Clinical Study
Factors Related to Long-Term Survival in Patients Affected by Well-Differentiated Endocrine Tumors of the Pancreas

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Aim. To identify factors related to survival in patients affected by well-differentiated PETs (benign, uncertain behavior, and carcinoma) who underwent R0 pancreatic resection. Methods. Retrospective study of 74 consecutive patients followed up from January 1980 to December 2011. Prognostic factors were sex, age, type of tumor, presence of symptoms, type of surgical procedure, size of tumor, lymph nodes status, WHO classification, and TNM stage. Overall survival was evaluated using the Kaplan-Meier method. Cox regression analyses were used to identify the factors associated with prognosis in univariate and multivariate analysis. Results. The mean follow-up of all the patients was 106 ± 89 months. The 5–10-year long-term survival was 90.9% and 79.1%, respectively. At univariate analysis, patient age < 55 years was significantly related to a better long-term survival compared to patients age ≥ 55 years (307 ± 15 months versus 192 ± 25 months; P = 0.010). Multivariate analysis showed that female gender (P = 0.006), patients without comorbidities (P = 0.033), and patients affected by well-differentiated benign pancreatic endocrine tumors (P = 0.008 and P = 0.002 in relation to tumors with uncertain behavior and carcinomas, resp.) were factors significantly related to a better long-term survival. Conclusions. Patients factors were strongly related to a better long-term survival in patients observed. WHO classification is a very useful prognostic tool for well-differentiated PETs.

1. Introduction
Pancreatic endocrine tumors (PETs) are rare neoplasms with a poorly defined natural history that, in general, have a more indolent tumor biology with better long-term survival rates than tumors of the exocrine pancreas [1]. Surgery is generally considered the treatment of choice and, for patients with localized disease, it can be curative. The biological behavior of PETs is variable, necessitating close long-term follow-up. The World Health Organization (WHO) [2, 3] as well as tumor node metastasis (TNM) [4, 5] classifications recognized different groups of PETs with different biologic behaviors. Moreover, several authors [6–11] reported factors predicting survival after the resection of PETs. To our knowledge, there are no studies in the literature that reported prognostics factors related to long-term survival in patients with well-differentiated PETs.

Thus, the present study was carried out in order to identify the factors related to long-term survival in patients affected by well-differentiated PETs (benign, uncertain behavior, and carcinoma) who underwent R0 pancreatic resection.

2. Patients and Methods
A retrospective study of a prospective database of 74 consecutive patients who underwent R0 pancreatic resection for well-differentiated PETs (benign, uncertain behavior, and carcinoma) was conducted from January 1980 to December 2011. All the patients were followed up, and for each patient long-term overall survival (OS) was calculated from the date of surgery to the date of the death or last follow-up. December 2011 was the end of the follow-up period for surviving patients. Prognostic factors considered for each
patient were sex, age (<55 or ≥55 years) [12] type of tumor (sporadic, functioning, nonfunctioning, and MEN-1), presence of symptoms, type of surgical procedure (typical or atypical resection), size of tumor (<2, 2–4, and >4 cm), lymph nodes status (N0, N1, and NX), WHO classification [2], and TNM stage [5]. No further therapy was initiated after R0 pancreatic resection even in cases with lymph nodes involvement. Follow-up examinations were conducted every 6 months for the first 2 years and every year subsequently with clinical examination, serum CgA, abdominal ultrasound, and computed tomography (CT) scan. Somatostatin receptor scintigraphic scanning (Octreoscan) of PET with Ga-Dotanoc was performed in selected cases in which there was the suspicion for recurrence of the disease. Surgical or medical therapy was performed in cases with recurrences.

3. Statistical Methods

Means, standard deviations, and frequencies were used to describe the data. OS was evaluated using the Kaplan-Meier method. Cox regression analyses were used to identify the factors associated with prognosis in univariate and multivariate analysis. Two-tailed P values less than 0.05 were considered statistically significant. All statistical analyses were carried out by running SPSS for Windows (version 13.0) on a personal computer.

