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The Management of Digestive Neuroendocrine Tumors: About 10 Cases

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Research Article

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Abstract

Objective: Digestive neuroendocrine tumors (NET) are a rare entity of neoplasia that represents 1% of digestive tumors, characterized by a heterogeneous biological, morphological, and clinical presentation. The aim of our study is to determine the particularities of the management of digestive NETs, as well as to evaluate the therapeutic modalities in comparison with the data of the existing literature, in order to improve the management of our patients.

Materials and methods: This is a descriptive retrospective study including all patients operated for histologically proven gastrointestinal NET, at the level of the department of visceral surgery A (Ibn Sina Hospital, Rabat) between January 2012 and December 2016. Demographic, clinical, paraclinical, histological, and therapeutic data, as well as the follow-up was produced using farms return.

Results: 10 patients were included in this study. Four patients had pancreatic tumors (40%), two had small bowel tumors (20%) and two had unknown primitives tumors (20%). Six patients were metastatic at the diagnosis (60%) in the liver. The surgery was for curative intent in eight patients (80%) and palliative in two patients (20%), three patients underwent surgery on the hepatic metastases (30%). Five patients were in stage IV of their disease (50%). One patient is alive with his disease (10%), two are alive without disease (20%) and three died from their disease (30%).

Conclusion: Improving the knowledge of NETs and accessibility of standard diagnostic means explain the increase in diagnosed cases. An update knowledge and collaboration between surgeons, pathologists, radiologists and oncologists are required.

Keywords: Gastro-Intestinal and Pancreatic Neuro-Endocrine Tumors; Octreoscan; Surgery

Introduction

Digestive neuroendocrine tumors represent a heterogeneous group of tumors with common functional and morphological characteristics related to their endocrine differentiation. They are heterogeneous tumors in their clinical presentation, their evolution and their prognosis.

Neuroendocrine tumors, in general, can develop from the endocrine glands themselves (pituitary, parathyroids, thyroid, endocrine pancreas, adrenals) or from tissues with a diffuse endocrine system, such as the digestive and respiratory mucous membranes, but also from organs apparently devoid of endocrine cells in the normal state. NETs are considered rare tumors. They represent about 1% of digestive tumors.

In practice, among digestive NETs, a distinction must be made between endocrine tumors of the gastrointestinal tract and pancreatic endocrine tumors. Likewise, the distinction between well-differentiated and poorly differentiated tumors is important because of the prognostic and therapeutic consequences it implies. Poorly differentiated NETs are in fact characterized by their aggressiveness and rapidity of progression, whereas well-differentiated tumors usually develop slowly.

Treatment approaches are numerous and the choice of therapeutic strategy depends essentially on the site of the primary tumor, the extension and the evolution of the tumor. In all cases, the therapeutic strategy must be taken during a multidisciplinary consultation.

The aim of our study is to determine the particularities of the management of digestive NETs, as well as to evaluate the therapeutic modalities in comparison with the data in the existing literature, in order to improve the management of our patients.

Materials and Methods

This is a descriptive retrospective study including all patients operated for histologically proven digestive NET at the level of the department of digestive Surgery A between January 2012 and December 2016.

The list of patients to be included was determined from the anatomopathological report registers (2012-2016) of the department.

Patients with a non-digestive NET and / or a lost medical record were excluded from the study.

A farm return dedicated to the study including demographic, clinical, paraclinical, histological, therapeutic and evolutionary data was produced on Google form.

The data was collected from the medical records. For patients who had a pancreatectomy and/or hepatectomy, the data were completed from the service's prospective databases.

For data relating to the follow-up of the disease, patients and/or their relatives were contacted by telephone.

Results

Ten patients were included in the study. The ages of the patients ranged from 25 to 73 years, with an average age of 55.9. The female sex represents 60% of the cases in our study, while the male sex represents 40%.

No history of multiple endocrine neoplasia (MEN), hyperthyroidism, hyperparathyroidism or neoplasia was not identified in patients, nor was a family history of MEN.

In our series, the majority of patients presented with a tumor syndrome consisting mainly of abdominal pain (epigastralgia or pain in the right hypochondrium) i.e. 70% of cases, jaundice represented 20% of cases, carcinoid syndrome and digestive hemorrhages were observed in 10% of cases; then 10% of patients were asymptomatic.

