# Clinicopathological Features of Pancreatic Endocrine Tumors: A Prospective Multicenter Study in Italy of 297 Sporadic Cases

Alessandro Zerbi, MD[1], Massimo Falconi, MD[2], Guido Rindi, MD[3], Gianfranco Delle Fave, MD[4], Paola Tomassetti, MD[5], Claudio Pasquali, MD[6], Vanessa Capitanio, MD[1], Letizia Boninsegna, MD[2], Valerio Di Carlo, MD[1] and the members of the AISP-Network Study Group

OBJECTIVES: **Information on pancreatic endocrine tumors (PETs) comes mostly from small, retrospective, uncontrolled studies conducted on highly selected patients. The aim of the study was to describe the clinical and pathological features of PETs in a prospective, multicenter study.**

METHODS: **Newly diagnosed, histologically proven, sporadic PETs observed from June 2004 to March 2007 in 24 Italian centers were included in a specific data set.**

RESULTS: **Two hundred ninety-seven patients (mean age 58.6±14.7 years, females 51.2%, males 48.8%) were analyzed. In 73 cases (24.6%), the tumor was functioning (F) (53 insulinomas, 15 gastrinomas, 5 other syndromes) and in 232 (75.4%) it was non-functioning (NF); in 115 cases (38.7%), the diagnosis was incidental. The median tumor size was 20 mm (range 2–150). NF-PETs were significantly more represented among carcinomas ($P<0.001$). Nodal and liver metastases were detected in 84 (28.3%) and 85 (28.6%) cases, respectively. The presence of liver metastases was significantly higher in the NF-PETs than in the F-PETs (32.1% vs. 17.8%; $P<0.05$), and in the symptomatic than in the asymptomatic patients (34.6% vs. 19.1%; $P<0.005$). At the time of recruitment, the majority of patients (251, 84.5%) had undergone surgery, with complete resection in 209 cases (83.3%).**

CONCLUSIONS: **This study points out the high number of new cases of PETs observed in Italy, with a high prevalence of NF and incidentally discovered forms. The size of the tumor was smaller and the rate of metastasis was lower than usually reported, suggesting a trend toward an earlier diagnosis.**

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## INTRODUCTION

Pancreatic endocrine tumors (PETs) are considered a rare pathology with a wide spectrum of clinical presentations. Their real incidence is quite controversial; although they are found in about 1% of autopsies, their clinical incidence is reported to be only about 0.5–1/100,000 (1,2). This discrepancy can only partially be explained by the small size and the silent clinical behavior of many PETs.

The natural history of PETs is also largely unknown; despite recent improvements in their classification (3,4), diagnosis and treatment (2,5,6), the relationships between pathologic and clinical characteristics, type of treatment and prognosis are only partially understood (1).

Our knowledge of PETs derives mostly from small, retrospective, uncontrolled studies. Moreover, many reports involve highly selected patients [surgical series of resected patients (7,8), oncological series mainly of metastatic patients (9,10), series focused on benign functioning (F) neoplasms (11,12)], thus restricting the true picture.

Owing to the aforementioned reasons, in 2004, the Italian Association for the Study of the Pancreas (AISP) planned a prospective, observational, multicenter study on the clinical features, staging and management of PETs in Italy. Twenty-four centers were involved. They were distributed throughout Italy and were representative of different clinical areas: 12 surgical departments,

[1]Department of Surgery, Pancreas Unit, San Raffaele Scientific Institute, Milan, Italy; [2]Department of Surgery, University of Verona, Policlinico "GB Rossi," Verona, Italy; [3]Department of Pathology and Laboratory Medicine, University of Parma, Parma, Italy; [4]Department of Medicine, II Clinica Medica, Policlinico S. Andrea, Rome, Italy; [5]Department of Medicine, University of Bologna, Sant'Orsola Malpighi Hospital, Bologna, Italy; [6]Department of Surgery, Hospital of Padua, Padua, Italy.
**Correspondence:** Alessandro Zerbi, MD, Department of Surgery, Pancreas Unit, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milano, Italy.
E-mail: zerbi.alessandro@hsr.it
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6 oncological centers, 5 endocrinological centers, and 1 center of nuclear medicine (12 surgical and 12 non-surgical centers overall).

In this paper, we report the preliminary data concerning the clinicopathological features of the entire series of patients affected by PETs.

## METHODS

All newly diagnosed adult cases of pancreatic endocrine neoplasms consecutively observed during the period from June 2004 to March 2007 in the 24 participating Italian centers (listed in Appendix A) were included in the study. Inclusion criteria were the availability of a histological diagnosis, obtained from the surgical specimen or intraoperative biopsy or from percutaneous or endoscopic ultrasound (EUS)-guided biopsy. Rules for histological diagnosis were discussed, adapted, and approved among a group of experienced pathologists belonging to the participating centers, under the supervision of one of the authors (G.R.); in particular, the Ki67 proliferative index was expressed as a percentage based on the count of Ki67-positive cells in 2,000 tumor cells in areas with the highest immunostaining using the MIB1 antibody (DBA, Milan, Italy). A histological diagnosis was made according to the WHO classification (13); subsequently, relying on original pathological and radiological files, patients were also classified according to the tumor-node-metastasis (TNM) classification (3), not available at the time the study was planned. The study involved patients observed by the centers after 1 June 2004 and not later than 31 March 2007 and was approved by the Ethics Committee of each participating center. In addition, informed consent was obtained from all participating patients. After inclusion, each case was followed up for a minimum of 2 years, during which time the data of the patients were updated at 6-month intervals. The study had an observational non-interventional design as each diagnostic investigation and medical or surgical treatment was performed according to the current clinical practice of each individual center.

