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The role of 68-Ga-DOTATOC CT-PET in surgical tactic for gastric neuroendocrine tumors treatment: Our experience: A case report

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ABSTRACT

Gastric neuroendocrine tumors (g-NETs), which originate from gastric enterochromaffin-like (ECL) mucosal cells and account for 2.4% of all carcinoids, are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy.

Often silent and benign, g-NETs may however, be aggressive and sometimes they mimic the course of gastric adenocarcinoma.

Current nosography distinguishes those occurring in chronic conditions with hypergastrinemia, as the type 1 associated with chronic atrophic gastritis, and the type 2 associated with Zollinger–Ellison syndrome in MEN1.

Conversely, type 3 and 4 (according to some authors) are unrelated to hypergastrinemia and are frequently malignant, with a propension to develop distant metastases.

While there is a general agreement concerning the treatment of malignant gastric neuroendocrine tumors, for types 1 and 2, current possibilities include surveillance, endoscopic polypectomy, surgical excision, associated or not with surgical antrectomy, or total gastrectomy.

This report, based on our clinical experience, discusses how the size, number, depth, histological grading, staging with CT, MRI, and the use of recently developed somatostatin receptor tracers (68Ga-DOTATATE, 68Ga-DOTA-TOC) could allow the correct identification of a benign or malignant propensity of an individual tumor, thus avoiding underestimation or overtreatment of these uncommon neoplasms.

1. Introduction

The neuroendocrine tumors of the stomach represent a wide spectrum of neoplasms that arise mainly from gastric enterochromaffin-like (ECL) cells.

According to data from the Surveillance, Epidemiology and End Results program (SEER) in the US, well differentiated neuroendocrine tumors (NETs) of the stomach demonstrated a tenfold incidence increase in the US in the last 30–35 years. The prevalence in the US of gastrointestinal well differentiated NETs has recently been calculated at 35/100,000 [1–3].

A recent analysis [4,5] of the National Cancer Institute SEER database by Modlin et al. demonstrated that, from 1992 to 1999, gastric NETs comprised 8.7% of all gastrointestinal carcinoid tumors.

Nowadays most neuroendocrine tumors of the stomach are diagnosed at an early stage because of the widespread use of upper gastrointestinal endoscopy. Moreover the diagnostic strategies, the management, and the prognosis has improved greatly over time.

According to a recent analysis of the SEER data by Landry et al. [6] 5-year-survival is now as high as 71%. We describe two cases of

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gastric NETs who presented to our surgical division: one case affected by multifocal type I gastric NET with locoregional lymphnode metastases and one case of type III gastric NET with synchronous adenocarcinoma of the stomach. In both cases an accurate diagnostic workup with 68Ga-DOTA-TOC CT-PET has significantly influenced the surgical strategy.

1.1. Our experience

Seven patients (pts) were treated in our institution between January 2006 and December 2012 for gastric neuroendocrine neoplasm. All lesions, incidentally discovered, were <10 mm. All patients except three, were successfully treated endoscopically. No recurrence has been recorded in our series. Interestingly two patients demonstrated unexpected node involvement in perigastric lymphnodes. Their clinical history and management will be described.

1.2. Case n. 1

A 60 year old white woman, with a 12-mo history of dyspeptic symptoms and mild weight loss, presented to our surgical department.

Her medical history was significant for an autoimmune atrophic gastritis, macrocytic anemia (Hb: 7.8 g/dl, MCV: 115 fL, vit.B12: <150 pg/ml, Ab-anti parietal cells positive) and a sensory neuropathy. Physical examination was negative except for a slight distal dysesthesia (glove shaped/sock shaped) and moderate ataxia attributable to the aforementioned peripheral neuropathy.

The upper endoscopy showed a polypoid neoformation (7 mm) within an irregularity of the sub-cardial gastric mucosa. It demonstrated also a mucosal deformity, with surrounding erosions, located in the antrum: several biopsies were performed.

The histological examination revealed a multifocal, well-differentiated endocrine tumor, with muscularis mucosae invasion, on a contest of severe chronic atrophic gastritis, widespread intestinal metaplasia and foci of low-grade dysplasia.

The proliferative activity (Ki-67, MIB1 index) was below 2%. The immunohistochemistry stained positive for synaptophysin and chromogranin A.

