hospital. Surgical excision is the only curative treatment for NETs. In our study, 52.50% of cases were operated on: 35% underwent resection surgery for their primary tumors. This contrasts with the results of the Lombard-Bohas study where surgical resection of the primary tumor was performed in 87% of the digestive tumors. Garcia-Carbonero also reported in his study that 2/3 of his patients underwent surgery. It was for curative purposes in 65% of them and palliative in 14% of cases. This can be explained by the diagnosis at the advanced stages in our series [17]. The benchmark chemotherapy for pancreatic PDD is the adriamycin-STZ combination with 70% objective response. However, the results of this randomized trial are probably overestimated, with the response rate in daily practice being around 40%. For tumors of the digestive tract, the standard chemotherapy is the 5FU-STZ combination with response rates of around 30% [18].

Other substances can be proposed: dacarbazine associated or not with 5FU, 5FU oral, temozolomide [19-21]. Concerning metastatic poorly differentiated endocrine carcinomas, chemotherapy with cisplatin-etoposide is the reference recommended for first-line treatment. Response rates vary from 40 to 70% depending on

the trial, but overall survival varies from 15 to 19 months and the two-year survival rate remains below 20%. Despite their chemosensitivity, these tumors have a very poor prognosis [22,23]. In our study, 2 patients (5%) benefited from Sunitib. In the essay by Raymond, *et al.*, In patients with progressively differentiated pancreatic NETs [24]. Patients received either 37.5mg/day of Sunitinib orally continuously or a placebo. The median PFS was 11.1 months in the Sunitinib arm and 5.5 months in the placebo arm 71 vs 43% of the patients were respectively free from progression at six months in the two groups. Overall, well-differentiated NETs have a better prognosis compared to poorly differentiated NETs, indeed according to a Swedish study, the survival rate of well-differentiated NETs is 50% at 5 years contrasting with a survival of 4.5% at 5 years in poorly differentiated NETs [25,26]. However, our study shows lower percentages compared to these studies; all the cases of well-differentiated NETs had already died after 5 years.

The high percentages of advanced stages in our study explain these low survival rates in our patients. For well-differentiated NETs, the unavailability of somatostatin analogs, targeted molecular therapies, and certain techniques such as hepatic intra-arterial chemoembolization and metabolic radiotherapy also explain the lower survival rates. In recent years, however, we have seen better management of these tumors thanks to the obtaining of marketing authorization for somatostatin analogues, the better availability of antiangiogenic agents and above all thanks to collegial management within the consultation meeting. Multidisciplinary digestive cancer research.

## Conclusion

Digestive NETs are rare tumors, but their incidence has increased sharply in recent years. This would be due to a better understanding of these tumors, the diagnosis of which becomes easier with the advent of new morphological and biological techniques.

## Acknowledgements

None.

## Conflict of Interest

None.

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