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Review

Pancreatic neuroendocrine tumors: Nosography, management and treatment

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ABSTRACT

Pancreatic neuroendocrine tumors (pNETs) represent about 7% of all NETs, 8.7% of gastroenteropancreatic NETs (GEP-NETs) and 1–2% of all pancreatic neoplasms. In the last two decades, the increased diagnosis of pNETs has generated great interest and the development of different classifications, grading and staging systems. Recently, several trials were performed in order to improve the knowledge of biomarkers and imaging and to provide an early diagnosis, but their role is still under debate. Nowadays, surgery represents the only curative approach for pNETs. Approximately 90% of pNETs are silent and non-functional; therefore, most patients are diagnosed in late stage and present metastatic (60%) or locally unresectable advanced disease (21%) with a poor prognosis. Not many therapeutic options are available for pNETs, with different treatments for G1-G2 and G3 tumors, because these diseases are still rare and trials are made up of few series of patients. At present, medical treatments is controversial. On these bases, we believe that a multidisciplinary team composed of surgeons, oncologists, endocrinologists, radiation oncologists, radiologists, pathologists and medicals nuclear is required. This paper presents a review of present state-of-the-art in the field of pNETs.

1. Introduction and epidemiology

Neuroendocrine tumors (NETs) are a heterogeneous group of diseases, which includes tumors arising from pluripotent endocrine cells in different sites, presenting with different signs and symptoms, various malignant potential and different prognosis. The most common primary location of NET is the gastrointestinal tract (58%), followed by the lungs (15%) [1]; in the first, pancreatic neuroendocrine tumors (pNETs) arouse great interest nowadays. In fact, although pNETs represent about 7% of all NETs, 8.7% of gastroenteropancreatic NETs (GEP-NETs) and 1–2% of all pancreatic neoplasms, they are increased considerably in the last two decades, especially due to the larger use of diagnostic imaging [2,3].

In general, pNETs are more common in Caucasian (84%) and in males, with an incidence that increases with age, reaching a pick in the fifth-sixth decades (the mean age in patients with functional and non-functional disease is 55 and 59 years respectively) [4,10]. Most of pNETs are sporadic, while 10–30% of these occur within hereditary syndrome, such as Multiple Endocrine Neoplasia type I (MEN1), type IV (MEN4), neurofibromatosis type I (NF1), von Hippel-Lindau disease (VHL) and tuberous sclerosis [4]. Despite the increased diagnosis of incidental lesions, today about 60–70% of patients have a metastatic disease at diagnosis, with differences based on histology kinds.

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2. Classification, clinical presentation and staging system

The classification and staging of pNETs have been debated in the past. Today, we classify pNETs into groups relying on different characteristics: molecular mutations, functionality, histology grading and stage.

For molecular mutations, pNETs are distinguished in sporadic and hereditary, characterized by different clinical presentation and different gene alterations, such as gene on cr.11 encoding menin in MEN1 [5]. (Table A1).

pNETs are also divided into functional and non-functional tumors. A tumor is called functional when its hormone hypersecretion causes clinical syndrome and non-functional when clinical syndrome does not occur, often in the presence of a hormone secretion. About 10% of pNETs are functional with symptoms related to the type of hormone secretion; in this group, insulinomas are the most common (30–40%), followed by gastrinomas (16–30%), glucagonomas (<10%), VIPomas (<10%) and somatostatinomas (<5%) [5,6]. (see also Table A2).

Insulinomas are mainly sporadic and may arise in any area of the pancreas. They typically show a triad of symptoms, also kwon as Whipple's triad: sign and symptoms of hypoglycemia (tremors, palpitations, sweating, etc), blood glucose < 45 mg/dl and symptoms regression with glucose uptake. These symptoms typically occur during exercise or fasting and are due to insulin hypersecretion resulting in hypoglycemia and increase levels of circulating catecholamines; they can persist for many years before diagnosis [7,8].

Gastrinomas are characterized by gastrin ectopic release and can be detected in pancreas, but, more often, they are located in the duodenum [6,9]. The gastrin secreted by tumors caused secretory diarrhea and multiple refractory peptic ulcers, known as Zollinger-Ellison syndrome. Gastrinomas are sporadic or hereditary and representing the most common type of pNET in MEN1 syndrome, with a worse prognosis than in the first case [11–13].