The determination of serum gastrin (normal value <50 pg/ml) and chromogranin A (vn 19.4–98 pg/ml) demonstrated respectively values of 698 pg/ml and 298 pg/ml.

The biochemical markers of renal function, liver, pituitary and parathyroid were within normal range.

To assess the degree of infiltration an ultrasonographical endoscopy was performed: it revealed a hypoechoic thickening of muscular and submucosal layer located in the incisura angularis (7 × 5 mm), and a hypoechoic thickening of mucosa and submucosa of the gastric body (8 mm).

Some lymph nodes of uncertain nature (6–7 mm) were observed along the lesser curvature and a group of nodes was detected medially to the arc of the splenic artery.

The CT scan confirmed the presence of nodes enlargement (7 mm) along the left gastric artery (station 7 according JGCA) and the presence of some nodes surrounding the proximal splenic artery (station 11p according JGCA). There was no evidence of distant mestastases.

Despite the US and CT scan evidence, the nature of those nodes was still not clear thus body receptor scintigraphy was also performed.

The 111-In Octreoscan was performed using thoracic WB/SPECT methodic and abdominal SPECT detection at 4, 24, 48 h after injection of the tracer: no pathological accumulation of tracer was detected.

The Total body CT-PET with 68-Ga-DOTA-OctreoTATE (DOTATATE) was also performed: tracer accumulation was detected on the gastric wall and also detected on 7-9-11p gastric lymphnode stations. No distant metastases were found (Fig. 1).

The patient underwent total gastrectomy with meticulous D2 lymphadenectomy paying particular attention on harvesting all nodes surrounding the proximal splenic artery.

The post operative course was regular and complication free, patient was discharged in post operative day 8.

Histological examination of the surgical specimen confirmed the diagnosis of multifocal neuroendocrine tumors infiltrating the muscularis, with metastasis to regional lymph nodes (T2 N+).

1.3. Case n.2

A 66 year old white male presented to our surgical unit with a past medical history significant for hypertension. Physical examination was negative except for a slight epigastric pain.

The Upper endoscopy showed some irregularities of mucosa along the posterior wall of the stomach: several biopsies were performed. The histological examination revealed a well-differentiated endocrine tumor (synaptophysin+, chromogranin A+, Ki 67 proliferative activity < 2%).

The determination of serum chromogranin A (vn 19.4–98 pg/ml) demonstrated a value of 135 pg/ml. The values of gastrin, renal function, liver, pituitary and parathyroid were within normal range.

To assess the degree of infiltration an ultrasonographical endoscopy was performed: it revealed a hypoechoic thickening of muscolar and submucosal layer located in the posterior wall of the stomach, and a hypoechoic thickening of mucosa and submucosa of the gastric body (8 mm). It also revealed no perigastric lymphnode enlargement. There was no evidence of enlarged nodes in the mesentery root or along the 7–9 node stations.

The CT scan confirmed the presence of a multiple gastric wall thickening (2 cm) and the presence of nodes enlargement in the splenic hilum of uncertain nature (station 10 according JGCA). There was no evidence of distant mestastases.

Because of the synchronous nature of endocrine tumors, the 111-In Octreoscan was performed: no extragastric clear pathological accumulation of tracer was detected.

Total body CT-PET with 68-Ga-DOTA-OctreoTATE (DOTATATE) was also performed: the tracer accumulation, detected on the gastric wall, was multifocal. Tracer accumulation was also detected in the splenic hilum. No distant metastases were found (Fig. 2).

The patient underwent total gastrectomy with D2 lymphadenectomy, extendend to the splenic hilum.

Post operative course was regular, the patient was discharged in P.O.D. 7.

The histological examination of the surgical specimen confirmed the diagnosis of synchronous multifocal neuroendocrine tumor infiltrating the muscular wall, with metastasis to regional lymph nodes in the splenic hilum (T2 N+).

2. Discussion

2.1. Classification

An optimal management of gastric NETs implies an accurate study of the type, biology, and stage of the tumor as well as the individual situation.

The World Health Organization (WHO) classification distinguishes well differentiated NETs, well differentiated neuroendocrine carcinomas, and poorly differentiated neuroendocrine carcinomas of the stomach.