All patients underwent a computed tomography (CT) and abdominal ultrasound. Hepatic magnetic resonance imaging (MRI) was performed in 50% of cases. Only one patient benefited from an Octreoscan, while no patient had a positron emission tomography (PET).

40% of patients had a tumor of the pancreas, 20% with tumors of the small intestine or with an unknown primary tumor, and 10% had tumors of the stomach or colon. 60% of patients were non-metastatic at the time of diagnosis, thus the remaining 40% presented with metastases. The liver was the only site of metastases in the patients in our case series, 25% of these liver metastases were metachronous and 75% were synchronous.

20% of cases underwent palliative surgery: a total cleanliness gastrectomy, or a Monobloc resection of the small intestine. 80% of cases underwent curative surgery: cephalic duodeno-pancreatectomy in 30% of cases, spleno-duodeno-pancreatectomy in 10% of cases, left colectomy in 10% of cases, minor hepatectomy (segmentectomy) in 10% of cases, right major hepatectomy in 10% of cases, a right major hepatectomy with left segmentectomy in 10% of cases.

In our serie, only one patient presented grade IIIa complications according to the classification of surgical complications according to Clavin (10% of cases); such as intraperitoneal and pelvic abscessed collections diagnosed by an abdomino-pelvic CT, following a deterioration in the general condition of the patient. The patient underwent ultrasound-guided drainage for accessible abscessed collections, and parenteral antibiotic therapy, with good clinical and biological progress. The other cases presented simple postoperative consequences.

80% of patients underwent lymph node dissection, of which 50% of cases were positive and 30% of cases were negative. 70% of patients had non-tumor resection limits while 30% had tumor margins.

40% of cases had grade 2 tumors, 30% of grade 3 tumors, 20% of cases with grade 1 tumors, and 10% of cases with a grade not defined on the pathological study. the well-differentiated type was the most frequent, represented in 70% of cases. 50% of patients were in stage IV of their disease, 30% in stage IIIb, and 10% in stage IIa and Ia.

At the last consultation, 20% of cases are alive without disease, 10% of cases are alive with disease, 30% of cases have died of their disease, 40% of cases are lost to follow-up. Only one patient presented with tumor recurrence (10% of cases). 20% of the cases in our series are in complete

remission of their disease, with periodic monitoring by imaging (CT).

Discussion

Neuroendocrine neoplasms (NENs) are tumors derived from the neuroendocrine cell system. Most NENs arise from the gastro-entero-pancreatic tract (GEP-NENs) that constitute a rather rare group of tumors. Their incidence is estimated at approximately 2.5 to 5 cases per 100,000. Data from the SEER (Surveillance Epidemiology and End Results) indicate that the prevalence and incidence of NEN-GEPs have increased since the mid-1980s. Several factors can explain this clear increase: better screening, a large number of imaging techniques performed for other reasons, better knowledge of NETs by endoscopists and pathologists; Furthermore ; demographic changes and the increase in the elderly population.

NETs most commonly occur in adults around the 5th and 6th decade, with an average age of around 55 years [1]. Although the vast majority of NEN-GEPs are sporadic, there are nonetheless four hereditary genetic predisposition syndromes associated with a risk of developing NEN-GEPs: type 1 MEN, Von Hippel-Lindau syndrome, neurofibromatosis type 1, and Tuberous Sclerosis of Bourneville.

The World Health Organization (WHO) adopted in 2010, a system grading with two categories, based on differentiation and histological maturity grading [2]. The first category consisted of well-differentiated neoplasms, with the Ki-67 proliferation index between 0-20% (well differentiated NET G1 and G2). The second category included neuroendocrine neoplasms termed neuroendocrine carcinoma NEC, with a Ki-67 proliferation index above 20% (poorly differentiated carcinoma G3). In 2019, the WHO updated its GEP-NEN classification, with two major modifications: two groups were distinguished in NEC, large cell or small cell carcinomas. In addition, the recognition that a small subset of NEC is histologically and genetically well differentiated and should not be included in the NEC category [3]. NEN grading according to WHO 2019 is presented in Table 1.