Glucagonomas are rare glucagon-secreting tumors, and can be presented with different signs and symptoms, such as stomatitis, diabetes, diarrhea, weight loss, deep vein thrombosis, but the most common is the migratory necrolytic erythema, which may also appear many years before diagnosis. This peculiar sign consists in a dermatitis characterized by perioral, inguinal, perineal, gluteal or limbs skin lesions that evolve in the sequence erythema-vesicle-necrosis-pigmented scars [14,15].

VIPomas represent <10% of functional pNETs and secrete vasoactive intestinal polypeptide (VIP), leading to Verner-Morrison syndrome, also known as WDHA syndrome or pancreatic cholera, characterized by watery diarrhea, hypokalemia, hypochlorhydria, hyperglycemia, hypercalcemia and dehydration [8].

Finally, somatostatinoma is the less frequent functional pNET. This tumor shows different clinical features due to multiple somatostatine activity, such as inhibition of insulin, glucagon, gastrin secretions, decrease of fat absorption and increase of bowel motility. Therefore, patients affected by somatostatinoma may present diabetes, steatorrhea and cholelithiasis, even if these occur together only in a very few cases [7].

Approximatively 90% of non-functional pNET tumors are silent, therefore in most patients are diagnosed in late stage, appearing as metastatic or locally advanced disease in 60% and 21% respectively [8,9]. These types of tumors, in fact, show unspecific symptoms, related to local invasion, such as abdominal or back pain, lack of appetite, weight loss and dyspepsia or do not show symptoms so their early diagnosis is difficult or incidental.

From histological point of view, the 2010 World Health Organization (WHO) classification system is the most used grading system. It divides pNETs into three grading groups with different prognosis, basing on mitotic count and ki-67 index, expression of the proliferative activity of tumor cells [16]. On this basis, tumors with ki-67 $\leq$ 3% and <2 mitoses per 10 HPF are considered Grade 1 (G1), tumors with ki-67 between 3 and 20% and mitotic count between 2 and 20 per 10 HPS are Grade 2 (G2) and tumors with ki-67 > 20% and >20 mitoses per 10 HPS are Grade 3 (G3). Grade 1 and 2, known as NETs, are well differentiated and represent about 90% of tumors with a 5-year survival rate of 85% and 78% respectively. Grade 3 neoplasms represent 10% of all pNETs; they are poorly differentiated with a 5-year survival rate of 10% and they are classified as neuroendocrine carcinomas (see Table A3).

Among different pNETs staging systems developed over the last decades, nowadays the most common classification systems are the 2006 European Neuroendocrine Tumor Society's (ENETS) and 2010 American Joint Committee on Cancer's (AJCC) [17,18]. These systems have similar and dissimilar features: both classifications divide pNETs into IV stage based on TNM [19]; both correlate every stage with specific 5-year survival with a no statistical small difference; while ENETS staging system provides a division of stages II and III into IIa-IIb, IIIa-IIIb, in AJCC, developed from the pancreatic adenocarcinoma TNM, stage III is no divides and stages I and II are divided into Ia-Ib, IIa-IIb; in ENETS classification the metastasis in regional lymph node (N1) defines IIIb stage, while in AJCC N1 defines IIb stage (Table A4).

3. Diagnosis, biomarkers and imaging

The early diagnosis of pNETs is uncommon or incidental, because about 90% of these tumors are non-functional or appear with mild symptoms, therefore about 60–70% of patients present a metastatic disease at diagnosis. Biochemical assessment and imaging are widely used for diagnostic assessment.

To diagnose an insulinoma, the gold standard is the 72 h fast test: in case of insulinoma, in fact, the physiological inhibition of insulin secretion is altered due to fasting already after 12–36 h; in this test, the patient shows signs and symptoms of hypoglycemia and blood glucose <40 mg/dl. Furthermore, the hormone assessment shows hyperinsulinemia with increase of proinsulin and C-peptide blood levels, revealing the endogenous hypersecretion

Table 1
Hereditary pNETs and syndromes.

