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Pre-operative Diagnosis of Pancreatic Neuroendocrine Tumors with Endoscopic Ultrasonography and Computed Tomography in a Large Series

Raffaele Manta[1], Elisabetta Nardi[2], Nico Pagano[3], Claudio Ricci[3], Mariano Sica[1], Danilo Castellani[2], Helga Bertani[1], Micaela Piccoli[4], Barbara Mullineris[4], Alberto Tringali[5], Francesco Marini[6], Ugo Germani[6], Vincenzo Villanacci[7], Riccardo Casadei[3], Massimiliano Mutignani[5], Rita Conigliaro[1], Gabrio Bassotti[2], Angelo Zullo[8]

1) Gastroenterology and Digestive Endoscopy Unit, Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena;
2) Gastroenterology Section, Department of Medicine, University of Perugia School of Medicine, Perugia;
3) Department of Internal Medicine and Surgery (DIMEC), University of Bologna, Sant'Orsola-Malpighi Hospital, Bologna;
4) Department of General Surgery, Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena;
5) Endoscopy Unit, Niguarda Ca-Granda Hospital, Milan;
6) Gastroenterology Unit, Ospedali Riuniti Ancona;
7) Pathology Unit Spedali Civili, Brescia;
8) Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome, Italy

Address for correspondence:
Raffaele Manta MD,
Gastroenterology and Endoscopy Unit,
Nuovo Ospedale Civile Sant'Agostino-Estense,
Viale Giardini 1355
41125 Baggiovara-Modena, Italy
r.manta@libero.it

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ABSTRACT

Background & Aims: Diagnosis of pancreatic neuroendocrine tumors (p-NETs) is frequently challenging. We describe a large series of patients with p-NETs in whom both pre-operative Computed Tomography (CT) and Endoscopic Ultrasonography (EUS) were performed.
Methods: This was a retrospective analysis of prospectively collected sporadic p-NET cases. All patients underwent both standard multidetector CT study and EUS with fine-needle aspiration (FNA). The final histological diagnosis was achieved on a post-surgical specimen. Chromogranin A (CgA) levels were measured.
Results: A total of 80 patients (mean age: 58 ± 14.2 years; males: 42) were enrolled. The diameter of functioning was significantly lower than that of non-functioning p-NETs (11.2 ± 8.5 mm vs 19.8 ± 12.2 mm; P = 0.0004). The CgA levels were more frequently elevated in non-functioning than functioning pNET patients (71.4% vs 46.9%; P = 0.049). Overall, the CT study detected the lesion in 51 (63.7%) cases, being negative in 26 (68.4%) patients with a tumor ≤10 mm, and in a further 3 (15%) cases with a tumor diameter ≤20 mm. CT overlooked the pancreatic lesion more frequently in patients with functioning than non-functioning p-NETs (46.5% vs 24.3%; P = 0.002). EUS allowed a more precise pre-operative tumor measurement, with an overall incorrect dimension in only 9 (11.2%) patients. Of note, the EUS-guided FNA suspected the neuroendocrine nature of tumor in all cases.
Conclusions: Data of this large case series would suggest that the EUS should be included in the diagnostic work-up in all patients with a suspected p-NET, even when the CT study was negative for a primary lesion in the pancreas.

Key words: neuroendocrine tumor – pancreas – diagnosis – endoscopic ultrasonography – computed tomography.

Abbrevations: CgA: chromogranin A; EUS: Endoscopic Ultrasonography; FNA: fine-needle aspiration; p-NETs: pancreatic neuroendocrine tumors.

INTRODUCTION

Neuroendocrine tumors (NETs) comprise a heterogeneous group of neoplasms arising from neuroendocrine cells, mainly scattered through the gastro-entero-pancreatic tract and the lung [1]. Although their incidence has increased in the last decades, NETs remain rare diseases (3.65/100.000 individuals per year) [2]. Overall, pancreatic neuroendocrine tumors (p-NETs) account for 7% of all NETs, and less than 2% of all pancreatic tumours [2]. From a clinical point of view, p-NETs may be associated with either a functional syndrome (functional p-NETs) or with no distinct clinical syndrome (non-functional p-NETs) [3, 4]. The main functioning p-NETs include insulinoma, carcinoid, gastrinoma, VIPoma, glucagonoma, and somatostatinoma [5]. In these cases, diagnosis is generally suspected based on symptoms. More than 70% of p-NETs are non-functioning, and their detection is incidentally performed during an abdominal ultrasound or symptoms related to the mass effect of the tumor or metastases [3, 6]. Diagnosis of p-NETs may be challenging, particularly when the lesion is small. It has been found that Computed Tomography (CT) imaging shows an overall sensitivity less than

