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Original Article

Non-functioning gastroenteropancreatic (GEP) tumors: a ^{111}In-Pentetreotide SPECT/CT diagnostic study

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Abstract: In a retrospective study performed in non-functioning GEP tumor patients we further investigated ^{111}In-Pentetreotide SPECT/CT usefulness in diagnosis, staging and follow-up also evaluating whether the procedure may give more information than conventional imaging procedures (CIP), such as CT, MRI, US. We enrolled 104 consecutive patients with non-functioning GEP tumors, 30 in initial diagnosis and staging phases (IDS) and 74 in follow-up (FU). All patients underwent somatostatin receptor scintigraphy (SRS) whole body scan at 4, 24 and, if necessary, 48 hours followed by abdominal and chest SPECT/CT after ^{111}In-Pentetreotide 148-222 MBq i.v. injection. The patients previously underwent 2 to 3 CIP. At both CIP and SPECT/CT, 34/104 patients were classified as no evidence of disease (NED); in 70/104 patients, neoplastic lesions were ascertained and 12 IDS and 17 FU were classified as not operable and treated with octeotride or chemotherapy. SPECT/CT and CIP were concordantly positive in 44 patients, while only CIP was positive in 6 cases and only SPECT/CT in 20. Both per-patient sensitivity and accuracy of SPECT/CT (91.4 and 94.2%, respectively) were higher than CIP (71.4 and 80.8%, respectively), but not significantly. Globally, 292 lesions were ascertained: 141 hepatic, 78 abdominal extra-hepatic and 73 extra-abdominal. CIP detected 191/292 (65.4%) lesions in 50 patients, while SPECT/CT 244/292 (83.6%) in 64, the difference being significant ($p<0.0001$). No false positive results were found at both SPECT/CT and CIP. Both SPECT/CT sensitivity and accuracy were higher than CIP in G1, G2, neuroendocrine carcinoma (NEC) and mixed adeno-neuroendocrine carcinoma (MANEC) patients, but significantly only for G1. Globally, SPECT/CT incremental value than CIP was 35.6%. SPECT/CT correctly modified CIP classification and patient management in 27.9% of cases, while it down-staged the disease than CIP in 9.6% of cases. However, the two procedures combined use could achieve the highest accuracy value. ^{111}In-Pentetreotide SRS, acquired as SPECT/CT, showing high sensitivity and accuracy values, more elevated than CIP in the present study, can still have a wide employment in the routine diagnostic protocol of non-functioning GEP tumors with significant impact on patient management and therapy planning. The procedure is simple to perform, has limited cost and wide availability in all Nuclear Medicine Centers.

Keywords: Non-functioning gastroenteropancreatic (GEP) tumors, carcinoid, neuroendocrine carcinoma (NEC), mixed adeno-neuroendocrine carcinoma (MANEC), chromogranin A, ^{111}In-Pentetreotide, SPECT/CT, conventional imaging procedures (CIP)

Introduction

Gastroenteropancreatic (GEP) neuroendocrine tumors represent a heterogeneous group of rare neoplasms characterized by an overexpression of somatostatin receptors (SSR) and an increased production of hormones, peptides or other biologically active substances often producing clinical symptoms due to systemic effects of their uncontrolled production and secretion. The tumors may grow slowly thus permitting long survival, but they can be malignant also producing metastases which can represent the first manifestation of the disease, seriously affecting patient prognosis [1, 2].

Both clinical symptoms and the various substances secreted by these tumors are often

diagnostic for the tumor type, particularly if the associated tumor secretions are in very high concentration in blood [3, 4].

However, some tumors are non-functioning since, although they may secrete hormones and other substances, such as chromogranin A (CgA), synaptophysin and neuron-specific enolase (NSE), these substances can also not be released into the circulation despite their immune-histochemical evidence [5]. Moreover, it is likely that non-functional tumors can secrete one or more hormones that are as yet unidentified; alternatively, they can produce insignificant amounts of biological active hormones or inactive forms of hormones. These tumors may also secrete high-molecular-weight precursors of peptide hormones that have different biologic activities than those of the mature peptides; consequently, the concentration of immune-active hormones in plasma may not correspond to the level of biologic activity [6]. Therefore, in some patients clinical symptoms can be minimal or absent, except for those due to mass effect or distant metastases; in the latter cases, the diagnosis of primary tumor and metastases is often ascertained in more advanced stages. Most non-functioning GEP tumors originate from pancreatic islets of Langerhans, but also from small intestine, and account for 15-52% of neuroendocrine pancreatic tumors [7, 8].

No histologic difference between functioning and non-functioning tumors has been described, but at surgery the non-functioning tumors are generally larger; moreover, these tumors can also be malignant, like the functioning forms, developing aggressive metastatic lesions which can already be present when diagnosed, seriously affecting patient prognosis.

Conventional imaging procedures (CIP), such as CT, ultrasound (US) and MRI, represent the most available diagnostic methods to detect GEP tumors and their metastases, also guiding biopsies. In particular, MRI is considered the most sensitive radiologic method for liver metastases although these, when small in size, are sometimes difficult to be localized [9].