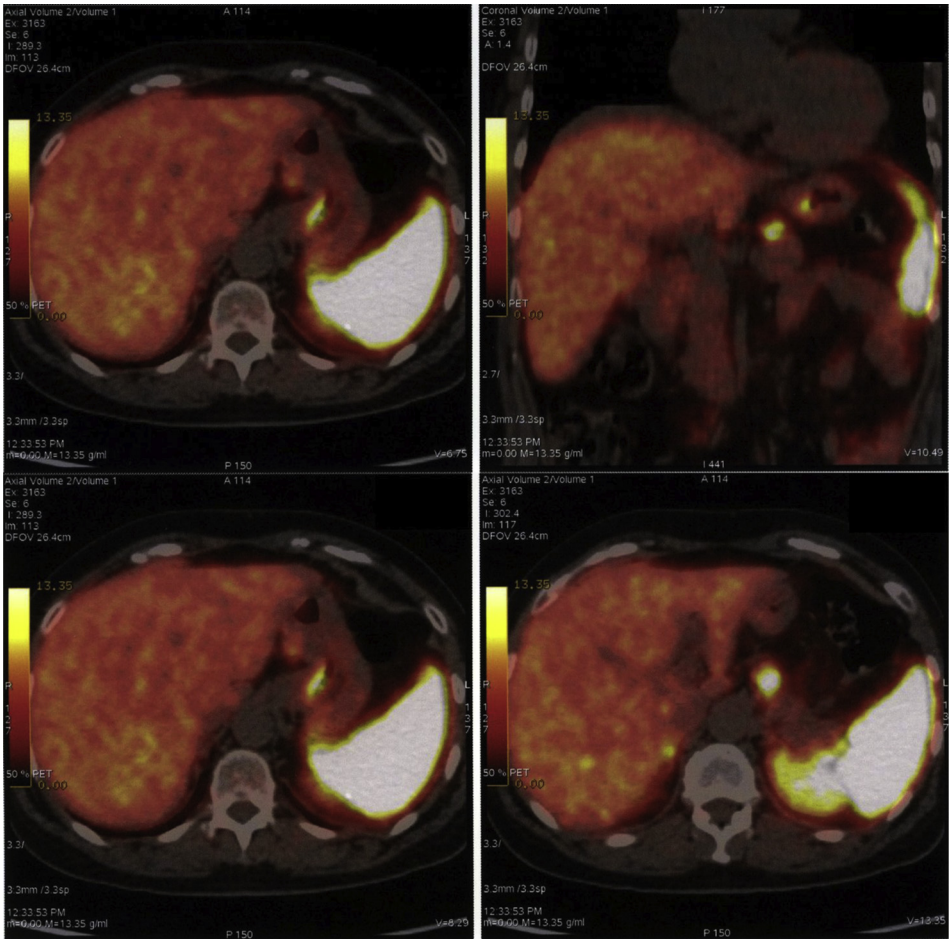

Fig. 1. 68-Ga-DOTATOC: lymph nodes of uncertain nature (6–7 mm) along the lesser curvature and a group of nodes medially to the arc of the splenic artery.

The term "neuroendocrine carcinoma" refers to tumors exhibiting histological angioinvasion or invasion of the muscularis propria or that have metastasized.

Stage is determined, according to the TNM classification, by tumor size, depth of invasion, and the presence of lymph node and liver metastases [6–8].

According to the proliferative activity, gastric NETs are graded as G1 (Ki-67: 0–2%), G2, (Ki-67:3–20%) or G3 (Ki-67: >20) [6–9].

The commonly used clinicopathological classification of the gastric NETs distinguishes fourth types of neuroendocrine neoplasms of the stomach [9–11].

2.1.1. Type 1

About 70%–80% of gastric neuroendocrine neoplasms are associated with fundic chronic atrophic gastritis (often autoimmune) and enterochromaffin-like (ECL) cell hyperplasia.

Patients have a mean age of 50 years and female sex is the more involved [11–14].

These tumors generally present (in 75% of cases) as multifocal polypoid mucosal protrusions (<10 mm) in the corpus and/or fundus of the stomach. Enterochromaffin, Enterchromaffin-like or somastatin cells can be identified: these tumors commonly express synaptophysin, chromogranin A, monoamine transporter 2 and often alfa-HCG [10].

The proliferative activity (Ki-67, MIB1 index) usually is 2% or below.