75% for p-NETs detection [7, 8]. Endoscopic ultrasonography (EUS) may discover pancreatic lesions as small as 0.2–0.5 cm in diameter [9]. Indeed, EUS has been found to have an overall 79-100% sensitivity for p-NETs [10, 11], and therefore it is particularly useful for evidencing also small tumors.

We describe a large series of patients diagnosed with pNETs in whom both EUS and CT were performed before pancreatic resection.

METHODS

Patients

This was a retrospective analysis of p-NET cases consecutively collected in three Italian centres. Both functioning and non-functioning p-NET cases were considered. In the first group, diagnosis was suspected due to various symptoms (hypoglycaemia, chronic diarrhoea, flushing, tachyarrhythmia, multiple peptic ulcer, etc.). In the latter group, the diagnostic work-up was initiated due to an incidental discovery of a pancreatic mass at abdominal ultrasound or, in some cases, due to either jaundice or chronic diarrhoea with elevated chromogranin A (CgA) levels. Only those patients in whom EUS confirmed the presence of a p-NET following an EUS-guided fine-needle aspiration (FNA), and who subsequently underwent a pancreatic surgical resection were included in this series. Those cases associated with MEN-1 were excluded from this study. Demographic data, anatomical and histological details, presentation symptoms, and surgical treatment were collected for each patient.

Diagnostic procedures

All patients underwent standard CT study performed with multidetector CT scanners, with at least 64 detector rows, allowing for slice thickness of less than 1.5 mm. Multiplanar reconstruction after intravenous iodinated contrast media was performed, including early arterial contrast phase, portal venous contrast phase, and venous contrast phase [12]. In detail, 100 millilitres of nonionic iodinated contrast agent (Iopromide, Ultravist 370; Bracco, Italy) were administered at a flow rate of 4 mL/s followed by a saline flush (40 mL; 4 mL/s). Bolus tracking techniques were applied for optimal phase timing of the early arterial contrast phase (e.g. 100-Hounsfield-unit threshold in the aorta plus 5-10 s). For portal-venous and venous contrast phases fixed scan delays of 55–70 and 90–120 s was used. Similarly, all patients underwent pre-operative EUS study. The EUS was then performed by using a linear echoendoscope (Olympus GF UCT 180 or GF UCT 140; Pentax EG-3870UTK) under conscious sedation with midazolam and meperidine. The EUS-FNA using a 19, 22 or 25 G needle was performed in all cases. Different radiologists and endoscopists, all with >10 years experience, performed the diagnostic procedures. The final histological diagnosis was achieved on the post-surgical specimen. According to the World Health Organization (WHO) classification, which takes into account cell differentiation and the proliferation index, p-NETs are classified at histology as G1 (well differentiated; mitosis index <2%), G2 (well differentiated; mitosis index >2-20%) and G3 (poorly differentiated; mitosis index >20%) [13]. The pathological report was considered as the gold standard for both the tumor size measurement and the final histological diagnosis.

Statistical analysis

The *t* test for unpaired data was used to compare parametric data, whilst non-parametric data were compared by using either the chi-squared test or the Fisher's exact test, as appropriate.