Each participating center was provided with specifically developed software with 116 descriptors for the first data entry and 60 descriptors for each follow-up entry, as designed by the Scientific Committee of the study. At inclusion (first data entry), the following parameters were recorded: demographic data, anatomical and histological details, biochemical data, clinical data including presentation symptoms, diagnostic investigations and staging, surgical treatment and any other treatment (medical, radiometabolic, ablative, chemotherapeutic). Patients presenting symptoms suggestive of an excess of hormone production were considered as being affected by a functioning tumor (F-PET), requiring subsequent laboratory confirmation according to the standard guidelines. The remaining patients with a lack of any specific syndrome were considered as suffering from a non-functioning tumor (NF-PET). Surgical resection was considered complete if no gross residual tumors or metastases were detectable at the end of the procedure. At every follow-up observation, the following data were recorded: modifications in symptoms, biochemical data, imaging data, variations in medical treatment, new surgical treatments, other new treatments and definition of the case (disease-free, stable residual disease, disease progression). The data were collected and tabulated centrally. During the study period, a careful monitoring process was implemented; at the end of the study, additional quality controls (concerning completeness and congruence of each chart) were performed.

Data are presented as median, mean, s.d., and 95% confidence intervals. Additional statistical tests (Student's *t*-test, $\chi^2$ test, Pearson's test, Fisher's exact test, Levene's test, analysis of variance) were used when appropriate. Relationships between the variables were tested using regression analysis. The difference was considered significant for a $P$ value $<0.05$. Statistical analysis was performed using SPSS software version 10.

## RESULTS

### General data

Three hundred twenty-one cases of PETs were collected; 11 of them (3.4%) were subsequently excluded from the final analysis because of incompleteness and/or inconsistency of the charts. Thirteen cases (4.2%) were associated with MEN-1 and were excluded from this study for their different characteristics and natural history. Therefore, 297 patients were analyzed: 223 (75.1%) were recruited in the 12 surgical centers and 74 (24.9%) in the 12 non-surgical centers. Each center enrolled a mean of 12 patients (range 1–81). Diagnosis was obtained from surgical specimens in the 236 patients undergoing resection (79.5%), from intraoperative biopsy in the 15 cases undergoing surgery without resection (5.4%), from percutaneous biopsy of liver metastasis in 34 metastatic non-operated patients (12.2%), and from EUS-guided fine-needle aspiration in 12 non-metastatic non-operated patients (4.3%). The mean age was 58.6±14.7 years. There were 152 females (51.2%) and 145 males (48.8%); the female gender was significantly more represented in F- than in NF-PETs: 63.1% vs. 47.9%, $P<0.05$ (**Table 1**). The greatest proportion of enrolled patients was in the 61- to 70-year age group, as shown in **Figure 1**. No significant differences in mean age were observed between patients belonging to different histological categories according to the WHO classification: well-differentiated tumors (B-Ts), mean age 58.9 years; tumors with uncertain behavior (UB-Ts), 56.7 years; well-differentiated carcinomas (WDECs), 58.4 years, and poorly differentiated carcinomas (PDECs), 63.2 years ($P=0.2$).

### Clinical data

Clinical presentation was associated with a syndrome in 73 cases (24.6%) (F-PETs). The syndrome was related to an excess of insulin production in 53 cases (72.6%), to gastrin production in 15 cases (20.5%), and to other hormones released in the remaining 5 cases (6.8%) (2 glucagonomas, 2 somatostatinomas, and 1 ACTH-producing tumor). The comparison of demographic and pathological characteristics between patients with F or NF-PETs is reported in **Table 1**: among F-PETs, B-Ts were significantly more frequent than among NF-PETs (57.5% vs. 21.9%, $P<0.0001$), whereas WDECs were less frequent (23.3% vs. 52.2%, $P<0.0001$); both nodal and hepatic metastases were less frequent in F-PETs than in NF-PETs