Syndrome	Gene alteration	% pNETs	Type NET
Multiple Endocrine Neoplasia type 1 (MEN1)	11q13: Menin	20–80%	Gastrinoma (54%) Insulinoma (18%) Glucagonoma (3%) VIPoma (3%) Non functional pNETs
Von Hipple Lindau Disease (VHL)	3q25	10–17%	Non functional pNETs (98%)
Neurofibromatosis 1 (NF-1) Von Recklinghausen	17q11.1: neurofibromin	0–10%	Duodenal NET, rare pNETs
Tuberosis Sclerosis	9q34: hamartin (TSC1) and tuberin (TSC2)	Rare	Non functional pNETs

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Table 2
Functional pNETs.

Type of tumor	Secretion	% pNETs	Main symptoms
Insulinoma	Insulin	30–40%	Whipple triad
Gastrinoma	Gastrin	16–30%	Zollinger-Ellison syndrome
Glucagonoma	Glucagon	<10%	Migratory necrolytic erythema, diarrhea
VIPoma	VIP	<10%	Verner-Morrison syndrome
Somatostatinoma	Somatostatina	<5%	Diabetes, steatorrhea, cholelithiasis

Table 3
WHO grading system of pNETs.

	G1	G2	G3
Ki-67 index	<3%	3–20%	>20%
Mitotic count	<2/10 High power field (HPF)	2–20/10 HPF	>20/10 HPF

[20].

The diagnosis of gastrinoma is confirmed when the fasting serum gastrin level is higher (>1000 ng/L) and the gastric pH is lower than 2.5. Sometimes, a secretin stimulation test is required to show an increase in gastrin levels >50% of the basal. However, it is important to make a differential diagnosis with other conditions that can cause hypergastrinemia, such as H. Pylori infection or use of proton pump inhibitors [21].

Patients affected by glucagonoma may experience anemia, hypoalbuminemia, hypocholesteremia and hyperglycemia with blood glucagone >200 ng/dl, which increases after oral glucose intake. In these cases, it is also important to note that various non-neoplastic conditions (pancreatitis, diabetes, sepsis or prolonged fasting) lead to glucagone hypersecretion [22].

In case of VIPoma we can observe severe serum electrolytes alterations, such as hypokalemia, hypochlorhydria, hypercalcemia, and the increase of plasma VIP level >500 pg/ml and/or the lack of osmolar gap in the analysis of the stool fluid, suggesting a secretory disease [23].

Common biochemical alteration is the increase of somatostatina plasmatic levels in case of somatostatinoma [24].

Among different available biomarker used for diagnosis of pNETs, Cromogranina A (CgA) is the main one in terms of sensibility. CgA is a protein contained in neurosecretory vesicles of NET cells and increases in most pNETs, but its specificity is limited due high frequency of false positive; in fact, CgA levels increase in several stress conditions, liver o renal disorders, or during therapy with proton-pomp inhibitor. Furthermore, CgA is a predictor of disease progression and survival (prognostic value), treatment response and often represents the first sign of disease recurrence, so the plasma CgA assessments are largely used for the follow-up in pNETs patients [25,26].

Radiological assessment is critical to detect the primary tumor, site and tumor extension, expecially in order to define the surgical resection. Often pNETs are small or the primary site cannot be located and the diagnosis by imaging is really hard. Computed tomography (CT) scan is the first used in most cases, especially for staging and differential diagnosis, while RMN may follow CT if primary tumor is very small and no detected by CT. These techniques are also used for abdominal or brain staging.

Nowadays, the main player is the positron emission tomography (PET) using 18-FDG-PET or 68Ga-labeled somatostatin PET (^{68}Ga-DOTA-SSTa), in association with CT, in G3 and well differentiated pNETs, respectively. In fact, G3 pNETs are characterized by high metabolism and intake the glucose, while ^{68}Ga-DOTA-SSTa is used in G1 and G2 tumor on the basis that well differentiated tumor cells express somatostatin receptors on their surface. This characteristic allows the intake of 68Ga-labeled somatostatin in tumor cells, resulting in detection of the tumor [27]. This assumption is also adopted in the somatostatin receptor scintigraphy (SRS), which use 111Indium-labeled somatostatin (octreoscan) to detect primary well differentiated pNETs, expecially glucagonoma; SRS is also used for staging, detecting metastasis or recurrence in follow-up or evaluating the sensibility of tumors in order to use target radiation therapy. Both ^{68}Ga-DOTA-SSTa and octreoscan should be used cautiously in insulinoma, because often this tumor does not express somatostatin receptor [28].