RESULTS

The study enrolled a total of 80 patients, the mean age was 58 ± 14.2 years, and there were 42 (52.5%) males. The pattern of patients' symptoms is provided in Table I. Overall, the case series included 43 (53.8%) non-functioning and 37 (46.2%) functioning p-NETs, eventually characterized as insulinomas (25 cases), carcinoids (7), glucagonomas (3), somatostatinoma (1), and VIPoma (1), whilst no case of gastrinoma was encountered. These were classified as G1 (59%), G2 (36%), and G3 (5%). The mean age of patients with functioning p-NETs was significantly lower than that of patients with non-functioning neoplasia (53.8 ± 14.6 vs 61.6 ± 12.8 years; P = 0.007), but the sex distribution did not differ significantly (M/F: 21/16 vs 21/22). At post-surgical histological assessment, the mean neoplasia size was 15.8 ± 10.7 mm (range: 4-50 mm), with a diameter ≤10 mm in 38 patients, ≤20 mm in 20, ≤30 mm in 14, and >30 mm in the remaining 8 cases. The diameter of functioning p-NETs (mean: 11.2 ± 8.5 mm) was significantly (P = 0.0004) lower than that of non-functioning p-NETs (mean: 19.8 ± 12.2 mm). Chromogranin A levels were available in 53 patients, including 32 with functioning and 21 with non-functioning tumor. The CgA levels were more frequently elevated in non-functioning than functioning pNET patients (71.4% vs 46.9%; P = 0.049).

Overall, the CT study detected a pancreatic lesion in 51 (63.7%) cases, and the results were negative in the remaining 29 patients. In detail, the CT failed to find a lesion in 26 (68.4%)

Table I. Symptoms in patients with different pNETs.

Type	Symptoms (no. of patients)	Asymptomatic
Functioning		
Insulinoma (25)	Hypoglycaemia (25)	-
Carcinoid (7)	Tachyarrhythmia + flushing (3)	-
	Tachyarrhythmia + flushing + diarrhoea (2)	-
	Diarrhoea + flushing (1); Diarrhoea (1)	-
Glucagonoma (3)	Diabetes + flushing (1); diabetes (1)	1
Somatostinoma (1)	Diarrhoea (1)	-
VIPoma (1)	Diarrhoea (1)	-
Non-Functioning		
NET G1 (17)	Jaundice (1); diarrhoea (1)	15
NET G2 (11)	Jaundice (1); diarrhoea + weight loss (1)	9
NEC G3 (15)	Jaundice (4); diarrhoea (1)	10

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.

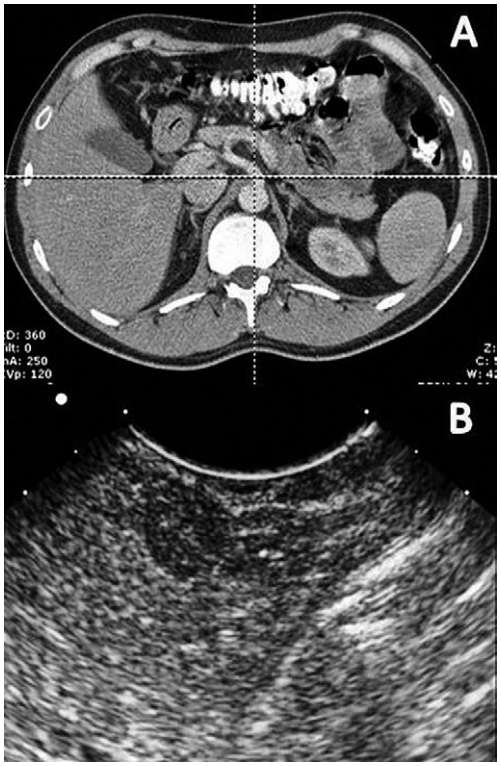

Fig. 1. Negative CT finding in a 32-year old male with recurrent hypoglycemia episodes (A). A 5 mm lesion in the pancreatic body was detected at EUS (B).

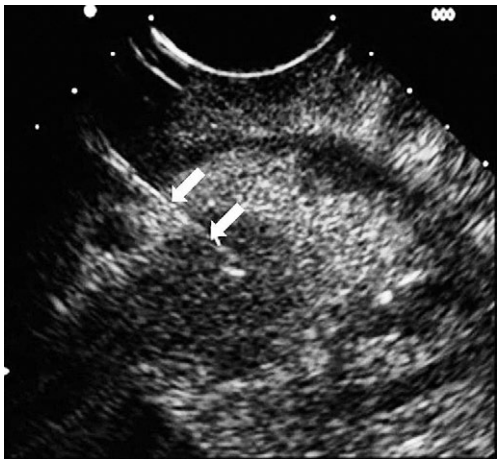

Fig. 2. EUS-guided fine needle aspiration of a p-NET located in the head of the pancreas.