**Table 1. Demographic and pathological characteristics of 297 patients with functioning or non-functioning pancreatic endocrine tumors**

| Characteristic | Functioning | Non-functioning | *P* | OR | 95% CI |
|---|---|---|---|---|---|
| Number (%) | 73 (24.6) | 224 (75.4) | — | — | |
| Male gender (%) | 27 (37.0) | 118 (52.7) | | 1 | |
| Female gender (%) | 46 (63.0) | 106 (47.3) | 0.021 | 0.52 | 0.30–0.90 |
| Age (mean), years | 56.0 | 59.5 | NS | — | — |
| Tumor diameter (median), mm | 15.0 | 28.0 | 0.001 | — | — |
| *Tumor site (%)* | | | | | |
| Pancreatic head | 28 (38.3) | 83 (37.0) | NS | — | — |
| Pancreatic body-tail | 41 (56.2) | 135 (60.3) | NS | — | — |
| Pancreatic diffuse | 4 (5.5) | 6 (2.7) | NS | — | — |
| *WHO classification (%)* | | | | | |
| Well-differentiated tumor | 42 (57.5) | 49 (21.9) | 0.0001 | 0.21 | 0.12–0.39 |
| Uncertain behavior | 12 (16.4) | 37 (16.5) | NS | — | — |
| Well-differentiated carcinoma | 17 (23.3) | 117 (52.2) | 0.0001 | 3.13 | 1.69–5.79 |
| Poorly differentiated carcinoma | 2 (2.7) | 21 (9.4) | NS | — | — |
| Lymph node metastases (%) | 9 (12.3) | 75 (33.5) | 0.002 | 3.3 | 1.54–7.03 |
| Hepatic metastases (%) | 13 (17.8) | 72 (32.1) | 0.032 | 2.07 | 1.06–4.04 |
| *Ki67 values (%)* | | | | | |
| <2% | 54 (74.0) | 113 (50.4) | — | 1 | |
| 2–5% | 10 (13.7) | 39 (17.4) | NS | — | — |
| 6–10% | 2 (2.7) | 23 (10.3) | 0.026 | 5.43 | 1.22–24.0 |
| >10% | 5 (6.8) | 35 (15.6) | 0.0029 | 3.05 | 1.12–8.30 |
| Not assessed | 2 (2.7) | 14 (6.2) | — | — | — |

CI, confidence interval; OR, odds ratio; WHO, World Health Organization.
Data related to regression analysis have been adjusted by sex; univariate analysis and odds ratio were carried out for non-functioning tumors.

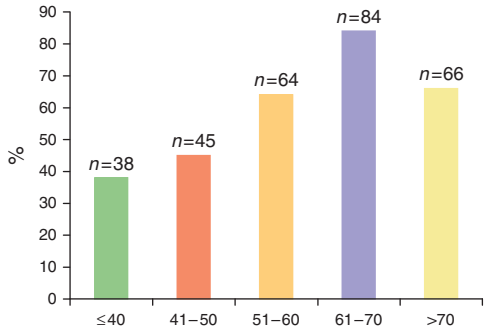


**Figure 1.** Distribution of 297 patients with endocrine pancreatic tumors by age group ($P<0.001$, analysis of variance).

(12.3% vs. 33.5%, $P<0.002$ and 17.8% vs. 32.1%, $P<0.03$, respectively). The 232 NF-PETs (75.4%) were clinically asymptomatic in 115 cases (51.4%, incidental diagnosis; 38.7% of the whole series), whereas pain was present in 80 cases (35.7%), weight loss in 35 (15.6%), jaundice in 15 (6.7%), and other symptoms in 31 (13.8%) cases (overall, 109 symptomatic cases, 48.6%, some patients had more than one symptom). The comparison of demographic and pathological characteristics between patients with symptomatic (F or NF) or asymptomatic (NF) PETs is reported in **Table 2**: symptomatic cases were more often located in the head (43.4% vs. 27.8%, $P<0.01$) and had a greater risk of developing liver metastases (34.6% vs. 19.1%, $P<0.005$), whereas the greater incidence of nodal metastases we observed (31.3% vs. 23.5%) did not reach statistical significance ($P=0.14$).

## Pathological data

The site of the tumor (in case of multifocality, the largest lesion was considered) was the head of the pancreas in 111 cases (37.4%) and the body-tail in 176 cases (59.2%), whereas the tumor was diffuse to the whole gland in 10 cases (3.4%). No differences in the site of the neoplasm were observed between F- and NF-PETs (**Table 1**). In 21 cases (7.1%), the tumor was multifocal; 5 cases (23.8%) were F-PETs and 16 (76.2%) were NF-PETs. The rate of multifocality was the same in NF-PETs and F-PETs (7.2% vs. 6.8%).

The median size of the tumor (in case of multifocality, the largest lesion was considered) was 20 mm (mean size 31.7 mm, range 2–150). Dimension correlates both with the clinical presentation (15 mm in F vs. 28 mm in NF, $P<0.001$) and the histological classification: 15 mm in B-T, 20 mm in UB-T, 40 mm in WDEC, 40 mm

**Table 2. Demographic and pathological characteristics of 297 patients with symptomatic or asymptomatic pancreatic endocrine tumors**