Somatostatin receptor scintigraphy (SRS), using the somatostatin analogue ^{111}In-Pentetreotide as radiotracer that preferentially binds to SSR subtypes 2, 3 and 5, especially the former, has proven to be an important diagnostic functional imaging procedure for diagnosis, stage and follow-up of neuroendocrine (NET) tumors, both pulmonary and in particular GEP tumors [10-14]. For over 20 years, the procedure has been considered a first line imaging technique. In particular, SPECT has obtained a better performance than planar in the identification of primary and metastatic lesions derived from both functioning and non-functioning GEP tumors [15-17]. In the latter type of tumors some studies have reported a lower sensitivity of planar SRS in respect of CIP but these data have not been confirmed by others [18-20]. In the last years, the utility of SRS has been further augmented with the employment of the hybrid system technologies, such as SPECT/CT; this latter procedure has permitted a better localization and functional characterization of GEP tumors and a correct identification of areas of physiologic uptake, reducing false-positive results on planar and SPECT images and correctly classifying lesions. In particular, SPECT/CT has been reported to provide an incremental diagnostic value than both planar and SPECT images, even more using a SPECT/multiphase CT [21-26]. Some somatostatin analogues labelled with ^{99m}Tecnetium, such as ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotride and ^{99m}Tc-HYNIC-TOC, have also been employed with SPECT/CT acquisition providing reasonable accuracy, in particular in the evaluation of the pancreatic masses suspected to be neuroendocrine tumors [27, 28]. Conventional positron emission tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) appears of limited value in the diagnosis of GEP tumors, except for the most aggressive forms with high proliferation and with less favourable prognosis [29, 30].

More recently, PET/CT with somatostatin analogues (DOTATOC, DOTATATE and DOTANOC) labelled with positron emitting radionuclides, as ^{68}Gallium, which have showed a high affinity for SSR subtypes 2-5, have obtained high sensitivity and specificity values in patients with both thoracic NETs and GEP tumors [31-33].

Up to day, ^{111}In-Pentetreotide is still the current standard technique for SSR imaging and, unlike PET with somatostatin analogues, it has been approved for many years for marketing in the

Europe and USA. Only more recently, USA-FDA has approved ^{68}Ga-DOTATATE injection for localization of NETs in adult and pediatric patients.

In the present study, we further investigated the diagnostic usefulness of ^{111}In-Pentetreotide hybrid SPECT/CT imaging in a series of patients with non-functioning GEP tumors, also evaluating whether this procedure may give more useful information than CIP in the diagnosis, staging and follow-up; we also assessed whether SPECT/CT may have a better clinical impact in the management of patients affected by this type of neuroendocrine tumor whose identification can often happen late.

Material and methods

Patients

One hundred and four consecutive patients were retrospectively studied, 54 males and 50 females, aged 17-86 years (average: 59.4± 16.5), and observed in three different University Centres of Nuclear Medicine. All patients were affected by non-functioning GEP tumors, 30 being in the phase of initial diagnosis and staging (IDS) for a primary tumor and 74 in follow-up (FU) with previous ascertained primary tumor. Twenty-one/30 IDS patients have foregut carcinoid, 5/30 midgut carcinoid, 1/30 hindgut carcinoid and 3/30 indeterminate neuroendocrine tumor. Eighteen/30 IDS patients were classified as operable and were submitted to surgery after scintigraphy and 12/30 as not operable because of disseminate metastases and serious clinical conditions and underwent medical therapy (octeotride in 9 cases and chemotherapy in 3 cases). Before our observation, 57/74 FU patients had undergone surgery for: foregut carcinoid (29 cases), midgut carcinoid (26 cases), hindgut carcinoid (2 cases). Fifteen/57 patients of these had limited hepatic metastases, 21 had abdominal extrahepatic and 2 extra-abdominal metastases, 10 had both hepatic and abdominal extrahepatic metastases and 9 both abdominal extra-hepatic and extra-abdominal metastases; moreover, 33/57 patients had undergone only surgical procedures, while 16/57 had also octreotide therapy and 8/57 chemotherapy. The remaining 17/74 FU patients with GEP tumors were considered not operable for disseminated metastases, with primary tumors being foregut carcinoid (12 cases), midgut carcinoid (4 cases) and indeterminate neuroendocrine tumors (1 case). Twelve/17 not operable patients were on octeotride therapy which could be interrupted in 8 cases in average 10-14 days prior to scintigraphy, while in 4 the therapy was continued because of their serious clinical conditions; the remaining 5/17 not operable patients had previously been submitted to chemotherapy.

Furthermore, in presence of hepatic metastases the classification as non-resectable tumors had been performed on the basis of both the number of lesions (numerous and disseminated in both hepatic lobes) and their location (porta hepatis, confluence of hepatic veins entering into inferior vena cava); furthermore, surgery was not considered feasible when the metastatic lesions were too extensive in patients with serious clinical conditions and with other distant metastases, in the latter cases even if hepatic metastases were considered resectable.

In all 104 cases, the definitive diagnosis of the primary tumors was obtained on the basis of histopathologic analysis by haematoxylin and eosin and immune-histochemical method, with positive staining for one or more hormones or peptides, such as CgA and/or NSE, gastrin, vasoactive intestinal peptide (VIP), somatostatin, glucagon and pancreatic peptides (PP).

The diagnosis of recurrent tumor and/or metastases was based on histology of neoplastic sites and/or on imaging features of progressive malignancy, using MRI, contrast-enhanced CT, transabdominal US, endoscopic US, nuclear medicine procedures including bone scintigraphy and ^{18}F-FDG PET/CT, with a follow-up period of 6-36 months.

According to WHO 2010 Classification of tumors of the Digestive System, the 104 primary GEP tumors were classified on the basis of proliferative rate assessed as the number of mitoses per unit area of tumor and the percentage of neoplastic cells immune-labelling for the proliferation marker Ki67. The patients were classified as neuroendocrine tumor grade 1 (G1; 65 cases), neuroendocrine tumor grade 2 (G2; 22 cases), neuroendocrine carcinoma (NEC), large cell (LCNEC) or small cell (SCNEC) type (12 cases), mixed adeno-neuroendocrine carcinoma (MANEC; 5 cases).