Terminology	Differentiation	Grade	Mitotic rate*, mitoses/2 mm²	Ki-67 index*, %
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	Feb-20	Mar-20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type	Poorly differentiated	High	>20	>20
NEC, large cell type	Poorly differentiated	High	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)	Well or poorly differentiated	Variable	Variable	Variable

Table 1: Neuroendocrine neoplasms grading according to WHO 2019.
*Final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher category.

Hormones		Symptoms
Insulinomas	Insulin	*Hypoglycemia occurring during fasting or exercise
Gastrinomas	Gastrin	*Duodenal ulcers refractory to PPIs.
		*secretory diarrhea.
VIPomas	VIP	*Severe secretory diarrhea.
		* Hypokalemia
		* Hypovolemia.
		* Achlorhydria.
Glucagonomas	Glocagon	*Glucose intolerance or diabetes.
		* Deep venous thrombosis.
		*Depression.
Smatostatinomas	Somatostatin	* Cholelithiasis.
		* Steatorrhea.
		* Achlorhydria.
		*Diabetes

Table 2: The different clinical patterns observed during a functional GEP-NET.

The GEP-NETs are classified into two groups according to their clinical presentation, there are functional tumors revealed by a symptomatology related to tumor hormone production, and non-functional tumors identified incidentally or in case if non-specific tumor symptomatology.

Duodeno-pancreatic endocrine tumors are often functional hormone-secreting tumors. Several clinical presentations are observed depending on the type of hormones secreted (Table 2).

In case of non-secreting tumors, symptoms are site-specific. Gastric-NET may be revealed by hematemesis or symptoms similar to gastric adenocarcinoma. Duodenal-NET can cause bleeding, jaundice, or obstruction with nausea and vomiting [4]. Small intestinal tumors present with abdominal pain and bowel obstruction [5]. Colon-NET can be diagnosed with impaired general condition or abdominal pain. Rectal tumors present with rectrorrhagies or masquerade as hemoirroids [6].

Carcinoid syndrome is one of the many secretory syndromes, is due to hyperserotonemia, and occurs when the tumor of often ileal origin releases hormones or peptides, mainly: serotonin, or 5-hydroxy tryptamine, but also tachykinins or prostaglandins. In the majority of cases, the existence of a carcinoid syndrome reflects the presence of hepatic metastases or a large tumor (exceeding hepatic metabolic capacities and passage of tumor secretions in active form to the systemic circulation). This syndrome includes symptoms such as flushes, diarrhea, abdominal pain, bronchospasm and telangiectasias [7]. Late complications include fibrosis (carcinoid valvular disease and mesentery fibrosis) and nutritional deficiency (tryptophan and niacin). The carcinoid crisis is a major complication that can endanger the vital prognosis of patients, characterized by hemodynamic instability, which can be the consequence of surgery, manipulation of the tumor, or initiation of treatment with a large tumor size or higher tumor hormonal activity [8].

The majority of cases in our series had non-functioning NETs, no patient in our series had symptoms typical of functional tumors, either these symptoms are overlooked by patients or the diagnosis was at an early stage. Note that no case of carcinoid heart disease has been reported; However, according to the data in the literature, approximately 40% of patients with carcinoid syndrome presented with carcinoid heart disease, i.e. 5 to 10% of all patients with NETs, this discrepancy is explained by the fact that it does not 'has probably been sought.

Imaging plays an essential role in the management of NETs, it serves to locate the tumor, make an extension and operability assessment, and evaluate the tumor response after treatment.

CT is the basic exam; it used to detect primary lesions, lymph node metastases and liver metastases. The CT scan must be performed in two phases: a late arterial phase (30 seconds), then portal (70 seconds) because well-differentiated, highly vascularized tumors are enhanced in the late arterial phase (9). MRI has better performance in the detection of liver and bone metastases [10]. Hepatic MRI is essential in the presence of potentially resectable metastases to look for other lesions not visible by the scanner. Neuroendocrine tumor liver metastases have low signal intensity on T1-weighted sequences and a high signal intensity on T2-weighted sequences compared with the hepatic parenchyma [10].

The search for extrahepatic localization should be systematic, in case of hepatic metastases, and should include spinal MRI [11]. Preoperatively, angio-CT / MR angiography are necessary to study the relationship of the tumor mass mainly with the superior mesenteric artery [12].