| Characteristic | Symptomatic | Asymptomatic | *P* | OR | 95% CI |
|---|---|---|---|---|---|
| Number (%) | 182 (61.3) | 115 (38.7) | — | — | |
| Male gender (%) | 84 (46.1) | 61 (53.0) | | | |
| Female gender (%) | 98 (53.8) | 54 (46.5) | NS | — | — |
| Age (mean), years | 57.9 | 59.9 | NS | — | — |
| Tumor diameter (median), mm | 20 | 23 | NS | — | — |
| *Tumor site (%)* | | | | | |
| Pancreatic head | 79 (43.4) | 32 (27.8) | 0.011 | 1.91 | 1.14–3.18 |
| Pancreatic body-tail | 96 (52.7) | 80 (69.6) | 0.008 | 0.51 | 0.31–0.85 |
| Pancreatic diffuse | 7 (3.8) | 3 (2.6) | NS | — | — |
| *WHO classification (%)* | | | | | |
| Well-differentiated tumor | 54 (29.7) | 37 (32.2) | NS | — | — |
| Uncertain behavior | 32 (17.6) | 17 (14.8) | NS | — | — |
| Well-differentiated carcinoma | 83 (45.6) | 51 (44.3) | NS | — | — |
| Poorly differentiated carcinoma | 13 (7.1) | 10 (8.7) | NS | — | — |
| Lymph node metastases (%) | 57 (31.3) | 27 (23.5) | 0.145 | 1.48 | 0.87–2.53 |
| Hepatic metastases (%) | 63 (34.6) | 22 (19.1) | 0.005 | 2.23 | 1.28–3.90 |
| *Ki67 values (%)* | | | | | |
| <2% | 101 (55.5) | 66 (57.4) | NS | — | — |
| 2–5% | 29 (15.9) | 20 (17.4) | NS | — | — |
| 6–10% | 15 (8.2) | 10 (8.7) | NS | — | — |
| >10% | 24 (13.2) | 16 (13.9) | NS | — | — |
| Not assessed | 13 (7.1) | 3 (2.6) | NS | — | — |

CI, confidence interval; OR, odds ratio; WHO, World Health Organization.
Data related to regression analysis have been adjusted by sex; univariate analysis and odds ratio were carried out for asymptomatic tumors.

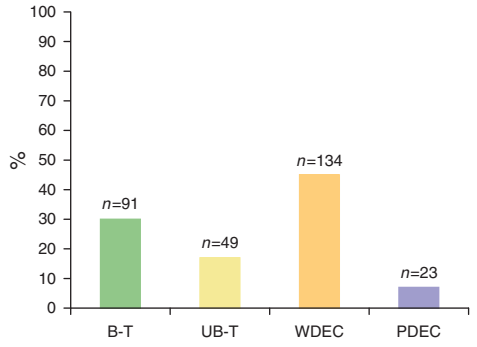


**Figure 2.** Distribution of 297 endocrine pancreatic tumors according to World Health Organization classification (Heitz *et al.* (13)). B-T, well-differentiated tumor; PDEC, poorly differentiated carcinoma; UB-T, tumor with uncertain behavior; WDEC, well-differentiated carcinoma.

in PDEC ($P<0.001$). No relationship was observed between the median size of the tumor and the site of the neoplasm (head or body-tail of the pancreas).

According to the WHO classification, the distribution of cases was: B-T, 91 cases (30.6%); UB-T, 49 cases (16.5%); WDEC, 134 cases (45.1%); PDEC, 23 cases (7.7%) (**Figure 2**). Patients with NF-PETs showed a threefold higher risk of having a WDEC with respect to patients with F-PETs (**Table 1**). Distribution of patients according to the TNM system was as follows: stage I, 114 cases (38.3%); stage IIa, 24 cases (8.1%); stage IIb, 9 cases (3.0%); stage IIIa, 24 cases (8.1%); stage IIIb, 37 cases (12.5%); stage IV, 89 cases (30.0%). Grading was assessed in 270 cases (90.9%); its distribution was: 164 cases grade 1 (55.2%), 85 cases grade 2 (28.6%), 21 cases grade 3 (7.1%). In **Table 3,** the relationships between WHO classification and TNM staging are reported.

At diagnosis, metastases were detected in 124 patients (41.7%) (nodal in 84 cases (28.3%), hepatic in 85 cases (28.6%), and at other sites in 14 cases (4.7%). In this latter group, the bone was involved in 6 cases, the lung in 4, the spleen in 3, the peritoneum in 2, and the brain, adrenal gland, and gallbladder in 1 case each. No patient had metastases in other sites without the liver and/or lymph node involvement. Considering the 85 cases with liver metastases, a single metastasis was present in 12 cases (14.1%), whereas multiple metastases were detected in the remaining 73 cases (85.9%) (unilobar in 16 cases, bilobar in 57). Among the 157 patients with WDECs or PDECs, no metastases were

**Table 3. Correlation between distribution of 297 endocrine pancreatic tumors according to the WHO classification (Heitz *et al.* (13)) and the TNM classification (Rindi *et al.* (3))**

| WHO classification | TNM stage I | TNM stage II | TNM stage III | TNM stage IV | Total |
|---|---|---|---|---|---|
| B-T | 91 (79.8%) | 0 | 0 | 0 | 91 |
| UB-T | 23 (20.2%) | 26 (78.8%) | 0 | 0 | 49 |
| WDEC | 0 | 7 (21.2%) | 52 (85.2%) | 75 (84.3%) | 134 |
| PDEC | 0 | 0 | 9 (14.7%) | 14 (15.7%) | 23 |
| Total | 114 | 33 | 61 | 89 | 297 |

B-T, well-differentiated tumor; PDEC, poorly differentiated carcinoma; TNM, tumor-node-metastasis; UB-T, tumor with uncertain behavior; WDEC, well-differentiated carcinoma; WHO, World Health Organization.