Table 1. ^{111}In-Pentetreotide SPECT/CT and CIP in 104 patients with GEP neuroendocrine non-functioning tumors, 74 in follow-up (FU) and 30 in the phase of initial diagnosis and staging (IDS)

	CIP	SPECT/CT
True positive	50	64
True negative	34	34
False negative	20	6
False positive	0	0
Sensitivity %	71.4	91.4
Specificity %	100	100
Positive predictive value %	100	100
Negative predictive value %	63	85
Accuracy %	80.8	94.2

At the time of our observation, none of the 104 patients had clinical signs of hormone excess and thus they were classified as affected by non-functioning GEP tumors although a slight increase of CgA serum levels was present in 10 patients, 7 FU and 3 IDS (3 FU and 1 IDS operable and 4 FU and 2 IDS inoperable). However, 23 patients referred–malaise, dyspepsia, epigastric and abdominal pain, 11 also had weight loss and 5 also obstructive jaundice.

Within a month before scintigraphy, the patients had been submitted to at least 2 CIP, such as US, CT, and MRI, all of these centred over abdomen, thorax and other suspect regions; in 7 cases a conventional whole body scan after i.v. injection of 740 MBq of ^{99m}Tc-methylendiphosphonate (MDP) was also performed, as well as in 2 cases of ^{99m}Tc-tetrofosmin whole body scan and in 3 cases whole body ^{18}F-FDG PET/CT.

According to CIP data the patients were initially classified as with no evidence of disease (NED) or with operable or not operable neoplastic lesions on the basis of the aforementioned criteria.

All clinical and instrumental examinations were performed in University Hospitals setting as part of the clinical care of neuroendocrine tumor patients. This retrospective study was performed in accordance with the regulations of the Institutional Review Board and in accordance with Helsinki Doctrine. Routinely, written informed consent had been obtained by all patients whose data were treated in accordance with the local privacy rules and regulations.

^{111}In-Pentetreotide SRS and SPECT/CT

In the present study, all patients underwent a low residue diet for 3 days before and 2 days after tracer injection and also took a laxative the day before and daily for 2 days after to better unsure a bowel cleaning, thus to reduce interfering background radioactivity by intestinal content. Scintigraphic images were obtained with 2 hybrid variable-angle dual-head gamma cameras including a low dose x-ray tube, the Millenium VG Hawkeye (GE Medical System) in 49 cases and with Infinia Hawkeye (GE Medical System) in 55 cases, equipped with an integrated x-ray transmission system (low-dose CT) to provide anatomic maps for attenuation correction and image fusion. CT apparatus has a fixed anode oil-cooled x-ray tube installed on the slip-ring gantry of the gamma camera and operates at 140 Kev and up to 2.5 mA. The x-ray tube and the detector array are rotated together in a fixed geometry, at 2.0 rpm for a 90° L-mode scan. Medium energy, parallel-hole collimators were always used in both machines with 20% energy windows centered on the ^{111}In photon peaks (173 and 247 Kev).

A whole body planar in anterior and posterior views with a speed of 5 cm/min for a total time of 30 min (1024×256 matrix) were always obtained at 4th, 24th and, when necessary, at 48th hours following i.v. injection of 148-222 MBq of ^{111}In-Pentetreotide (Octreoscan, Mallinkrodt Medical, Petten, The Netherlands), whose labelling efficacy was carried out according to the manufacture instructions and always was > 95%. To minimize patient movement during acquisition, we used a special vacuum cushions to stabilize the position.

The planar acquisitions were first always followed by SPECT over 360° (180° per head over abdomen, thorax and other suspect regions) using different acquisition and processing parameters according the two different types of gamma cameras. A 128×128 matrix was used with a 30 angular step, an acquisition time of 40 sec. per frame and a zoom factor ranging from 1 to 1.2 according to the individual patient. The body contouring system was used to minimize the distance between the

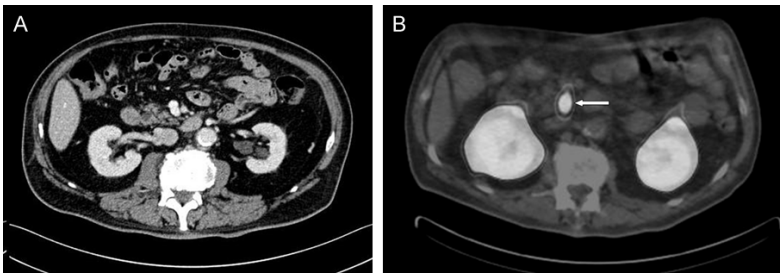

Figure 1. A 73-y-old man with GEP tumor (G1) of duodenum. The patient was asymptomatic for hormone overexpression and negative for characteristic secretory pattern, but he referred malaise, weight loss, abdominal pain and some diarrhoea episodes. Diagnostic CT (A) excludes the presence of any nodules or masses in abdomen as it had also been observed at previous ultrasound. ^{111}In-Pentetreotide SPECT/CT 24 h acquisition image (B) shows a focal area of somatostatin analogue uptake of 18 mm in size sited in the inferior part of duodenum (arrow). A laparoscopic biopsy evidenced a lesion with a typical trabecular structure, intense immunoreactivity for chromogranin A and synaptophysin, absence of necrosis and rare cells with 1 mitosisx 10 hpf and a Ki 67 index <2%.

patient and the collimator. SPECT was followed by CT and multiple CT slices were obtained in the helical mode (four 5 mm-thick slices obtained simultaneously with a beam coverage of 2 cm in each gantry rotation and reconstructed online to a 512/512 image matrix). CT scan were acquired within 4.5 min. Cross-sectional attenuation images (128×128 image matrix), in which each pixel represents the attenuation of the imaged tissue, were generated in all cases.

SPECT was first acquired always followed by CT and the images, reconstructed with the iterative method (OSEM), were fused with those of CT using a dedicated software package (Xeleris Workstation; GE Medical System), thus obtaining a SPECT/CT in all cases.