Finally, endoscopic ultrasound (EUS) is still essential in pNETs diagnosis, because it allows detecting small lesions in pancreas or

Table 4
Staging systems.

Definitions	ENETS TNM	UICC/AJCC/WHO 2010 TNM
T1	Limited to the pancreas, < 2 cm	Limited to the pancreas, ≤ 2 cm in greatest dimension
T2	Limited to the pancreas, 2–4 cm	Limited to the pancreas, > 2 cm in greatest dimension
T3	Limited to the pancreas, > 4 cm or invading duodenum or bile duct	Beyond the pancreas but without involvement of the superior mesenteric artery
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)	Involvement of celiac axsis or the superior mesenteric artery (unresectable tumor)
Stage I	T1N0M0	NA
Stage IIa	T2N0M0	NA
Stage IIb	T3N0M0	NA
Stage IIIa	T4N0M0	NA
Stage IIIb	anyT N1M0	NA
Stage IV	anyT anyN M1	NA
Stage IA	NA	T1N0M0
Stage IB	NA	T2N0M0
Stage IIA	NA	T3N0M0
Stage IIB	NA	T1-T3 N1M0
Stage III	NA	T4 anyN M0
Stage IV	NA	anyT anyN M0

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other gastro-intestinal tract – also in intraoperative setting – and performing biopsies of these lesions for the histology analysis [29].

4. Surgical treatment

4.1. Resectable disease

All patients with resectable disease should be candidate for curative surgery. Depending on the primary tumor location, the options are: simple enuclation, distal pancreasectomy, with or without splenectomy, central pancreasectomy, pancreaticoduodenal resection (Whipple's operation) and total pancreasectomy. For insulinomas or small pancreatic lesions, which are often less than 2 cm, enucleation or central pancreasectomy can be considered the procedures of choice if technically appropriate [30–33], while distal pancreasectomy is indicated for lesions in the body or tail of pancreas. Spleen salvage following distal pancreatectomy should be preferable for benign or low-grade malignant disease [34,35]. Otherwise, splenectomy is clearly indicated in patients with non-insulinoma pNETs, in which an adequate lymph node clearance is mandatory to ensure the oncologic resection. Pancreaticoduodenectomy is the gold standard for neuroendocrine tumors of pancreatic head. Usually, total pancreasectomy is rarely performed due to associated risk of post-operative complicances [36–38]. Laparoscopic approaches for these procedures have also been developed in high-volume centers for pancreatic cancer surgery, showing low rate of post-surgery complications [39–42]. However, at present, there are no data available about long-term survival and outcomes in patients treated by laparoscopic surgery.

4.2. MEN 1

The management of neuroendocrine tumors in the context of MEN1 is not well established. In patients with functional non-gastrinoma pNETs, non-functional tumors >2 cm or with resectable metastatic disease, surgical resection is recommended [43]. Despite the multifocality of pNETs in MEN1 (more than 80% of cases) total pancreasectomy is not routinely recommended in view of the high rate of mortality and morbidity and, if applicable, parenchyma-preserving resections should be performed. In general, in patients with small gastrinoma (<1 cm) or non-functional pNETs (<2 cm) a program of close follow-up can be adopted [44–46].

4.3. Advanced disease

Although controversial, the mainstay of therapy for metastatic pNETs remains surgery. Surgical resection of primary tumor, regional lymph nodes and liver or other metastases with curative intent or palliative debulking is usually performed when more than 90% of tumor burden can be removed [47–51]. A recent retrospective review of metastatic non-functional pNETs has shown no significant difference in terms of survival rate between patients who were underwent to R0 or R1 (>90% of tumor burden) surgery. These data suggest the feasibility of this approach with the additional advantage of relief from non-functioning tumors causing symptoms related to mass effect. Resection of primary non-functioning pNET in patients who have unresectable synchronous liver metastases is not routinely recommended [52].