**Table 4. Pathological characteristics according to Ki67 value in 281 patients with endocrine pancreatic tumor**

| Ki67 value | No. of patients | Lymph node metastases | Hepatic metastases | Tumor size (median) mm |
|---|---|---|---|---|
| 0–2% | 167 | 27 (16.1%) | 21 (12.6%) | 16 |
| 3–5% | 49 | 14 (28.6%) | 21 (42.9%) | 33 |
| 6–10% | 25 | 11 (44.0%) | 14 (56.0%) | 40 |
| >10% | 40 | 28 (70.0%) | 23 (57.5%) | 37.5 |
| Not assessed | 16 | 4 (25.0%) | 6 (37.5%) | 20 |
| *P* | | <0.001* | <0.001* | <0.001** |

Data were calculated in patients with availability of Ki67 proliferative index assessment (**P* value was calculated using analysis of variance; ***P* value was based on Fisher's exact test).

detected in 33 cases (21.0%), only metastases to lymph nodes were present in 39 cases (24.8%), only liver metastases in 40 cases (25.5%), and metastases to both lymph nodes and the liver in 45 cases (28.7%). The median size of the neoplasm was significantly greater in the presence of liver metastases (M+ 40 mm vs. M0 18 mm; $P<0.01$) and nodal metastases (N+ 40 mm vs. N0 18 mm; $P<0.01$). Nodal and liver metastases rates were significantly higher in NF-PETs than in F-PETs (odds ratio: 3.3 and 2.07, respectively) (**Table 1**); the presence of liver metastases was also significantly higher in symptomatic than asymptomatic patients (odds ratio: 2.23) (**Table 2**).

The Ki67 proliferative index was assessed in 281 cases (94.6%): in 270 cases on histological specimen and in 11 cases on fine-needle aspiration specimen. A significant correlation was found between Ki67 values and nodal and liver metastases as well as between Ki67 values and median tumor size (**Table 4**). Ki67 values were significantly higher in NF than in F-PETs (**Table 1**), whereas no differences were observed between symptomatic and asymptomatic patients (**Table 2**).

### Biochemical data

At recruitment, chromogranin A (CgA) was assessed in 175 cases (58.9%). In 74 cases, it was within normal values (42.3%), whereas it was increased in the remaining 101 cases (57.7%). No relationship was found between clinical presentation (F vs. NF-PETs) and the presence of the pathological values of CgA (data not shown). On the contrary, CgA was elevated more frequently in WDECs and PDECs than in B- and UB-Ts (77.3% vs. 33.3%, $P<0.001$). Moreover, in patients with elevated CgA values, nodal and liver metastases were observed frequently (in 53.5% and 47.5% of cases, respectively).

Neuron-specific enolase was assessed in 117 cases (39.4%) and was elevated in only 19 of them (16.2%). In the subgroup of patients with abnormal neuron-specific enolase values, the pathological characteristics (WHO histological classification, degree of differentiation, and presence of nodal and liver metastases) were similar to those of the remaining patients.

### Diagnostic investigations

At the time of enrollment in the study, abdominal ultrasound (US) was performed in 238 cases (80.1%), computed tomography (CT) in 260 (87.5%), magnetic resonance in 105 (35.3%), EUS in 78 (26.2%), and somatostatin receptor scintigraphy (SRS) in 142 (47.8%). Data on the sensitivity of these diagnostic investigations in recognizing the primary pancreatic tumor, and the presence of loco-regional, liver, and distant metastases are reported in **Table 5**. EUS showed the highest sensitivity in detecting the primary tumor (96.1%, vs. CT 93.1%, MR 91.4%, US 84.9%, SRS 67.6%); CT, US, and MR showed similar sensitivity rates in detecting liver metastases (96.3%, 95.4%, and 93.7%, respectively), whereas the detection of nodal metastases was slightly different (63.8%, 54.7%, and 41.7%, respectively). No differences in the sensitivity of different diagnostic investigations were detected in comparing F- and NF-PETs, except for SRS, which was more sensitive in NF- than in F-PETs (75.2% vs. 45.9%; $P<0.001$).

**Table 5. Sensitivity of diagnostic investigations in recognizing the primary pancreatic tumor and the presence of loco-regional, hepatic, and other metastatic sites in 297 patients with pancreatic endocrine tumors**

| | Primary tumor (297 cases) | | Loco-regional metastases (84 cases) | | Liver metastases (86 cases) | | Other metastatic sites (14 cases) | |
|---|---|---|---|---|---|---|---|---|
| | No. of pts. examined | Evidence of disease | No. of pts. examined | Evidence of disease | No. of pts. examined | Evidence of disease | No. of pts. examined | Evidence of disease |
| US | 238 | 202 (84.9%) | 70 | 37 (52.8%) | 65 | 62 (95.4%) | — | — |
| CT | 260 | 242 (93.1%) | 78 | 47 (60.3%) | 82 | 79 (96.3%) | 12 | 5 (41.7%) |
| MR | 105 | 96 (91.4%) | 25 | 10 (40.0%) | 16 | 15 (93.7%) | 3 | 2 (66.6%) |
| EUS | 78 | 75 (96.1%) | 12 | 4 (33.3%) | 4 | 3 (75.0%) | — | — |
| SRS | 142 | 96 (67.6%) | 42 | 22 (52.4%) | 54 | 47 (87.0%) | 11 | 5 (50.0%) |

CT, computed tomography; EUS, endoscopic ultrasounds; MRI, magnetic resonance; pts., patients; SRS, somatostatin receptor scintigraphy; US, abdominal ultrasound. Data on loco-regional and liver metastases are referred to histologically proven cases with nodal and hepatic metastases (reported in parentheses in the column).