out of 38 tumors with a diameter ≤10 mm, and in a further 3 (15%) out of 20 lesions with a diameter between 11 mm and 20 mm and no lesions >21 mm were overlooked. Moreover, the CT measured the tumor diameter wrongly in as many as 21 (41.2%) out of 51 cases in whom it was positive, with an over-estimation in 10 and an under-estimation in 11 of these cases (Table II). Of note, CT overlooked the pancreatic lesion more frequently in patients with functioning (20 out of 37 cases) than non-functioning (9 out of 43 cases) p-NETs (46.5% vs 24.3%; P = 0.002). The median of the tumor diameter was 6 mm (range: 4-13 mm) in the 20 patients with functioning p-NETs not detected by CT. The CT study in the 9 patients with a non-functioning tumor was performed due to either jaundice (6 cases) or chronic diarrhoea with elevated CgA levels (3 patients).

At the EUS study, the p-NET was located in the pancreatic head in 26 patients, in the body in 26, in the tail in 17, neck in 7, and in the uncinate process in the remaining 4 cases. The EUS allowed a more precise pre-operative tumor measurement, with an overall incorrect size in only 9 (11.2%) patients, including 4 over-estimations and 5 under-estimations (Table II). Of note, although the FNA diagnosis was not conclusive in defining the pNET type in 10 insulinomas, 3 glucagonomas, 1 somatostinoma, and 1 VIPoma, it suspected the neuroendocrine nature of tumors in all cases.

Following the diagnostic work-up, a wedge-resection was performed in 32 patients, pancreaticoduodenectomy in 22, distal pancreatectomy with spleen preservation in 17, and distal pancreatectomy with splenectomy in the remaining 9 cases.

Table II. Concordance between pathology and either CT or EUS for measurement of neoplasia diameter.

Diameter (mm)	Pathology (N)	CT pos correct	CT pos incorrect	CT neg	EUS pos correct	EUS pos incorrect
≤10	38	8	4 (20 mm: 2) (17 mm: 1) (15 mm: 1)	26	37	1 (17 mm)
11-20	20	8	9 (22 mm: 1) (10 mm: 5) (9 mm: 2) (7 mm: 1)	3	16	4 (22 mm: 1) (10 mm: 3)
21-30	14	7	7 (55 mm: 1) (43 mm: 1) (40 mm: 2) (35 mm: 1) (20 mm: 2)	0	11	3 (45 mm: 1) (31 mm: 1) (18 mm: 1)
≥31	8	7	1 (23 mm: 1)	0	7	1 (25 mm: 1)

DISCUSSION

Diagnosis of p-NETs may be challenging, particularly when the lesion is small (<2 cm). Indeed, data of 11 studies including 343 patients found an overall CT sensitivity of 73% (range: 39–94%) for detection of p-NETs [14]. Similarly, a mean 73% (range: 50–94%) detection rate for p-NETs by using Magnetic Resonance Imaging (MRI) was calculated in 5 studies including 192 patients [14]. A distinctly higher sensitivity was found in EUS, with a mean detection rate of 90% (range 77–100%) in 10 studies comprising 261 patients [14]. Consequently, EUS is recommended as the most accurate diagnostic tool for p-NETs when performed by experienced operators [1]. Surgery is considered the treatment of choice for any localized pancreatic tumor, since it is associated with significant benefits in terms of survival [4, 15]. Indeed, pancreatic resection is a safe option even for selected elderly patients [16]. Therefore, the precise location and size of the primary tumour is helpful. Obviously, the status regarding the primary tumour is important, but also the staging of regional and distant metastases needs to be accurately performed with CT for a correct surgical planning.