Data analysis

^{111}In-Pentetreotide SPECT/CT images were independently interpreted by four experienced nuclear medicine physicians (AS, OS, FD, GM) who were informed of the clinical reason pertinent to the scintigraphy, but were unaware of the results of any investigations. SPECT/CT data were classified as normal with physiologic tracer distribution or positive with scans evidenced of neoplastic lesions. Disagreements were resolved by consensus. The results of SPECT/CT were compared with those of CIP, considering that 5 or more hepatic lesions per patient were counted as 5. SPECT/CT data were confirmed by pathological findings or by clinical and radiological follow up for at least a period of 6-36 months in presence of recurrences or/and metastases when histology was not available.

Statistical analysis

The McNemar test was used to assess the statically significance of the differences between per-patient sensitivity, specificity and accuracy and per-lesion sensitivity of SPECT/CT and CIP imaging in the detection of GEP tumor lesions. The results were considered significant when $p<0.05$.

Definitive diagnosis

All SPECT/CT imaging data were related to the definitive diagnosis obtained by surgery, laparotomy, percutaneous CT or by US biopsy. Histopathological and immune-histochemical analyses performed as above, confirmed neuroendocrine origin from local recurrences or distant metastases in 74 FU patients (23 pancreas, 10 stomach, 3 duodenum, 3 gallbladder, 9 appendix, 20 small intestine, 3 colon, 2 sigmoid colon and rectum, 1 retro-peritoneum) and diagnosed as primary GEP tumors in 27 IDS (12 pancreas, 6 stomach, 2 duodenum, 2 appendix, 2 small intestine, 1 sigmoid colon, 2 retro-peritoneum), while the remaining 3 IDS were indeterminate GEP tumours.

Results

The overall results of CIP and ^{111}In-pentetreotide SPECT/CT in the 104 GEP tumor patients are reported in **Table 1**.

As shown in the Table, both per-patient sensitivity and accuracy were higher for SPECT/CT in respect of CIP, but not significantly. In particular, in 70/104 patients, 40 FU and 30 IDS, all asymptomatic for neuroendocrine hormone overexpression, notwithstanding a slight increase of serum CgA in 7 cases (4 FU and 3

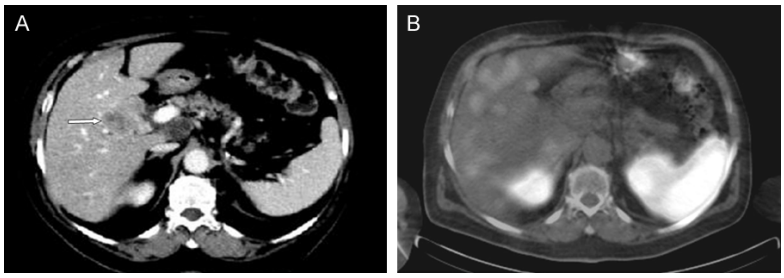

Figure 2. A 74-y-old women with ileal GEP tumor (G3) previously operated and treated with 3 cycles of chemotherapy with carboplatinum and etoposide. The patient is asymptomatic for hormone over-expression and negative for characteristic secretory pattern, but she refers malaise, abdominal pain, vomiting episodes, weight loss and poor condition. Diagnostic CT (A) ascertained an inhomogeneous mass in the hepatic hilum with central areas of hypodensity as colliquative necrosis (arrow). ^{111}In-Pentetreotide SPECT/CT (B) did not evidence foci of pathological uptake. The biopsy of the mass in hepatic hilum showed hepatic infiltration from neoplasia with trabecular structure, abundant dysplasia and solid cells, numerous necrosis areas, cellular immunoreactivity for CAM 5.2, cytokeratin 19 and CD 56; mitosis index > 20 and Ki-67: 80%. This aspect is indicative for hepatic metastasis from G3 GEP tumor.

Table 2. ^{111}In-Pentetreotide SPECT/CT scintigraphy and CIP-data in 70 GEP tumours with ascertained hepatic, abdominal extra-hepatic and extra-abdominal lesions

Lesions	Hepatic	Abdominal extra-hepatic	Extra-abdominal	Total
No	141	78	73	292
CIP Positive	113 (80.1%)	40 (51.3%)	38 (52%)	191 (65.4%)
SPECT/CT Positive	117 (83%)	67 (85.9%)	60 (82.2%)	*244 (83.6%)

*p<0.0001 when compared with corresponding CIP.

IDS, 6 of whom not operable), neoplastic lesions were ascertained concordantly at both CIP and SPECT/CT in 44 patients, only at CIP in 6 cases and only at SPECT/CT in 20; CIP were completely false negative in 20 patients (11 FU, 9 IDS), while SPECT/CT was positive; 4 (2 IDS, 2 FU) of these 20 patients were primary tumours: 1 stomach (G1), 1 duodenum (NEC-G3), 1 pancreas (G1) and 1 sigmoid-colon (G1) with size ≤ 10 mm in G1 patients and ≥ 15 mm in NEC-G3 case; the others 16/20 cases, 13 G1 (≤ 10 mm), 2 NEC G3 (≥ 30 mm) and 1 MANEC (20 mm), had recurrences or metastases in the liver and/or in the abdominal extra-hepatic or extra-abdominal regions (1 mediastinum, 1 bone), being single in 8 cases and multiple in different sites in 6. One of the 20 GEP tumor cases negative at CIP and positive only at SPECT/CT is illustrated in **Figure 1**.

SPECT/CT was completely false negative in 6 patients (3 FU, 3 IDS), while CIP were positive; 5 of these patients (1 G1, 4 NEC G3) had single metastases (3 hepatic, 2 abdominal extra-hepatic lesions) and the remaining patient (NEC G3) had 2 extra-abdominal metastases in mediastinum; all the lesions were > 10 mm in size, except for the G1 case (4 mm). One of the G3 cases with a liver metastasis negative at SPECT/CT and positive at CIP is illustrated in **Figure 2**.