### Treatment

Two hundred fifty-one patients (84.5%) underwent surgery at the time of recruitment in the study. The non-operated patients were observed in 18 cases (39.1%) in surgical centers and in the remaining 28 cases (61.9%) in non-surgical centers; the rate of operated patients was 91.8% in surgical centers and 62.2% in non-surgical centers. The 46 non-operated patients were represented by 2 B-Ts, 35 WDECs, and 9 PDECs; liver metastases were present in 34 cases (73.9%) and nodal metastases in 22 cases (47.8%); the median size of the tumor was 44.5 mm; the neoplasm was an F-PET in 6 cases (13.0%) and an NF-PET in 40 cases (86.9%); in 8 cases (17.4%), it was asymptomatic. Pancreatic resection was performed by laparoscopy in only a minority of cases (21 cases, 8.4%). The surgical procedure was a complete resection in 209 cases (83.36%; 70.4% of the whole series), a palliative resection (debulking) in 27 cases (10.7%), an exploratory laparotomy in 12 cases (4.8%), and a bypass procedure in 3 cases (1.2%). The type of complete resection performed was a pancreatoduodenectomy (PD) in 45 cases (21.5%), a distal pancreatectomy in 91 cases (43.5%), an enucleation in 48 cases (23.0%), a middle pancreatectomy in 15 cases (7.2%), and a total pancreatectomy in 10 cases (4.8%) (**Figure 3**). When a palliative resection was performed, a PD was carried out in 9 cases (33.3%) and a distal pancreatectomy in 18 cases (66.6%). Liver resection was performed in 26 cases (10.3%): in 9 cases with radical intent and in 17 cases as part of a debulking procedure.

Postoperative mortality was 1.6% (4 cases) and morbidity was 40.6% (102 cases). All four deaths occurred after a PD (classified as complete resection in 2 cases and as a palliative resection in the other 2). Morbidity rate was higher after complete resection (44.5%) than after palliative resection (29.6%), exploratory laparotomy (8.3%), or by-pass procedure (0%).

A complete resection was performed more frequently in F- than in NF-PETs (82.2% vs. 66.5%, $P < 0.05$). Moreover, complete resection was also more frequent in B- and UB-Ts than in WDECs and PDECs (97.9% vs. 45.8%, $P < 0.001$), whereas palliative resections were equally represented in WDECs and PDECs (17.1% vs. 13.0%, $P = 0.15$). On the contrary, liver resection was more frequently performed in PDECs than in WDECs (21.4% vs. 15.6%, $P < 0.05$).

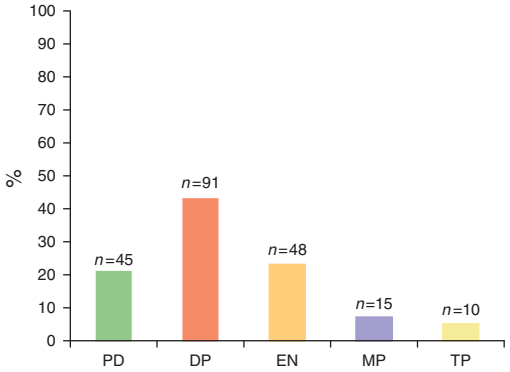


**Figure 3.** Type of resection performed in 209 patients undergoing complete resection for endocrine pancreatic tumor. DP, distal pancreatectomy; EN, enucleation; MP, middle pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy.

## DISCUSSION

This study represents one of the few available prospective surveys on PETs (14–16) with the advantage of no relevant selection bias at the time of diagnosis. For this reason, it can be regarded as a true representation of PET characteristics, and diagnostic and therapeutic attitudes in Italy. The only bias in patient recruitment could be represented by the high number of surgical centers and mostly by the high recruitment rate observed in these centers compared with non-surgical ones. Nonetheless, this difference in recruitment rates reflects the current status in PET management in Italy.

Despite the fact that the exact epidemiology of the disease cannot be defined, some important considerations can be drawn. Taking as the referral incidence that which is estimated between 0.12 and 0.6/100,000 (1) in Western countries, this study enrolled 90 cases/year, about 1/4 of the cases expected in the entire country. If true, it means that, in Italy, there is a trend to refer PETs to a few specialized centers. This process of centralization has to be regarded as positive, in view of obtaining better results in the treatment of this disease (17,18).