In our large case series, the CT showed an overall sensitivity of nearly 64% for detecting p-NETs. In detail, the CT failed to detect the lesion in more than 68% of p-NETs with a diameter less than 10 mm, and in a further 15% of patients with a lesion diameter between 11 and 20 mm. Of note, we found that the CT overlooked a functioning p-NET in nearly half of the patients (46.5%). This finding strongly suggests performing an accurate EUS study of the pancreas in all patients presenting clinical signs suggestive of a functioning NET despite CT negative results. Indeed, our data showed that the EUS was able to detect even very small tumors, including those lesions with a diameter ranging from 4 mm to 10 mm, which accounted for 47.5% in our series. In addition, the EUS-FNA suggested the NET nature of the pancreatic lesion in all cases. The pathological characterization of the lesion, together with the precise measurement of the diameter, and location in the pancreas confer to the pre-operative EUS-FNA procedure, a very relevant role for p-NET patients' management. Indeed, all this information is required to plan the more appropriate surgical approach, such as enucleation, distal pancreatectomy or a Whipple's procedure. Therefore, the EUS (detection and categorization) and CT (staging) should be considered as complimentary procedures to be performed in all patients with a suspected p-NET. It has been reported that when the results of CT are combined with experienced EUS, a sensitivity of 100% can be achieved [17]. Interestingly, in our series where the EUS was systematically employed in all cases, the mean tumor size was 15.8 mm, a diameter lower than the 20 mm observed in another Italian study where the EUS was performed in only 26.2 % cases [18]. In contrast to the previous Italian series [18], our data did not find a higher prevalence of females among functioning versus non-functioning p-NETs. Moreover, we found that patients with functioning p-NETs were significantly younger, less frequently had elevated CgA levels, and had a smaller neoplasia than the patients with non-functioning p-NET.

A limitation of our study is that we considered only patients who had underwent a surgical removal of a sporadic p-NET. Therefore, we are dealing with a selected patient population which may be not representative of the overall p-NET patients.

CONCLUSION

Our data in a large large case series would suggest that the EUS should be included in the diagnostic work-up in all patients with a suspected p-NET, even when the CT study was negative for a primary lesion in the pancreas.

Conflicts of interest: None to declare.

Authors' contribution: M.R. designed the study; M.R, M.S., M.F, G.U, P.N, R.C, N.E, C.D, B.H, P.M, and M.B collected data; C.R, C.R, V.V, B.G, T.A and M.M revised the manuscript for important intellectual content; Z.A. analyzed and drafted the manuscript. All authors read and approved the final version to be published.

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Diagnosticul preoperator al tumorilor pancreatice neuroendocrine la o serie mare de pacienți cu ajutorul eco-endoscopiei și tomografiei computerizate

ABSTRACT / REZUMAT

Premize și Scop: Diagnosticul tumorilor pancreatice neuroendocrine (pNET) este frecvent dificil. Noi prezentăm o serie mare de pacienți având pNET la care s-a efectuat atât eco-endoscopia (EUS) cât și tomografia computerizată (CT).
Metodă: Am efectuat analiza retrospectivă a unor pacienți cu pNET sporadic, recrutați propspectiv. Toți pacienții au fost examinați cu CT standard multidetector și cu EUS cu aspirație prin ac fin (FNA). Diagnosticul final a fost stabilit pe specimen chirurgical. A fost măsurat și nivelul cromograninei A (CgA) la acești pacienți.
Rezultate: Au fost înrolați 80 pacienți (vârsta medie 58 ± 14.2 ani; 42 bărbați). Diametrul pNET funcționale a fost semnificativ mai mic decât al pNET nefuncționale (11.2 ± 8.5 mm vs 19.8 ± 12.2 mm, P = 0.0004). Nivelul seric al CgA a fost mai frecvent crescut la pacienții cu pNET nefuncționale decât la cei cu pNET funcționale (71.4% vs 46.9%, P = 0.049). Examinarea CT a detectat leziunea în 51 (63.7%) cazuri, și a fost negativă la 26 (68.4%) pacienți cu o tumoră ≤10 mm, și la alți 3 (15%) pacienți cu tumoră având diametrul ≤20 mm. CT a omis leziunea mai frecvent la pacienții cu pNET funcționale față de cei cu pNET nefuncționale (46.5% vs 24.3%, P = 0.002). Eco-endoscopia a permis o măsurare preoperatorie mai exactă a dimensiunii tumorii, cu evaluarea incorectă a acesteia la doar 9 pacienți (11.2%). Menționăm faptul că FNA ghidată prin EUS a suspectat natura endocrină a tumorii în toate cazurile.
Concluzii: Rezultatele obținute la această serie mare de pacienți sugerează că EUS trebuie să fie inclusă în evaluarea diagnostică a tuturor pacienților la care se suspectează o pNET, chiar dacă examinarea CT a fost negativă pentru o leziune primară pancreatică.