Type 1 NETs are minimally invasive with 90% confined to the mucosa or submuscosa and only 10% invading the muscularis propria. Only 2–9% of patients presents lymph node metastase. In particular lymph node metastases are generally associated with tumors greater than 20 mm, infiltrating the muscularis propria or angioinvasive [8–13].

The 5-and 10-year survival of those patients appears not to differ from those of the general population [11,13,15].

2.1.2. Type 2

About 5% of all gastric NETs occur in patients affected by multiple endocrine neoplasia type 1 (MEN1) and Zollinger–Ellison syndrome (ZES), primarily caused by a duodenal or pancreatic gastrinoma.

Gastric NETs develop in 15–30% of ZES/MEN1 patient: conversely, rare is the finding of GNETs in sporadic ZES.

Both sex are equally involved with a mean age, at the time of the diagnosis, of 45 years.

Similarly to type 1 tumors, type 2 gastric NETs are thought to originate from ECL cells. However, unlike type 1 tumors, both chief and parietal hyperplastic cells are contained in the mucosa. Type 2 gastric NETs typically express synaptophysin, chromogranin A, monoamine transporter 2 [10].

These tumors are generally small (<15 mm), almost multiple (92%) and limited to the submucosa/mucosa (90%) [13,14,16]. Risk factor for nodal involvement or metastases are tumor dimension (>20 mm), muscularis propria infiltration and angioinvasion [13,17].

The proliferative activity (Ki-67, MIB1 index) usually is 2% or below.

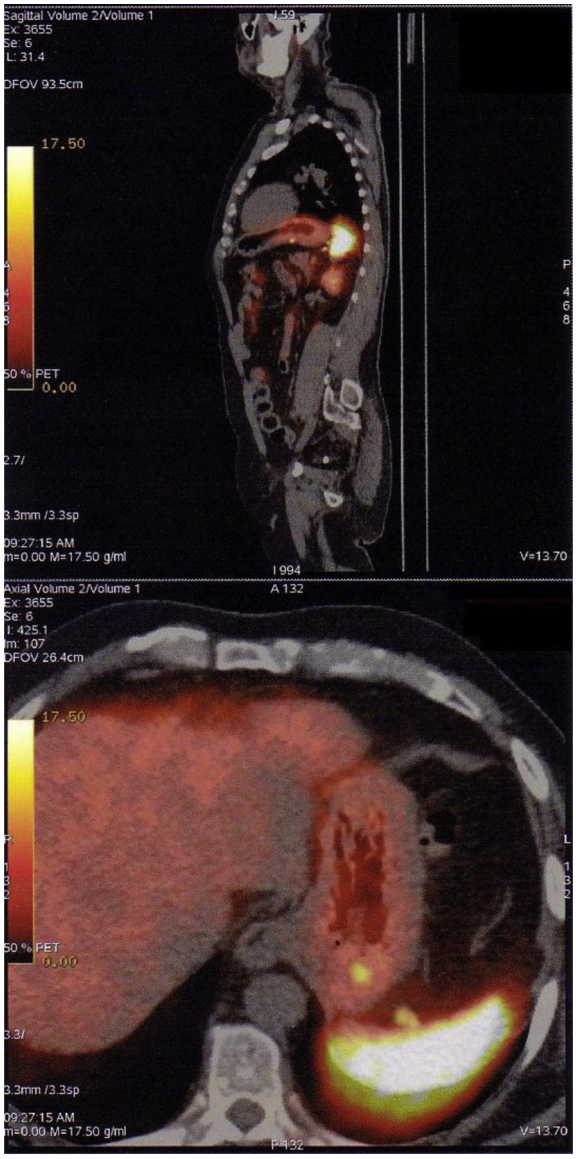

Fig. 2. 68-Ga-DOTATOC: tracer accumulation of uncertain nature, detected in the splenic hilum.

Lymph node metastases are found in 10%–30% of patients.

The 5-year survival rate is about 60%–75%: however this unfavorable rate is mainly related to the ZES/MEN1: tumor related deaths in this group has been described in fever than 10% [15,16].

2.1.3. Type 3

About 15–25% of all gastric NETs are sporadic neoplasm not associated with hypergastrinemia or ECL hyperplasia. The mean age of incidence is 50 years. Their proliferation rate often exceeds the 2% cut off level commonly shown by type 1 and 2 gastric NETs. At the time of diagnosis they often infiltrate the muscularis propria and become angioinvasive: most patients have already developed metastasis (liver or locoregional nodes) [11,14].