Upper digestive lesions are accessible on upper endoscopy. It can detect esophageal, gastric, and duodenal NETs. Lower digestive lesions predominate in the rectum; a simple rectosigmoidoscopy can be performed. However, a total colonoscopy should be done given that they are associated with adenocarcinoma of the colon in 20% of cases [12].

Endoscopic ultrasound (EUS) is only discussed as a second-line option for small millimeter-size tumors located in the gastric, duodenal, pancreatic or rectal level often not detectable with CT or MRI. For secreting duodeno-pancreatic tumors, EUS is clearly effective in searching for the primary tumor and studying its relationship with adjacent organs, in particular the vessels and the bile ducts [13]. It improves the detection of small submucosal tumors and allows evaluation of parietal and locoregional invasion [12].

EUS plays a significant role in the detection of pancreatic tumors and in particular primary insulinomas, small tumors that appear hypoechoic, homogeneous and well limited. Furthermore, its sensitivity is lower in extra-pancreatic insulinomas. Indeed, 80% of gastrinomas in type 1 MEN are found in the duodenum and in this case, upper endoscopy, CT or MRI should preferably be performed first.

EUS also has an important role in patients with type 1 MEN because they can present non-functional pancreatic NETs in 80% to 100% of cases and most often of small size (<0.5 cm), which can go unnoticed with conventional techniques.

Somatostatin is a peptide hormone, exerts a regulatory role on the majority of endocrine cells which results in the inhibition of many digestive functions such as secretion, motricity and cell proliferation. Six human subtypes of somatostatin receptors (SSTRs) have been identified (1, 2A, 2B, 3, 4, and 5). The expression of SSTRs has been demonstrated in most neuroendocrine tumors [14]. This property has been used for several years for their diagnosis and treatment. Well-differentiated NETs generally have overexpression of SSTRs, specially subtype 2A [15].

Somatostatin receptor scintigraphy (Octreoscan®) is a non-invasive technique allowing visualization, after injection of labeled octreotide ([111In-DTPA-D-Phe1] -octreotide), which is a synthesized analogue of somatostatin, neuroendocrine tumors whether they are primitive or secondary. The overall sensitivity of the technique varies between 60 and 100%. The visualization of tumors in SRS depends mainly on their density in the SSTRs subtype 2A and does not depend on whether or not the tumor is secreting. It is lower for insulinomas (60%), which express few type 2A receptors.

Currently positron emission tomography (PET) and CT imaging with new radiolabeled SSAs molecules have replaced octreoscan, and has become the new standard in the diagnosis of NETs. 68Gallium-DOTATATE is one of these molecules, its use has improved the detection rate of NETs compared to conventional Octreoscan-type imaging (95.1% vs 45.3%, $p < .001$) (16), and a lower radiation dose due to the shorter length of study (2 hours) [17].

There are also specific PET-CT techniques for tumor metabolism using ^{18}F-deoxyglucose (FDG). FDG-TEP-CT has demonstrated better diagnostic performance than SRS in patients with high-grade NETs with a high KI67 index (> 10%) and is an independent prognostic factor [18]. The main point of weakness of this type of functional imaging is the erroneous interpretation of a physiological uptake, especially at the level of the small lymph nodes. This misinterpretation of physiological lymph node uptake may falsely upstage the tumor stage [19].

The two main biochemical markers used in NETs are urinary 5-hydroxy-indol-acetic acid (5-HIAA) and chromogranin A (CgA).

5-HIAA is a metabolite of serotonin. The sensitivity and specificity of urinary 5HIAA for the diagnosis of intestinal NETs are 50 to 70% and 90 to 100%, respectively, with better diagnostic performance in case of liver metastases and carcinoid syndrome [20]. Since serotonin is produced almost exclusively by intestinal NETs, an elevation of urinary 5HIAA predicts an intestinal origin in front of metastases of NETs of unknown primary. Elevated levels of 5HIAA are associated with a poor prognosis and the development of carcinoid heart disease [21]. Nevertheless, the inter- and intra-individual variabilities of this marker are important and many false positives exist, in particular upon the consumption of certain food products rich in tryptophan and serotonin.

The measurement of plasma CgA is simple but the inter- and intra-individual variations are important and there are many causes of false positives (proton pump inhibitors, renal failure, absence of fasting, physical activity, corticosteroid therapy, etc.).