4.4. Liver metastases

Liver metastases develop in more than 50 percent of patients with pNETs, strongly influencing the prognosis [53]. The treatment best suited for liver metastases depends on number, size and location of the lesions, the extent of primary tumor and patient's performance status. Partial hepatectomy is employable in many patients with primary pNET and synchronous liver metastases and preferably it should be performed before the pancreatic surgery, in order to reduce the risk of forming hepatic abscess [54]. When the lesions are not resectable, there are two way to address liver metastases: locally ablative techniques and vascular approach.

Local ablative therapies include cryotherapy, microwave coagulation, ethanol injection and radiofrequency (RFA). Radiofrequency is the most common used technique and, in selected cases, it seems to be comparable to surgical resections in terms of local control and survival [55].

Based on the principle that metastatic tumor cells derive more than 90% their oxygenation and nutrition from the hepatic artery, for a high tumor burden due to unresectable disease or recurrence after resection, liver-directed therapies with vascular approach as well as hepatic artery embolization (TAE), hepatic artery chemoembolization (TAE), or radioembolization are warranted [56]. For patients with unresectable hepatic metastases, liver transplantation can be a feasible therapeutic option, especially in the cases of hormonal symptoms and pain refractory to medical management. Nevertheless, the role of liver transplant for NETs remains unclear, due to the absence of defined selection criteria and the lack of data regarding the long-term survival after transplantation [57–61].

5. Peptide receptor radiotherapy (PRRT)

PRRT with Somatostain-receptor (SSR) ligands is a novel and promising treatment modality for patients with SSR-expressing NET inoperable or with liver metastasis, because in the no SSR-expressing tumors there is not peptide intake. Today, there are two principles molecules of choice with no direct comparison: 90-Y DOTATOC and 177-Lu OCTREOTADE; these can be used alone or in combination, because the latter may be superior, as resulted in two different trials [62,63]. PRRT is generally well tolerated, with manageable toxicity, and response rate is 15–35%, as resulted in literature. Studies of combination between PRRT and other target therapies are ongoing.

6. Sistemic therapy

Complete surgical resection is the treatment of choice for localized cancers, but frequently the pNET are unresectable, because are diagnosed in a late stage. Many therapeutic modalities exist for management of advanced disease; they differ on the basis of tumor's differentiation in according to WHO.

6.1. Well differentiated (G1-G2) pNETs

Over 70% of pNETs express variable levels of somatostatin (SST) receptors on their cell surface. The role of specific SST receptor subtypes with SST antiproliferative effects has been identified as an indirect control of tumor growth [64–66], since SST 1,2,4 and 5 are mainly involved in the arrest of cell cycle progression while SST 2 and 3 are also able to activate pro-apoptotic pathways, as well as anti-angiogenic signals. Somatostatin analogues have been shown to be very useful for both symptomatic improvement and for growth tumor inhibition in patients with gastroenteropancreatic neuroendocrine tumor (GEP-NET) with a low proliferative index and higher percentage of somatostatin receptors [67,68]. There aren't data from randomized studies on the use of the SSA for specific pNET. From the CLARINET study, a randomized trial that compared Lanreotide Autogel 120 mg every 28 days versus placebo in a population of 204 patients (91 were pancreatic), it emerged

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that treatment with Lanreotide was better in term of progression-free survival if compared with placebo (HR 0.47; p = 0.0002), also in the subgroup of patients with pNET [69].

Somatostatin analogues have been used in conjunction with IFN and long-term survival gains have been observed. However, due to toxicity, IFN is not generally adopted as routine treatment for NETs [70,71]. Differently, targeting angiogenesis appears to be an intriguing strategy for treatment of pNETs and a number of new anti-angiogenic agents have been recently licensed. In particular, the efficacy of Sunitinib, a multitarget tyrosine kinase inhibitor, was evaluated in a recent phase III randomized in which the 86 treated-patients showed a longer PFS (11.4 vs 5.5 months). For this reason, the study was stopped earlier by allowing patients in the placebo group to receive Sunitinib in a separate open-label study, as an extension of the Protocol. The majority of adverse events were grade 1–2 in both groups and the most common grade 3–4 adverse events related to Sunitinib were neutropenia (12%) and hypertension (10%) [72].