Tumor related death from type 3 gastric NETs is seen in 25%–30% of patients, and the 5-year survival is 50% or less [11,14,15].

2.1.4. Type 4

According to some authors this group describes poorly differentiated solitary neuroendocrine carcinomas. They were lacking in the original classification by Rindi et al [9,14].

At the time of the diagnosis these tumors are often ulcerated and their dimension is considerable (50 mm or greater). Infiltration and angioinvasivity is common: their proliferation rate usually exceed 20%.

Their immunohistochemical stain express synaptophisin but rarely chromogranin or VMAT2 [10].

Histologically these tumors demonstrate a pattern reminiscent of small or large cell neuroendocrine lung carcinoma. Sometimes adenocarcinoma of squamous carcinoma elements are mixed.

Half of the patients affected by this disease die within 12 months [8,9,18].

2.2. Diagnostic workup

Type I and II gastric NETs are almost an incidental finding during a routine upper gastrointestinal endoscopy.

Type II gastric NETs in patients affected by ZES/MEN1 could be diagnosed because of gastroesophageal reflux disease, recurrent peptic ulcer, chronic diarrhea, gastrointestinal bleeding, anemia and dyspepsia.

Type III and IV may also be symptomatic: bleeding, chronic diarrhea and loss of weight are the symptoms often described.

Occasionally an atypical carcinoid syndrome with prolonged flushing that affect the extremities or the trunk could be the exordium.

The diagnostic workup implies an upper endoscopy with several tumor biopsies.

It is recommended to perform a sampling not only of the suspected lesions but also of the fundus (four samples) and a sampling of the antrum (two samples) to evaluate the presence of atrophic gastritis and the degree of ECL hyperplasia [16–19].

Biopsies must be stained for chromogranine and synaptophysin. An accurate calculation of mitotic count and Ki/67 index is mandatory [11,16–19].

Endoscopic ultrasound is the main technique to evaluate the tumor size and depth of invasion: moreover EUS can also allow fine-needle aspiration of submucosal lesions.

Abdominal and Thoracic CT scan is useful to stage the disease, to find distant metastases and to evaluate the degree of node involvement.

Somatostatin receptor scintigraphy is useful to complete the staging of the disease.

A determination of serum gastrin and chromogranin A is always recommended. Secretin stimulation test should be performed when suspecting the presence of a ZES and proton pump inhibitors should be suspended for 7–8 days. Evaluation of intrinsic factor antibodies, Vit B12 serum levels and an accurate histological mapping of gastric fundus could help in the differential diagnosis between a solitary type 1 or type 3 gastric NET.

The 5-hydroxylindoleacetic (5-HIAA) acid concentration in a 24 h urine collection, histamine metabolites or 5-hydroxytryphophan test may be useful in patients that exhibit carcinoid typic or atypic syndrome [11,17–20].

2.3. The role of somatostatin receptor tracers

Neuroendocrine tumors are able to over-express somatostatin receptors (SSTRs) in a pattern related to tumor type, origin, and grade of differentiation.

To date 5 receptor subtypes have been characterized (SSTR1–SSTR5): SST2, SST3 and SST5 receptors bind to the somatostatin analogue octreotide and are expressed in 85%–100% of gastrointestinal and pancreatic NETs. In most cases, SST2 receptor is overexpressed [21,22].

Several analogs are used for scintigraphic imaging or PET of NET. The most widely used tracer for scintigraphy is 111In-DTPA-octreotide (111In-DTPAOC, Octreoscan).

The sensitivity of 111In-DTPAOC for the detection of NETs has been variously reported between 67% and 100%. However, quite recently, SST positron emission tomography (PET) has shown its diagnostic superiority over scintigraphy in several studies [23–26].

In comparison to scintigraphy, positron emission tomography has a two to threefold higher spatial resolution (3–6 mm versus 10–15 mm) and facilitates quantification of tracer uptake.

Although 18F-FDG PET shows high spatial resolution, unlike for many other malignancies, it is not indicated primarily for NET because of its poor sensitivity to detect tumors with low metabolic activity and slow growth.