Several studies have shown that the plasma level of CgA is correlated with the size of the tumor mass and, in particular, the metastatic volume [22]. Therefore, although its sensitivity for the diagnosis of intestinal NETs is only 10 to 50% for localized tumors, it reaches 70 to 100% at the metastatic stage, which makes it the best diagnostic marker [22]. Variations in the concentration of CgA over time could reflect the evolution of tumor mass; in particular an early decrease under treatment could be predictive of a good response, while an increase seems to predict a relapse or progression [23].

Surgery is the only curative treatment; it offers the best chance of prolonged survival. The therapeutic attitude depends on many parameters: The location of the primary tumor, Size, grade of differentiation, and lymph node involvement, in case of localized tumor.

During duodeno-pancreatic surgery, enucleation and left pancreatectomies are the most frequently performed procedures. Enucleation is suggested for sporadic tumors, size <2cm, presumed benign and located at a distance from the main pancreatic duct. The main advantage of enucleation is the preservation of the pancreatic parenchyma, which helps to avoid the risk of diabetes and long-term pancreatic failure. The left or middle pancreatectomy is reserved for tumors located outside the head of the pancreas (body or tail), not accessible to enucleation, mainly because of their size (greater than 2-3 cm) and especially their close relationship with pancreatic duct, or their potential or claimed malignancy. When the tumor is located on the isthmus or on the right side of the body, a midline pancreatectomy may be offered. Cephalic duodeno-pancreatectomy (CPD) is performed in two situations: Large, deep, generally malignant cephalic tumors, or with malignant potential and benign tumors located deep near the main pancreatic duct. After CPD with pancreatic-digestive anastomosis, 30 to 60% of patients must be supplemented with pancreatic enzymes to correct clinical steatorrhea [24]. Resection of the lymph nodes in the celiac trunk and hepatic pedicle is necessary [25].

For the surgery of small intestines TNE, complete oncologic resection of the primary tumor, the resection of the mesentery and regional lymph nodes is the goal of surgery. A complete abdominal exploration must also be performed during laparotomy because of the usually multifocal nature of the lesions (20 to 30% of cases) [26], the frequency of hepatic metastases and the association with non-carcinoid intestinal tumor lesions. Lymph node dissection should be performed, going back to the origin of the upper mesenteric vessels in their retro-pancreatic portion. During all these operations, special care must be taken to leave 1.5 to 2 m of hail because short bowel syndrome is difficult to manage in association with carcinoid syndrome.

The appendix is the third most common site of GI-NETs. If the tumor size ≤ 1 cm, a simple appendectomy is sufficient without additional explorations. In case of a tumor size > 2 cm, a right hemicolectomy after searching for metastases is necessary. For 10- to 20-mm appendiceal NETs, additional surgery (right hemicolectomy with dissection) after appendectomy should be discussed in case of: appendicular base invaded, lymph node metastases, Mesoappendiceal invasion > 3 mm, venous or lymphatic emboli, G2 tumor, and young subject [27]. All appendiceal NECs should be resected with a right hemicolectomy irrespective of size and be managed as an adenocarcinoma [28].

Colic NETs frequently affects the ascending colon. Local resection is suggested for tumors smaller than 2 cm in size. However, the majority of patients have a larger tumor. The recommended treatment is right hemi colectomy with lymph node dissection. Patients with colonic NETs have a poor prognosis.

Rectal NETs lesions smaller than 1 cm can be treated in the majority of cases by endoscopic resection, except if the circumferential margins are invaded, a T2 tumor or ulcer, or if there are parameters of histological aggressiveness (high mitotic index, lymphatic or vascular invasion, adenocarcinoid tumor). Lesions larger than 2 cm should be treated by carcinological proctectomy with complete excision of the mesorectum. Lesions between 1 and 2 cm can be treated by local transanal resection, provided to get a complete transmural resection of the rectal wall and negative resection margins. If it is a T2 tumor or if there are parameters of histological aggressiveness, a complementary carcinological proctectomy should be offered [29].