Our study confirmed the tendency that the great majority of PETs are NF (about 75%) and that diagnosis is incidental in more

than one third of them. The clinical presentation of PETs seems to be very different from that of the past; until 3–4 decades ago, about 80% of all PETs were reported to be functioning (19,20). The advances in diagnostic investigations and the improvement in knowledge regarding these rare tumors led to a progressive increase in the detection of PETs not associated with a clinical syndrome and/or incidentally discovered. If clinical series published one decade ago reported equal frequency between F- and NF-PETs (21–23), more recent series describe a rate of NF forms between 58 and 71% (7,8,24–27). Our 75% rate is the highest reported; all our cases were newly diagnosed after 2004, and it is likely that this rate is closer to the clinical reality of recent years. More than one third of all PETs and about one half of NF-PETs were discovered incidentally: these patients represent a specific category of endocrine tumors, and their pathological characteristics are different from those of symptomatic ones, with a lower incidence of liver metastases.

Few data on the multifocality of PETs are available in the literature, apart from insulinomas (multifocal in about 5–10% of cases) and gastrinomas (multifocal in about 60–70% of cases) (28). The high rate of multifocality (7%) we observed points out the importance of a careful intraoperative search for multifocality, even in non-MEN 1 related cases, by wide exposure and palpation of the whole pancreas and by systematic utilization of intraoperative USs.

The size of the primary tumor observed in the present series was slightly smaller than those reported in other and older series: 3.6 cm according to Vagefi *et al.* (7), 4.5 cm according to Hochwald *et al.* (24), 6 cm according to Chu *et al.* (25). It is possible that the diagnosis of these neoplasms was made earlier than in the past, because of the improvement in diagnostic investigations and better awareness of the disease. As expected (7), the size was greater in NF- than in F-PETs, and in WDECs and PDECs than in B- and UB-Ts. This finding supports the observations that F-PETs are diagnosed earlier because of their symptoms and that size is an important prognostic factor for malignancy in PETs (3,24,29,30).

All our cases were classified according to both the 2004 WHO classification (13) and the TNM classification (3). No data comparing these two recently introduced classifications are yet available in the literature. In our study, we observed an overlap in benign forms between B-T and UB-T classes and stages I and II; TNM classification, on the other hand, seemed to better separate malignant forms into two groups (stages III and IV) in respect of WHO classification (the great majority of cases being classified as WDEC). We observed a higher rate of malignant forms among NF-PETs because of a higher risk of both nodal and liver metastases. As far as the WHO definition of malignancy of these neoplasms is concerned, it is interesting to observe that about 20% of our cases were classified as "carcinomas," in the absence of nodal or distant metastases, because of direct invasion into adjacent tissues or organs. This rate is the same as that reported by La Rosa *et al.* (4) in a recent detailed pathological analysis of 155 PETs and stresses the importance of an accurate pathological examination to achieve the correct classification of each case.

At the time of diagnosis, 41% of our cases showed the presence of metastases; this rate is a little lower than that currently reported in the literature where rates ranging from 46 to 73% are observed (8,22,23,25–27,31–40), even if it is difficult to make reliable comparisons, because of the marked heterogeneity of the studies. The separate incidences of nodal and liver metastases were also slightly lower than those currently reported (8,22–27,31,32,35,38–41): it is possible that our series of only newly diagnosed cases dealt with an earlier stage of disease, not yet metastasized. The high rate of incidentally diagnosed cases, as well as the relatively small size of the primary tumors we observed, might further support this observation.

In 95% of our cases, assessment of the Ki67 proliferative index was possible. A linear relationship was observed between Ki67 values and the presence of liver and nodal metastases, and also with the size of the tumor, confirming the prognostic role of Ki67 assessment (35). This information is of paramount importance in PETs' pathological classification, and it has to be stressed that Ki67 assessment is also possible on the fine-needle aspiration specimen (42). This option allows a more precise evaluation of the aggressiveness of small PETs in the preoperative setting and it may be useful in establishing non-operative strategies in selected cases.

Regarding diagnostic evaluation, CT and US were by far the most used imaging techniques (in >80% of cases), whereas SRS was performed in about 50% of cases, compared with magnetic resonance and EUS in about 30% of cases. The low utilization of EUS and SRS probably reflects both the scarce availability of these investigations throughout the entire national territory and the high proportion of patients undergoing surgical resection for NF-PETs. Overall, the results of tumor localization and staging were very satisfactory in our series, as a consequence of the technological evolution observed in recent years, with the development of more and more sensitive and accurate imaging techniques.

A very high proportion of the cases we recruited underwent surgery, in particular resection of the primary tumor. These data not only reflect the high number of patients recruited in surgical centers but also confirm that surgery is the cornerstone treatment for PETs, being the only potentially curative treatment for these tumors. As no other prospective data are available on the percentage of newly diagnosed cases undergoing surgery as a first treatment, our figure points out the current therapeutic attitude toward PETs in Italy. The finding that a median size of tumors without liver or nodal metastases was 18 mm could support an observational treatment for small PETs (< 2 cm). However, in this series, only two patients were directed to observational treatment, witnessing that currently this attitude is not widespread in Italy. Despite many reports claiming the advantages of laparoscopy in the surgical treatment of PETs (43,44), only 8% of our cases were treated with this approach. Pancreatic laparoscopic surgery is still regarded as a very demanding procedure and it is still far from a widespread application. A limited pancreatic excision (enucleation and middle pancreatectomy) was performed in 30% of cases, underlying the importance of parenchyma-sparing surgery in the treatment of PETs. However, it is still under debate and unclear when this type of procedure can be applied safely (only in functioning or also in non-functioning tumors?