4. Results

Characteristics of the 74 patients affected by well-differentiated PETs who underwent R0 pancreatic resections are summarized in Table 1. There was a slight prevalence of women (52.7%) compared to men (47.3%); they had a mean age of 53 ± 14 years, and the major part of the patients were ≥55 years (52.7%). Twenty-seven (36.5%) patients had one or more comorbidities. Pancreatic endocrine tumors were more frequently symptomatic (76.3%) and nonfunctioning (54.1%). Functioning tumors were present in 34 (45.9%) cases: the major part (25 cases (33.8%)) were insulinomas; the others (9 cases (12.1%)) were 5 gastrinomas, 2 Vipomas, 1 glucagonoma, and 1 PPoma MEN-1 syndrome was rarely observed (7 cases (9.5%)). The tumors were usually small (size <4 cm in 54 cases (72.9%)) and without lymph nodes involvement (66.2%). A typical resection was more frequently performed (73%) including left pancreatectomy (41 cases (55.4%)) pancreaticoduodenectomy (11 cases (14.9%)) and total pancreatectomy (2 cases (2.7%)). Atypical resection included 18 enucleoresection (24.3%) and 2 (2.7%) middle-pancreatectomy. Regarding the WHO classification of PETs, we observed, in the major part of the cases (45 cases (60.8%)), well-differentiated tumors, benign or with uncertain behavior. TNM stage III was the rarest (29.8%) stage with a prevalence of stage IIIb (23%).

The mean follow-up of all the patients was 106 ± 89 months. During follow-up, 13 (17.6%) patients died after a mean time from surgery of 76 ± 87 months: 1 (1.3%) patient died in the postoperative period, 5 (6.8%) for disease progression, and 7 (9.5%) for causes not related to the tumor but to the patients. Patients deaths disease-related have a mean long-term survival of 68 ± 45 months. The mean long-term overall survival was 271 ± 16 months; 5–10-year long-term overall survival was 90.9% and 79.1%, respectively (Figure 1). Recurrence rate was 18.9% (14 cases), and in these cases the mean disease-free survival was 87 ± 56 months. In these cases, only in 1 (7.1%) a reoperation,

| Factors                        | No. (%) |
|--------------------------------|---------|
| Sex                            |         |
| M                              | 35 (47.3) |
| F                              | 39 (52.7) |
| Age                            |         |
| <55 years                      | 35 (47.3) |
| ≥55–65 years                   | 39 (52.7) |
| Comorbidities                  |         |
| None                           | 47 (63.5) |
| One or more                    | 27 (36.5) |
| Symptoms                       |         |
| No                             | 19 (25.7) |
| Yes                            | 55 (74.3) |
| Hormonal status                |         |
| Nonfunctioning                 | 40 (54.1) |
| Insulinoma                     | 25 (33.8) |
| Others                         | 9 (12.1)  |
| MEN-1                          |         |
| No                             | 67 (90.5) |
| Yes                            | 7 (9.5)   |
| Size of tumors                 |         |
| <2 cm                          | 30 (40.5) |
| 2–4 cm                         | 24 (32.4) |
| >4 cm                          | 20 (27.0) |
| Lymph node status              |         |
| N0                             | 49 (66.2) |
| N1                             | 17 (23.0) |
| Nx                             | 8 (10.8)  |
| Type of resection              |         |
| Typical                        | 54 (73.0) |
| Atypical                       | 20 (27.0) |
| WHO classification             |         |
| WDT-B                          | 24 (32.4) |
| WDT-UB                         | 21 (28.4) |
| WDEC                           | 29 (39.2) |
| TNM stage*                     |         |
| I                              | 26 (35.1) |
| II                             | 26 (35.1) |
| III                            | 22 (29.8) |

WDT-B: well-differentiated tumor-benign; WDT-UB: well-differentiated tumor-uncertain behaviour; WDEC: well-differentiated carcinoma. *TNM-ENETS stage system modified according to Scarpa et al. [5].
consisting in a left pancreatectomy, was performed; the others were treated with somatostatin analogs.

At univariate analysis, symptoms, hormonal status, MEN-1 syndrome, size of tumor, lymph nodes status, type of resection, and TNM stage were not considered factors significantly related to long-term survival of the patients affected by well-differentiated PETs. Female gender presented a better long-term survival, but not statistically significant, compared to male (302 ± 19 versus 235 ± 27; P = 0.080) as well as patients without comorbidities compared to patients with comorbidities (290 ± 17 months versus 155 ± 21 months; P = 0.065). Regarding WHO classification, well-differentiated tumor-benign (WDT-B) showed a better, but not statistically significant, long-term survival than well-differentiated tumor-uncertain behavior (WDT-UB) and well-differentiated carcinoma (WDC) (280 ± 15 months versus 265 ± 34 and 235 ± 31 months, resp., P = 0.080). The only factor related to a significantly better long-term overall survival was the age: patients <55 years survived significantly more than patients ≥55 years (307 ± 15 months versus 192 ± 25 months; P = 0.010) (Table 2).