For a gastric NET in the context of fundal atrophic gastritis or MEN 1, the surgical procedure depends on the size of the tumor. If the size of the tumor <1 cm G1, the treatment is essentially based on endoscopic excision and simple monitoring of the gastric mucosa. If the tumor size is> 1 cm without mucosal invasion or lymph node metastases and G1, endoscopic resection by mucosectomy is recommended. For tumors larger> 1cm, histologically aggressive (muscle invasion), with lymph node metastases, G2, or recurrent after endoscopic resection: it is reasonable to discuss surgical resection of the tumor or tumors or antrectomy based on the terrain, location and number of tumors. In case of sporadic gastric NETs, they are most often single tumors, size> 1 cm and histologically aggressive. The treatment is modeled on that of gastric adenocarcinoma and in the majority of cases is based on partial or total gastrectomy with lymphadenectomy.

Liver is the most common site metastatic site for GI-NETs. The discussion of a resection / destruction of synchronous or metachronous liver metastases of well-differentiated NETs is only possible if all the visible tumors (metastases and primary tumor) appear entirely resectable or destructible, of "slow" growth, with an index Ki67 proliferation ≤ 10%, and in the absence of unresectable extrahepatic metastases.

The size of the procedure, the remaining foreseeable liver volume and the comorbidities must be taken into account in the surgical decision.

In case of hepatic metastases of well-differentiated NETs macroscopically resectable or completely destructible and not very progressive, surgical excision of the hepatic metastases is the goal; it also improves the duration and quality of life and facilitates the control of carcinoid syndrome. hepatectomy can be done in one step (Presence of a single liver metastasis or several liver metastases localized to the same hepatic lobe), or in 2 steps, the most used; performed in diffuse bilateral liver metastases. A study of 38 patients with liver-only metastases from NETs showed that patients who underwent liver resection had a higher 5-year survival (73% vs 29%) [30].

In case of a response to medical treatment of an initially inextirpable tumor mass, the surgical indication should be systematically re-discussed.

For unresecable NETs liver metastases, surgical cytoreduction can be considered [31]. A retrospective study of 120 patients showed that surgical cytoreduction provided longer symptomatic relief (35 ± 22.0 vs 22 ± 13.6 months, $p < .001$) and longer survival (50 ± 27.6 vs 32 ± 18.9 months, $p < .001$) than embolization [32]. The size of liver metastases and extrahepatic disease should be carefully considered in the decision of hepatic cytoreduction [33].

In the context of unresecable, central or bilobar hepatic metastases affecting more than ¾ of the hepatic parenchyma, without extrahepatic or extranodal metastases, liver transplantation may be discussed. It can be offered to selected young patients (<60 years), with a controlled primary tumor.

Less than 1% of patients with liver metastases from NETs are susceptible to liver transplantation [34].

Somatostatin analogues are a first-line therapeutic target, allowing inhibition of the secretion of hormones and vasoactive substances. Among the SSTRs, studies have shown that SSTR2 and SSTR5 were the receptors most able to mediate the anti-secretory effects of somatostatin in the pituitary gland and adenomas [35]. Many somatostatin analogues have been developed, the first of which called ocreotide has been tested in humans as early as 1982 [36]. Nowadays, many pharmaceutical forms have developed other more effective analogs, in particular with longer half-lives, optimized formulations and improved dosage methods, as is the case for Lanreotide. These two analogues bind with high affinity to SSTR2, and with lower affinity to SSTR 5 and 3. The control of hypersecretion by these analogues is effective in 40-60% of patients and allows a decrease or stabilization of tumor markers in approximately 30 to 75% of responding patients, depending on the tumor type considered.

Telotristat is an inhibitor, can be used in the treatment of diarrhea of carcinoid syndrome, in combination with somatostatin analogues, in case of insufficient control by somatostatin analogues alone.

NETs are highly vascularized tumors; they strongly express a large number of pro-angiogenic growth factors as well as their receptors, such as VEGF, the level of expression of which is correlated with greater tumor aggressiveness. Thus, the use of anti-antigenic agents has provided new therapeutic options that are effective in NETs.

Sunitinib (broad-spectrum tyrosine kinase inhibitor) is an anti-angiogenic agent currently validated in the treatment of well-differentiated pancreatic NETs, it allowed an improvement of the progression-free survival (PFS) (11 vs 5 months, $p < .001$) [37]. The other therapeutic class indicated in well-differentiated NETs is Everolimus, it is an inhibitor of the mammalian target of rapamycin (mTOR), a regulator of cell cycle and metabolism. The RADIANT-4 phase III trial (Everolimus vs placebo) in the treatment of advanced gastrointestinal and pulmonary NETs showed a significant increase in PFS with Everolimus (11.0 vs 3.9 months, $p < .00001$) [38].