The remaining 34/104 patients, all FU after primary non-functioning GEP tumor resection, and with absence of metastases at surgery, did not show focal areas of increased ^{111}In-Pentetreotide uptake and were also negative at CIP; moreover, these patients, who were apparently with no evidence of disease (NED) and without the characteristic serum pattern, except 3 cases with basal slight increase of CgA, remained NED at subsequent investigations and clinical follow-up.

No false positive results were observed at both SPECT/CT and CIP.

Globally, 292 neoplastic lesions were ascertained, as illustrated in **Table 2**; 141 were hepatic lesions, 78 abdominal extra-hepatic and 73 extra-abdominal.

All hepatic lesions in 40 patients were metastases from different GEP tumor origin.

Twenty-two/78 abdominal extra-hepatic lesions were primary tumours, 14 of which in 11 IDS patients all operable, including 4 stomach, 1 duodenum, 7 pancreas, 1 small intestine and 1 sigmoid-colon tumors; a case of pancreatic primary tumor evidenced by both CIP and SPECT/CT, but correctly characterized as GEP only by the latter, is shown in **Figure 3**. The other 8/22 primary tumors in FU patients, 1 in duodenum, 1 in stomach and 6 in pancreas, were classified as not operable at initial diagnosis. The remaining 56/78 lesions in 5 IDS and 14 FU patients

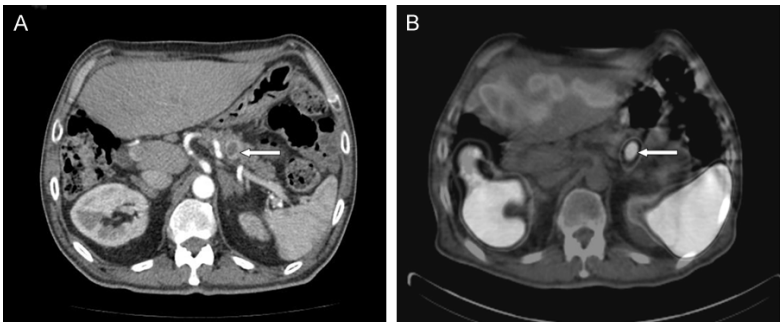

Figure 3. A 69-y-old man with pancreatic carcinoid (G1). The patient was asymptomatic for hormone overexpression and negative for characteristic secretory pattern, but he referred malaise, epigastric pain, weight loss. Diagnostic tri-phasic CT (A) showed an inhomogeneous hyper-density nodule of 13 mm with central area of hypo-density as colliquative necrosis in the body-tail passage of the pancreas (arrow) suspect of neoplasia of uncertain origin. At ^{111}In-Pentetreotide SPECT/CT imaging in transaxial view (B), a focal area of increased uptake of somatostatin analogue (arrow) was visualized in the body-tail passage of the pancreas corresponding to the nodule detected by CT. A laparoscopic biopsy ascertained a neuroendocrine G1 tumor of the pancreas with typical trabecular structure with epithelial habitus, intense immunoractivity for chromogranin A, synaptophysin, CD 56 and cytokeratin 19, absence of necrosis, 1 mitosisx10hpf and a Ki-67 index of 0.66%.

were 43 abdominal lymph node metastases and 13 local recurrences (4 duodenum, 1 stomach, 6 pancreas, 2 small intestine).

Moreover, 73 extra-abdominal metastatic lesions were ascertained in 22 of the patients (10 IDS, 12 FU), 5 lesions being sited in brain, 10 in lungs, 39 in lymph nodes (5 in supraclavicular region, 24 in mediastinum, 10 in pulmonary hilum) and 19 in bone; in particular, 3/22 had lesions only in extra-abdominal sites (2 in lung and 1 in mediastinum), 9/22 patients had each more lesions site in extra-abdominal, hepatic and abdominal extra-hepatic regions, 5/22 had both extra-abdominal and hepatic lesions and 5/22 both extra-hepatic lesions and extra-abdominal.

As shown in **Table 2**, CIP detected 191/292 (65.4%) lesions (113 hepatic, 40 abdominal extra-hepatic and 38 extra-abdominal) in 50 patients and SPECT/CT identified 244/292 (83.6%) lesions (117 hepatic, 67 abdominal extra-hepatic and 60 extra-abdominal) in 64 patients with a better performance of SPECT/CT in respect of CIP in both abdominal extra-hepatic and extra-abdominal lesions The difference of global sensitivity was significant for SPECT/CT in respect of CIP ($P<0.0001$).

In particular, both CIP and SPECT/CT concordantly identified 89 hepatic lesions in 19 patients (12 FU and 7 IDS), while CIP identified 24 lesions undetected by SPECT/CT in 13 patients (9 FU and 4 IDS), 3 of whom were the aforementioned completely negative cases (2 IDS, 1 FU) at SPECT/CT; 28 lesions were evidenced at SPECT/CT while these were not identified by CIP in 11 patients (7 FU and 4 IDS). Moreover, 29 abdominal extra-hepatic lesions (including 11 FU and 9 IDS patients with primary tumours) were detected by both CIP and SPECT/CT, while only CIP was positive for further 11 lesions (in 3 IDS with primary tumors and in 2 FU patients, one of whom completely negative at SPECT/CT) and only SPECT/CT was positive for further 38 lesions (in 7 FU patients and in 10 IDS patients).

Furthermore, SPECT/CT confirmed 25 extra-abdominal neoplastic lesions also ascertained by CIP in 7 patients (4 lesions in brain, 4 in lung, 5 in pulmonary hilum lymph nodes, 10 in mediastinum, 2 in para-tracheal lymph nodes), and was positive in 35 further lesions: 3 in lung, 12 in lymph nodes (4 in pulmonary hilum, 6 in mediastinum lymph node and 2 in para-tracheal region), 19 in bones and 1 in brain in 5 FU and 4 IDS, all negative at CIP.