The so-called 'borderline tumors' with histological evidence of a well differentiated phenotype, but Ki67 of 2–15%, represent a management dilemmas that may be clarified by future correlative studies assessing proliferation index with treatment outcomes.

In general, the well-differentiated tumors are not responsive to chemotherapy, due to their low mitotic rates, presence of high levels of antiapoptotic protein bcl-2 and high expression of the multi-drug resistance (MDR) gene. Therefore, systemic chemotherapy is indicated in patients who have a rapid disease progression, tumor with aggressive pathological characteristics and a high proliferative index.

Historically, streptomicin (STZ) based regimens represented the standard of care for G1-G2 pNETs. In fact, in small-randomized trials, the combination of STZ with either 5FU or doxorubicin showed a RR of 60% [73]. Nonetheless, the significant toxicity of this regimen limited its use. Between alkylating drug used in the NET, temozolomide has shown a better tolerability. In literature, there are increasing evidence of its activity but, due to low number of patients involved, identify a preferred schedule is difficult [74]. From recent reports, the combination of Temozolamide and Capecitabine has raised interest in pNETs, showing an impressive RR of 70%. Interesting data also emerged from the retrospective analysis of the Pancreas Center at Columbia University, that have evaluated the efficacy and safety of capecitabine and temozolamide (CAPTEM) in patients with well-differentiated neuroendocrine cancers and liver metastases who had failed of Sandostatina LAR, chemotherapy and hepatic chemoembolization [75]. Median PFS and OS resulted of 14.0 and 8.3 months, respectively. In particular, the response rate in the pNET was the highest (45%) and the treatment was well tolerated with only 11% of grade 3 thrombocytopenia.

Other combinations of chemotherapy regimens have shown achieving equivalent or better RRs in phase II studies. Capecitabine combined with oxaliplatin achieved a 30% objective RR in 27 patients with well-differentiated NETs.

Finally, Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in a phase II (RADIANT-2) [76] and in a phase III trial (RADIANT-3) conducted involving 410 patients with G1/G2 pNETs. In this last trial, median progression free survival was 11 month in the everolimus group vs 4.6 months of the placebo group [77]. Based on this study, everolimus became the first drug approved by the FDA for treatment of locally advanced, unresectable, or metastatic pNET, in the last thirty years. Everolimus may be most effective in combination with other therapies, including SSAs as previously mentioned, but further research is required to define its optimal role in pNET therapy.

6.2. Poorly differentiated (G3) pNETs

The most common medical treatment is chemotherapy, because G3 pNETs are chemosensitive, and cisplatin-etoposide based schedule represents the gold standard, with 42–67% response rate [78–80]. Carboplatin can replace cisplatin and irinotecan can replace etoposide in unfit patients with no detrimental effect in terms of activity [81,82]. Nevertheless, the results of the main trials are based on dated experiences, with few patients and different schedules of treatment.

The second line treatment in G3 pNETs after a platin-based chemotherapy is still under debate. The possible choices are represented by two main schedules: FOLFIRI and temozolomide as single agent or combined with bevacizumab. In the first schedule, FOLFIRI has shown a response rate of 31% in a very limited series (19 patients) in second line [83]. Welin et al. reported that temozolomide alone or in combination with capecitabine ± bevacizumab resulted in median PFS, median OS, median duration of response of 6, 22, and 19 months, respectively, with 33% response rate in 25 patients [84,85].

7. Conclusions

In the last 20 years, our understanding of pNETs, from epidemiology to treatments, is improved. Nevertheless, a multidisciplinary team made up of surgeon, oncologist, endocrinologist, radiation oncologist, radiologist, pathologist and medical nuclear should manage pNETs, due their variability and complexity. Further trials of treatments in first and second chemotherapy lines and in target therapy, of predictive and of prognostic factor are needed to improve the survival of patients affected by pNETs, which is still poor.

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Author contribution

MO: Partecipated substantially in conception, design, and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

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Conflicts of interest

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