for a size <1 cm, 2 cm, or 3 cm?) (45–48), but unfortunately our data do not allow us to give recommendations in this regard. In a small percentage of cases (10%), a palliative pancreatic resection was performed, sometimes combined with a palliative liver resection. The role of debulking surgery in the treatment of PETs is under debate (49–52), even if recent data failed to show any survival advantage after primary tumor resection in the presence of liver metastases (53), and ENETS guidelines do not recommend debulking for unresectable primary NF-PETs (29). The outcome of surgery in this multicentric series can be considered as satisfactory, taking into account the high rates of postoperative mortality and morbidity currently reported from the regional and national databases (17,18).

In summary, our report points out the high number of new cases of PETs observed in Italy and, in particular, of NF and incidentally discovered forms. The great majority of them undergo surgical resection at the first clinical observation. A trend toward an earlier diagnosis is suggested, having observed a smaller size of the primary tumor and a lower rate of metastasis than that usually reported. Among NF-PETs, malignant forms are more frequent than among F-PETs; symptomatic cases show higher rates of liver metastasis than asymptomatic cases.

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### CONFLICT OF INTEREST

**Guarantor of the article:** Alessandro Zerbi, MD.

**Specific author contributions:** Members of the Scientific Committee, designed the study and the specific software for collecting data: Alessandro Zerbi, Massimo Falconi, Guido Rindi, Gianfranco Delle Fave, Paola Tomassetti, Claudio Pasquali, Valerio Di Carlo; carried out the quality control, verifying the completeness and congruence of each chart: Vanessa Capitanio and Letizia Boninsegna; drafted the manuscript: Alessandro Zerbi; each author approved the final draft submitted.

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**Potential competing interests:** None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ The clinicopathological features and natural history of pancreatic endocrine tumors are largely unknown.
- ✓ Knowledge of pancreatic endocrine tumors derives mostly from small, retrospective, uncontrolled studies.

### WHAT IS NEW HERE

- ✓ Data are provided from a large, prospective survey conducted recently over a short period of time.
- ✓ Non-functioning tumors and incidentally discovered forms are highly prevalent.
- ✓ The size of the neoplasm and the rate of metastasis were lower than those usually reported.

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## APPENDIX A

### Members of the AISP-Network Study Group

| Investigator | | Center | City |
|---|---|---|---|
| Di Carlo | Valerio | OSPEDALE S. RAFFAELE | Milano |
| Pederzoli | Paolo | AZIENDA OSPEDALIERA VERONA (POLICLINICO) | Verona |
| Delle Fave | Gianfranco | AZIENDA OSPEDALE POLICLINICO S. ANDREA | Roma |
| Pedrazzoli | Sergio | AZIENDA OSPEDALIERA DI PADOVA | Padova |
| Tomassetti Casadei | Paola Riccardo | AZIENDA OSPEDALIERA POLICLINICO S. ORSOLA - MALPIGHI | Bologna |
| Garcea | Domenico | OSPEDALE PIERANTONI | Forlì |
| Uomo | Generoso | AZIENDA OSPEDALIERA "A. CARDARELLI" | Napoli |
| Colangelo | Ettore | OSPEDALE CIVILE | Pescara |
| Mosca | Franco | OSPEDALE CISANELLO | Pisa |
| Fronda | Gian Ruggero | OSPEDALE S. GIOVANNI BATTISTA MOLINETTE | Torino |
| Bresadola | Fabrizio | POLICLINICO UNIVERSITARIO A GESTIONE DIRETTA | Udine |
| Cantore | Maurizio | OSPEDALE CIVILE | Carrara |
| Leone | Biagio Eugenio | OSPEDALE S. GERARDO | Monza |
| Farinati | Fabio | AZIENDA OSPEDALIERA DI PADOVA | Padova |
| Toma | Sandro Salvatore | OSPEDALE CASA SOLLIEVO DELLA SOFFERENZA | San Giovanni Rotondo |
| Luppi | Gabriele | AZIENDA OSPEDALIERA POLICLINICO | Modena |
| Bene | Anna | AZIENDA POLICLINICO UNIVERSITARIO | Messina |
| Bajetta | Emilio | ISTITUTO NAZIONALE PER CURA TUMORI | Milano |
| Ruffini | Livia | AZIENDA OSPEDALIERA G. BROTZU | Cagliari |
| Gebbia | Vittorio | CLINICA MADDALENA | Palermo |
| Liguori | Luciano | OSPEDALE BELLARIA | Bologna |
| De Toma | Giorgio | AZIENDA UNIVERSITARIA POLICLINICO UMBERTO I | Roma |
| Dogliotti | Luigi | AZIENDA SANITARIA OSPEDALIERA "S. LUIGI" | Orbassano |
| Massidda | Bruno | POLICLINICO UNIVERSITARIO | Cagliari |