The compound most often used in functional imaging with PET is 68Ga-DOTATOC.

The affinity of 68Ga-DOTATOC in binding SSTR2 is 2.5 ± 0.5 nM: it has been proven tenfold higher than that of 111In-DTPAOC (22 ± 3.6 nM) [22].

Two studies evaluating four and eight patients, respectively, demonstrated 68Ga-DOTATOC PET to be more efficient than 111In-DTPAOC single-photon emission computed tomography (SPECT) in the detection of small NET lesions [23,24].

In 2007 Buchmann et al. prospectively examined twenty-seven NET patients: the authors concluded that 68Ga-DOTATOC PET is superior to 111In-DTPAOC SPECT in the detection of NET manifestations in the lung and skeleton and similar for the detection of NET manifestations in the liver and brain. They focused the advantage of 68Ga-DOTATOC in guiding the clinical management [25].

Gabriel M et al. (2007) prospectively studied eighty-four patients. According to their study Somatostatin receptor PET with 68Ga-DOTA-TOC is superior compared with SPECT and CT in various clinical situations (initial diagnosis, staging, and follow-up). The higher sensitivity for tumor detection has clinical impact in a considerable number of patients, especially when compared with CT. The more accurate results are achieved by the combination of PET and CT [26].

Recently the use of 68Ga-DOTATATE over 68Ga-DOTA-TOC has been proposed: however according Poeppel TD et al. (2013) the approximately 10-fold higher in vitro affinity for the sst2 of 68Ga-DOTATATE has not proven to be clinically relevant [27].

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues plays a growing role in the treatment of patients with inoperable or metastatic gastroenteropancreatic neuroendocrine tumors [28].

90Y-DOTATOC and 177Lu-DOTATATE (Yttrium-90 and Lutetium-177 beta emitters) nowadays are the most used radiopeptides for PRRT. The results that are very encouraging in terms of tumor regression (tumor response rates: 15–35%) and in terms of patients self-assessed quality of life.

Side effects are few and mild but amino acids should be used for kidney protection, especially during infusion of 90Y-DOTATOC.

Individual dosimetry could prevent damage to bone marrow and normal organs especially when different mixture of radiopeptides are administered.

Options to improve PRRT may include combinations of radioactive labelled somatostatin analogues and the use of radiosensitising drugs combined with PRRT.

The neo-adjuvant treatment and adjuvant therapy cycles in patients with progressive disease, after surgery have been proposed but further evidences are required.

If more widespread use of PRRT can be accomplished, PRRT may well become the therapy of first choice in patients with metastatic or inoperable GEP-NETs [28–30].

2.4. Management

Treatment strategies are greatly influenced by the type, grade and stage of the gastric NET.

Muscular wall infiltration, increased proliferation (Ki67 > 2%), and angioinvasion are considered risk factor for metastatic disease.

The invasion of the muscularis propria, angioinvasion, increased proliferation activity and the presence of nodal involvement lead an indication to surgical treatment even in well differentiated tumors.

Type 1 or 2 gastric NET that are 10 mm or smaller, in absence of risk factor like the aforementioned muscular wall infiltration, increased proliferation or angioinvasion, can either be managed conservatively with endoscopic surveillance (<10 mm) or removed by endoscopic mucosal resection (<20 mm): the specimen will be examined for histological signs of angioinvasion and evaluation of the proliferation activity. Surveillance by gastroscopy is repeated at 12–14 months intervals after the endoscopic treatment [11,15].

Despite the controversies in management of type 1 or 2 gastric NETs, there are no reports in the literature inheriting clinical relevant local recurrencies after polypectomy or mucosectomy of small (<20 mm) type I or II gastric NETs: the available retrospective data do not argue for a survival benefit of the surgical versus non surgical treatment of these small tumors when they are lacking risk factors. Conversely, small type 1 or type 2 (<20 mm) GNETs must be considered for surgery if they become angioinvasive, infiltrate the muscular wall, show G2 grading or have metastasized. Treatment recommendations for type 2 gastric NETs can only be based on case reports and small case series: they are often multiple and hypergastrinemia cannot be easily solved surgically, thus, according to some authors, total gastrectomy is often preferred to partial gastrectomy. However, especially in elderly patients, conservative or minimally invasive surgical therapy may be preferred. Treatment with somatostatin analogues could help in reducing the number and recurrence of small type 2 tumors in patient not candidated to surgery [31,32].