Bevacizumab, is a Vascular endothelial growth factor (VEGF) inhibitor , has also shown promising results in combination with cytotoxic drugs such as capecitabine, oxaloplatin, streptozocin and temozolide in phase II studies in patients with metastatic NETs and unresectable.

Interferon-α is an antiproliferative agent, who is combined with somatostatin analogues, appears to improve an increase in survival and a decrease in the risk of progression [39]. It is considered generally as a last resort for patients with advanced or progressive NETs [40]. However, the doses of interferon used generate significant toxicity.

Chemotherapy is useful in advanced and metastatics NETs. Several products are used and are most often associated. The first results which demonstrated the effectiveness of chemotherapy on NETs of the pancreas were in 1968. Murray-Lyon reported the effectiveness of streptozotocin (STZ) in a case of insulinoma.

Subsequently, a compilation of several studies confirmed this efficacy with a response rate of 42%, which, was probably overestimated since the assessments of the responses were not made at the time according to the WHO criteria. Other molecules are also active: adriamycin, 5-FU, its oral analogue capecitabine, dacarbazine, and its oral analogue temozolomide. For multidrug therapy, several combinations can be used: 5-FU + STZ, adriamycin + STZ, adriamycin + 5-FU, dacarbazine + 5-FU, temozolomide + capecitabine, FOLFOX.

Peptide receptor radionuclide therapy is a practice consists in radiolabeling somatostatin analogues, and thus allows better targeting of tumors by radiation. The first radio analog on the market is Octreoscan (111 In-ocreotide), and it helps increase patient survival. Nowadays, other more efficient and better-tolerated radionuclides have been developed, namely [^{68}Ga-DOTA-Tyr3] ocreotide and [^{68}Ga-DOTA-Tyr3] ocreotide [41]. This type of therapy is particularly recommended for cases of inoperable or metastatic NETs-GEPs. The response rates vary between 15 and 35% depending on the radiopeptides considered, and the side effects are moderate [42].

Hepatic artery embolization (HAE) is a technique causing tumor ischemia by injecting various agents (cyanoacrylate, polyvinyl alcohol, microspheres or rubber particles) into the hepatic artery. HAE is indicated for patients with an unresectable tumor, symptoms related to hormonal hypersecretion, and with rapid progression of liver metastases [43]. HAE reduces liver tumor volume and symptoms [44].

A study showed that HAE gave better results when followed by systemic chemotherapy [45]. The effectiveness of this surgical technique was therefore improved by coupling chemotherapeutic agents, thus giving rise to chemoembolization of the hepatic artery (CEHA), which will allow, in addition to the creation of an ischemia, to introduce chemotherapeutic molecules within the metastases, to the blood capillaries, and therefore to concentrate up to twenty times more chemotherapeutic agent compared to

conventional systemic treatment [46]. Despite this reported advantage, the majority of scientific studies do not note any significant improvement in CEHA compared to HAE on patient survival [47].

Radiofrequency (RF) is a technique for the local destruction of hepatic tumors, causing tumor cell death at a temperature above 60°C using a sinusoidal current of 400 to 500 Khz, causing irreversible cell denaturation. The effectiveness of RF does not depend on the histological type; only the size of the tumor influences the effectiveness of the treatment. Its target population is close to that of surgery, which today remains the best treatment demonstrated for resectable liver metastases [13].

External beam radiotherapy (EBRT) allows locoregional treatment. It rarely used in the treatment of locally advanced or metastatic NETs. A systemic review of EBRT showed that OS of patients with NET ranged from 9 to 19 months after EBRT. The radiological response rate was 46% and grade 3+ toxicity rates were 11% (acute) and 4% (late)[47].

Conclusion

NETs are rare tumors, with prevalence is significantly increasing in recent years. Surgery, the only curative treatment of localized endocrine tumors, plays a major role in therapeutic strategy. It also has a place in metastatic forms, essentially hepatic, complete resection improving survival. The creation of a reference center for digestive TNE in our country, intended to supervise medical teams facing this pathology, is not a simple additional asset but an indispensable condition for a better management.

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