CIP was positive in 13 further extra-abdominal neoplastic lesions negative at SPECT/CT in 2 IDS and 2 FU patients (1 FU, 1 IDS completely negative at SPECT/CT): 2 lesions were sited in lungs and 11 in lymph nodes, 2 of these being in pulmonary hilum, 8 in mediastinum and 1 in para-tracheal region.

The smallest lesion visualized by SPECT/CT was a liver metastasis of 5 mm in diameter.

As reported in **Table 3**, considering the patients according to the WHO 2010 Classification of Tumors of the Digestive System, it was observed that, when mutually comparing the 65 G1 patients, the 22 G2, the 12 NEC-G3 and the 5 MANEC cases, both sensitivity and accuracy of SPECT/CT were higher than CIP in G1, G2, and

Table 3. ^{111}In-Pentetreotide SPECT/CT and CIP results in 104 patients with GEP neuroendocrine non-functioning tumors according WHO 2010 Classification of Tumors of the Digestive System (65 G1, 22 G2, 12 NEC, 5 MANEC)

Patients	CIP positive				SPECT/CT positive			
	G1	G2	NEC	MANEC	G1	G2	NEC	MANEC
True positive	29	12	6	3	38	17	5	4
True negative	26	5	2	1	26	5	2	1
False negative	10	5	4	1	1	0	5	0
False positive	0	0	0	0	0	0	0	0
Sensitivity %	74.4	70.6	60	75	*97.4	100	50	100
Specificity %	100	100	100	100	100	100	100	100
Positive predictive value %	100	100	100	100	100	100	100	100
Negative predictive value %	72.2	50	33.3	50	96.3	100	28.6	100
Accuracy %	84.6	77.3	66.7	80	98.5	100	58.3	100

*p=0.04 when compared with corresponding CIP.

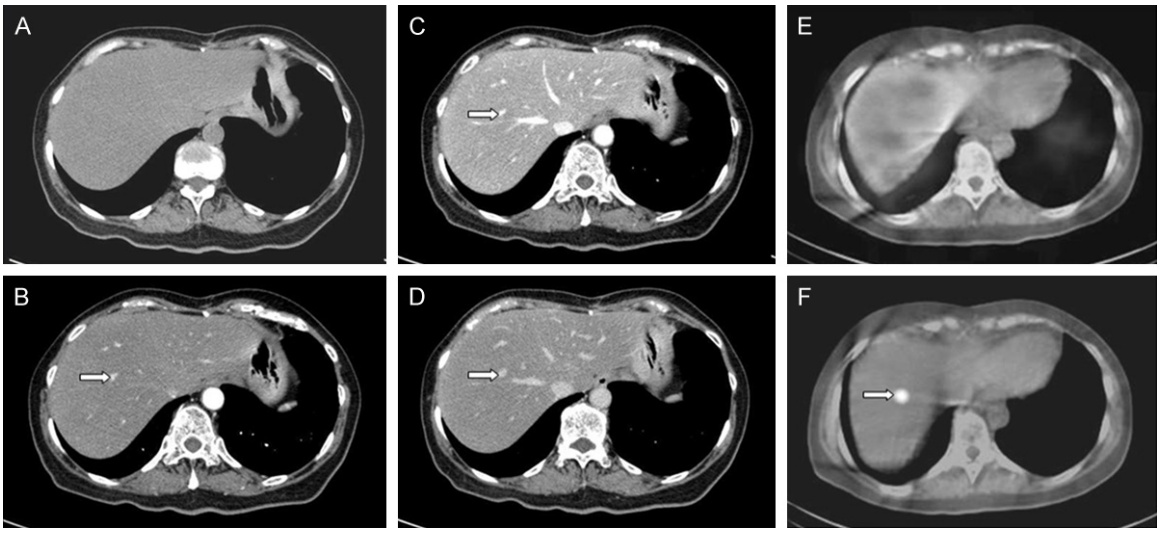

Figure 4. A 64-y-old female patient, previously operated for differentiated non-functioning ileal GEP tumor (G2) with large trabecular structure, moderate cell atypia, cell immonoreactivity for chromogranine A, synaptophysin, NSE, CD56 and cytokeratin AE1/AE3, 2 mitosisx10hpf and a Ki 67 index of 4%. The patient, treated with octreotide, is asymptomatic for hormone over expression and negative for characteristic secretory pattern. Triphasic CT (A-D) shows a nodular lesion of 9 mm in size in the VIII segment of the liver, not evident at basal scan (A), but better evident in arterial (B) portal (C) and equilibrium (D) phases after contrast medium injection, of unclear interpretation. ^{111}In-Pentetreotide SPECT/CT, performed after octreotide interruption, was negative at 24 h acquisition (E) and showed a focal area of uptake of the somatostatin analogue (arrow) only at 48 h acquisition image (F) corresponding to the liver lesion evidenced at CT. A laparoscopic biopsy confirmed a metastasis from G2 GEP tumor with hepatic infiltration and with morphological and immuno-histological aspects similar to those of the primary tumor.

MANEC patients while both parameters were higher in CIP than SPECT/CT in NEC-G3 patients. The difference was statistically significant (p=0.04) only in the comparison between SPECT/CT and CIP in G1 patients.

Moreover, only for the G1 Group of patients the difference was significant (p=0.02) comparing the global number of metastatic lesions evidenced by SPECT/CT in respect of CIP (110 versus 88), while in G2 and MANEC groups the number of lesions evidenced by SPECT/CT, even if more elevated in respect of CIP, the difference was not significantly as well as it was for CIP in respect of SPECT/CT in NEC-G3 patients.

In the present study, according to the involved structures, SPECT/CT performance was more elevated in duodenum, pancreas, small intestine, lymph nodes and bone lesions also of small size in respect of CIP, while the performance of the latter was higher in stomach lesions.