The treatment of type 2 GCs is further complicated by the controversies regarding the treatment of gastrinoma in MEN-1. Currently, no definitive evidence exists that surgery increase the survival or disease free survival in MEN-1. The role of duodenal-pancreatic surgery in patients with MEN-1 who have pharmacologically controllable ZES and no other clinically evident hormonal related syndrome is still object of debate.

Surgery is also the treatment of choice for type 3 gastric NETs (>10 mm) and localized type 4 poorly differentiated tumors. Only small (<10 mm) type 3 G1 gastric NETs confined to mucosa may be treated by endoscopic mucosectomy [11,15].

Because of the favourable tumor biology, surgery and or local ablation should be considered even in metastatic disease. Liver metastases should be treated by hepatic resection, ablative therapies, arterial embolization, radioembolization or peptide receptor targeted therapy. In the case of systemic, non resectable disease cytostatic therapy is generally advised. Exocrine-endocrine tumors (commonly called "collision tumors") share the diagnostic workup and the therapeutic strategies with the usual type of gastric carcinoma.

Long-acting somatostatin analogues are the drugs of choice for the medical control of the carcinoid syndrome (generally atypical) with promising results in 70%–90% of patients.

I they fail alpha interferon could be used. Moreover PPIs (protonic pump inhibitors) are the medical treatment of choice for ZES if surgical treatment fails [16,17,21,22].

2.4.1. Follow up and endoscopic surveillance

Surveillance by endoscopy with biopsies is recommended every 3–5 years in patient with fundic autoimmune or atrophic gastritis.

Surveillance for MEN 1 patient require regular gastroscopies every 2–3 years. If type 1 gastric NET disease has been diagnosed endoscopic histological surveillance is recommended every 12 months for recurring patients, and any 24 months for not-recurring cases. In case of type 2 tumors, endoscopy should be repeated yearly. In patients with type 3 tumors, followup should depend on tumor subtype and is confident with program suggested for gastric adenocarcinoma. Biopsies of every mucosal lesion should be performed. Follow-up should include radiological investigations (CT scan/MRI) and CgA [33–35].

3. Conclusions

Gastric lesions are often found during endoscopic examination of upper gastrointestinal tract. Those range from benign (i.e., fundic gland polyp, hyperplastic polyp, hamartomatous polyp, pancreas rest) to premalignant or malignant lesions (i.e., adenoma, neuroendoscrine tumors [G-NET] gastrointestinal stromal tumor [GIST], MALT lymphoma, adenocarcinoma) [36–40].

An accurate preliminary differential diagnosis is necessary, especially when ZES/MEN1 is suspected [41].

Our experience clearly demonstrates how an accurate diagnostic workup and the integration with 68Ga-DOTATOC CT-PET has a great influence in the correct management of gastric neuroendocrine tumors.

In the first case we describe a multifocal type 1 endocrine tumor: the adoption of ad US gastric endoscopy showed the suspicion of involvement of regional lymph nodes. This placed the indication for further diagnostic investigations.

In the second case we describe a multifocal type 3 endocrine tumor: it demonstrated nodes involvement at the splenic hilum.

We would like to emphasize about the importance played by CT – PET with Ga- 68 – DOTATOC to obtain a correct staging and then a proper treatment of the patients [23–26].

In our experience the surgical strategy was elaborated owing to the PET findings. The lymphadenectomy and the entity of gastric resection were extended with the aim of R0 resection.

Further parameters need to be evaluated to identify the small subset of patients that will develop more aggressive disease [42].

Ethical approval

This is a retrospective study based only on the analyses of recorded data and then no Ethical Approval was necessary.

Author contribution

Andrea Cavallaro: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Antonio Zanghì: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Marco Cavallaro: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Emanuele Lo Menzo: Partecipated substantially in the drafting and editing of the manuscript.

Isidoro Di Carlo: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Maria Di Vita: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Francesco Cardì: Partecipated substantially in conception, design and execution of the study and in the analysis and interpretation of data.

Gaetano Piccolo: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Paolo Di Mattia: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Alessandro Cappellani: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data. also partecipated substantially in the drafting and editing of the manuscript.

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Conflicts of interest

All Authors have no conflict of interests.

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