In most cases SPECT/CT performance was more elevated in the exams acquired at 24 h, but in 13 patients with high suspect of recurrences or metastases, the exams acquired at 48 h were determinant for the identification of more neoplastic lesions also changing CIP classification and patient management in 6 of these cases, 3 IDS (1 of whom operable) and 3 FU (a case is illustrated in the **Figure 4**).

Globally, the incremental value for SPECT/CT was 35.6% (37/104), while for CIP was 21.1% (22/104). SPECT/CT correctly modified CIP classification and patient management, also establishing operability or not operability, in 27.9% (29/104) of cases, while it down-staged the disease in 9.6% (10/104) in respect of CIP. The combined use of the two procedures was able to achieve the highest value of sensitivity (100%).

Discussion

Non-functioning GEP tumors represent the most frequent forms of GEP [3]. They grow slowly and not present clinical symptoms by overexpression of hormones or other active substances (endocrine syndrome), only secreting peptides or pro-hormones with slight or absent biological activity, thus remaining silent for a long time. However, they can be associated with not specific symptoms such as epigastric and abdominal pains, loss of weight, anorexia, nausea. Therefore, these tumors are of difficult diagnosis in early stage and are often identified late, only when the symptoms appear due to the compression by the mass (jaundice, intestinal obstruction) and/or to the invasion of adjacent organs and when metastases develop. On the other hand, non-functional GEP tumors are characterized by a high percentage of malignancy, but in most cases of low grading.

Tumor identification and differentiation in preoperative phase is very important for confirming neuroendocrine nature of the lesion as well as to obtain prognostic data and information on the grading of the tumor also in association with the assessment of Ki-67 proliferation index [34, 35]. Moreover, a pre-surgery diagnosis may be crucial for early establishing therapeutic strategy. In the patients with low risk of malignancy, surgery or clinical and instrumental follow-up can be suggested on the basis of the site and the extension of the tumor other than of its aggressiveness and proliferation index. However, in not operable patients the therapeutic strategy is based on cell proliferation degree and includes somatostatin analogues, peptide receptor radionuclide therapy, target therapy, chemotherapy and chemoembolization therapy.

Among the instrumental techniques, besides CIP, such as US, endoscopic US, CT and MRI, the radioisotopic procedures often represent the most valuable tools to identify GEP tumors, and, in particular, using somatostatin analogues as radiotracers, it is also possible to characterize their neuroendocrine origin. Until some years ago and over two decades, ^{111}In-Pentetreotide SRS has been considered the radioisotopic procedure of reference and proved useful for revealing the expression of SSR and the degree of differentiation of GEP tumors.

This radioisotopic procedure in the last years, using SPECT/CT technique, has achieved a great popularity in the management of GEP tumor patients since it proved to improve the value of planar SRS and SPECT alone [21-26]. The higher performance of SPECT/CT is due to the identification and anatomic localization of tumors, also of small size, and the characterization of lesions presenting as unclear focal areas of intense uptake. These lesions can be localized in extra-hepatic abdominal regions and, in particular, in mid upper abdomen as well as in extra-abdominal sites of not easy detection with the other imaging procedures. Thus SPECT/CT can increase sensitivity and accuracy and also give useful information for the correct staging and the evaluation of the response to treatment. Moreover, SPECT/CT is also able to reduce false positive findings of planar SRS in sites of physiologic tracer uptake.

In the last years, also PET radiotracers have been employed in the management of GEP tumors. PET with ^{18}F-fluorodihydroxyphenilalanine (^{18}F-FDOPA), which use is based on dopa-

mine secretion by GEP tumor cells, has been usefully employed in neoplastic lesion detection but with low sensitivity in pancreatic GEP tumors [36, 37]. Moreover, PET with ^{11}C-5-Hydrossitriptofan (^{11}C-5-HTP), that is a precursor of serotonin, was also used showing high sensitivity values in well differentiated GEP tumors, but with less performance in undifferentiated forms, in particular if non-functioning [38]. ^{18}F-FDG PET/CT has also been proved useful, but only in undifferentiated and more aggressive forms [29, 30].

At present, there is a growing interest on the employment of PET/CT with ^{68}Ga-somatostatin analogues (DOTATOC, DOTATATE, DOTANOC) that can provide superior detection capacity over ^{111}In-Pentetreotide scintigraphy, even when acquired with SPECT/CT, due to the higher spatial resolution of PET scanner [39, 40]. However, availability and cost represent limiting factors for PET tracers. Moreover, only recently ^{68}Ga-DOTATATE alone has been authorized for marketing in USA.

Very promising are also the preliminary results obtained in NET patients with new tracers such as somatostatin analogues labelled with ^{64}Cu (^{64}Cu-DOTATATE, ^{64}Cu-DOTATOC) and ^{44}Sc (^{44}Sc-DOTATOC), SSR antagonists (^{68}Ga-0PS202) nd glucagon-like peptide 1 receptor (GLP-1R) labelled with ^{111}Indium (^{111}In-DOTA-exendin-4) and ^{68}Gallium (^{68}Ga-NOTA-exendin-4) [41]. PET/CT with ^{64}Cu-DOTATATE, in particular, has showed advantages not only over ^{111}In-Pentetreotide SRS but also over ^{68}Ga-somatostatin analogue, detecting a higher number of lesions in NET patients, probably due to the lower positron range of ^{64}Cu in respect of that of ^{68}Ga [42, 43]. GLP-1R scintigraphy, on the other hand, seems to be able to give very high sensitivity values in the detection of benign insulinomas that are frequently missed at scintigraphy with somatostatin analogs [44, 45]. However, up to day, the data reported by different authors on the employment of the most recent aforementioned procedures of imaging are few and they need of further confirmation with more elevated number of cases; moreover, none of these radiotracers has been authorized for marketing.

The present study was retrospectively performed on a series of patients with non-functioning GEP tumors evaluated in three different University Centers. ^{111}In-Pentetreotide SPECT/CT was utilized as diagnostic tool in all cases after that they have been submitted to at least two CIP about a month before scintigraphy.

SPECT/CT, in our cases, was able to detect non-functioning GEP, also revealing their neuroendocrine origin, in 91.4% of patients who had neither clinical signs of hormone overexpression nor the characteristic secretion pattern in blood, while CIP was positive in 71.4% of cases. Moreover, SPECT/CT proved very reliable tool for correctly changing patient classification in respect of CIP data in an elevated number of patients (27.9%), including 20 cases completely negative at CIP which down-staged all these cases; 80% of the latter 20 patients had G1 tumors and SPECT/CT ascertained both primary and metastatic lesions, identifying the involved organs and their relationship with adjacent structures. New 53 tumor sites occult at CIP were identified, including 20 sited in extra-abdominal regions as pulmonary, mediastinal lymph node and bone small size metastases. SPECT/CT also contributed to determine resectability of circumscribed lesions, while excluding surgery in presence of extensive metastatic disease, thus permitting to select the most appropriate therapies.

SPECT/CT was also able to identify unknown primary tumors, that, as is known, cannot be easy to detect in some cases, as well as to stage patients after surgery and to monitor the affected patients in the course of systemic therapy, such as the somatostatin analogue octreotide and/or the chemotherapy, and to early detect recurrences or distant metastases during the follow up.

SPECT/CT was false negative in 6 patients who had metastases from NEC-G3 tumors in 5 cases (83.3%) and from G1 in the remaining case; in 5 patients the metastases were single and in 1 patient the lesions were two, all of these identified by CIP. Thus, SPECT/CT gave an incorrect classification probably for low receptor density or other receptor subtypes not detected by ^{111}In-Pentetreotide, as also hypothesized by other authors [46-49]; on the other hand, in our series SPECT/CT was true positive in 50% of NEC G3 patients, thus suggesting that SSR may also be present in some poor differentiated GEP tumors. However, in the 6

above mentioned false negative cases, size seems to have little importance in SPECT/CT detection, all lesions being > 10 mm, except for the G1 case in whom also the size could be one of the responsible factors since the lesion was 4 mm.

Thus, SPECT/CT in non-invasive way gave useful information for the most therapeutic strategy contributing in selecting both the patients to guide towards surgery, and, at the same time, those with diffuse metastases, who can also be not ascertained by CIP and in whom surgical resection is not indicated; these patients, however, could probably benefit from other treatments, including octeotride or radiolabeled somatostatin analogue therapy.

Moreover, with regard to grade, SPECT/CT sensitivity and accuracy were higher than CIP in all different groups, but significant in G1 group in which 16/20 (80%) patients (3 primary tumors), completely false negative at CIP, were positive at SPECT/CT; this latter result is very important since the early identification of tumor lesions of low grade could permit more correct and precocious non-invasive therapeutic procedures which can be decisive with more favorable disease prognosis.

In our series the highest performance of SPECT/CT has been obtained in most of exams acquired at 24 h and this result could suggest that an acquisition of SPECT/CT at 24 h may be sufficient, in agreement to other authors [26, 50]. However, in our 13 patients the exams at 48 h were determinant, in particular for identifying metastatic lesions, and in 6 cases they also changed patient classification and management, thus suggesting that, when the suspect of a metastatic disease is elevated, an acquisition over the 24 h could be useful.

Moreover, in our cases, SPECT/CT has been more sensitive in the identification of focal lesions than CIP and has also been helpful in differentiating pathological from physiological tracer uptakes with absence of false positive results; therefore, it could suggest that SPECT/CT may still be the method of choice for staging patients after surgery of primary tumors or for identifying patients with unknown primary tumor as well as for ascertaining recurrences or metastases during the course of therapy with octeotride or chemotherapy. CIP were true positive in the few cases false negative at SPECT/CT and vice versa the latter was positive in all false negative cases at CIP, thus suggesting that the combined use of the two procedures can achieve the highest sensitivity values, giving the most correct classification of the patients.

Notwithstanding the recent employment of PET/CT imaging with somatostatin analogous which proved higher sensitivity values in respect of ^{111}In-Pentetreotide, changing therapy decision in some cases, but still available in a few Centers, ^{111}In-Pentetreotide SRS can still represents a very useful diagnostic procedure with elevated accuracy when SPECT/CT is acquired. Despite some limitations due to tracer relative long decay time and prolonged time commitment by the patients, SPECT/CT gives higher imaging quality in respect of both planar SRS and SPECT with better characterization of focal areas of uptake excluding malignancy in physiologic sites of tracer uptake and with more correct anatomic lesion localization; moreover, the hybrid procedure demonstrates an elevated impact on patient management and therapy planning. SPECT/CT also presents a limited cost and a wide availability in all Nuclear Medicine Centers. Furthermore, ^{111}In-Pentetreotide has represented for many years the only tracer registered and approved for marketing in both the Europe and USA. However, these suggestions could be reassessed when somatostatin analogues marked with positron tracers will be duly authorized and, at the same time, the production systems may be available in all Centers and the radiotracers employed in an elevated number of cases.

In conclusion, ^{111}In-Pentetreotide SPECT/CT can still have a wide employment in the routine diagnostic protocol of non-functioning GEP tumors since it has demonstrated to play an important role in the early diagnosis of the neoplastic lesions, including the identification of unknown primary tumors, when still in a curative phase; this aspect is crucial for a correct choice of treatment. SPECT/CT demonstrated a high performance in the precise definition of tumor anatomic site and in the characterization of unclear lesions. It also achieved a more elevated sensitivity than CIP both in the diagnosis and in the disease staging, changing patient

CIP classification and clinical management in 27.9% of cases and also monitoring the response to treatment.

Disclosure of conflict of interest

None.

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