Multivariate analysis showed 3 factors significantly related to a better long-term overall survival: female gender (HR 0.2; C.I. 95% 0.4–0.6; P = 0.006), patients without comorbidities (patients with comorbidities = HR 4.8; C.I. 95% 1.1–20.6; P = 0.033), and patients affected by a WDT-B, according to WHO classification (WDT-UB = HR 25.3; C.I. 95% 2.3–280; P = 0.008, WDC = HR 45.6; C.I. 95% 4.1–500; P = 0.002) (Table 3).

5. Discussion

Despite a considerable amount of research, our understanding of the natural history and predictors of survival of the PETs remains incomplete. However, it is well known that PETs are rather slow-growing tumors and they have a biological behavior less aggressive than pancreatic adenocarcinoma [1] with a 5-year survival ranging from 59.3% [12] to 79.5% [8]. Surgical R0 resection is the only potential curative treatment for patients affected by PETs. However, a small percentage of patients died during follow-up and the recurrence rate in these patients ranged from 24.5% to 36.3% [11]. Thus, the long-term survival seems to be related with

### Table 2: Univariate analysis of factors influencing overall survival in the 74 patients who underwent R0 pancreatic resection for well-differentiated pancreatic endocrine tumors.

| Variables               | Survival (months, mean ± SE) | P value |
|-------------------------|------------------------------|---------|
| Sex                     |                              |         |
| M                       | 235 ± 27                     | 0.080   |
| F                       | 302 ± 19                     |         |
| Age                     |                              |         |
| <55 years               | 307 ± 15                     | 0.010   |
| ≥55 years               | 192 ± 25                     |         |
| Comorbidity             |                              |         |
| None                    | 290 ± 17                     | 0.065   |
| One or more             | 155 ± 21                     |         |
| Symptoms                |                              |         |
| No                      | 177 ± 22                     | 0.794   |
| Yes                     | 273 ± 18                     |         |
| Hormonal status         |                              |         |
| Nonfunctioning          | 262 ± 25                     | 0.430   |
| Insulinoma              | 268 ± 17                     |         |
| Others                  | 221 ± 50                     |         |
| MEN-1                   |                              |         |
| No                      | 268 ± 17                     | 0.646   |
| Yes                     | 253 ± 31                     |         |
| Size of tumors          |                              |         |
| <2 cm                   | 236 ± 23                     | 0.529   |
| 2–4 cm                  | 300 ± 23                     |         |
| >4 cm                   | 247 ± 36                     |         |
| Lymph node status       |                              |         |
| N0                      | 277 ± 21                     | 0.966   |
| N1                      | 243 ± 38                     |         |
| Nx                      | 129 ± 15                     |         |
| Type of resection       |                              |         |
| Typical                 | 272 ± 21                     | 0.836   |
| Atypical                | 270 ± 29                     |         |
| WHO classification      |                              |         |
| WDT-B                   | 280 ± 15                     | 0.080   |
| WDT-UB                  | 265 ± 34                     |         |
| WDC                     | 235 ± 31                     |         |
| TNM stage*              |                              |         |
| I                       | 241 ± 24                     |         |
| II                      | 303 ± 25                     | 0.462   |
| III                     | 229 ± 35                     |         |

SE: standard error; WDT-B: well-differentiated tumor-benign; WDT-UB: well-differentiated tumor-uncertain behaviour; WDC: well-differentiated carcinoma.
*TNM-ENETS stage system modified according to Scarpa et al. [5].
prognostic factors: age, sex, functional status of the tumor, pancreatic resection, the presence or absence of cancer at the surgical margin, tumor location, tumor size, lymph nodes involvement, distant metastases, grade of the tumor, and TNM stage were the factors more frequently related to long-term survival in patients affected by PETs [6–12]. Finally, Bilimoria et al. [12] reported the prognostic score predicting survival after resection of PETs.

WHO classification distinguished three groups of PETs: well-differentiated tumor (benign or with uncertain behavior), well-differentiated carcinoma, and poorly differentiated carcinoma. Several studies have suggested its prognostic significance and in particular they emphasize that well-differentiated tumors (benign, uncertain, and carcinoma) have a better long-term survival than poorly differentiated [7, 8]. To our knowledge, our study represents the first research of prognostic factors related to long-term survival in patients affected by well-differentiated tumors (benign, uncertain, and carcinoma) who underwent R0 pancreatic resection. First of all, it is underlined that the mean follow-up period was rather long (about 10 years) and the size sample was sufficient. Second, we reported that 5–10-year overall survival was excellent (90.9% and 79.1%, resp.), the recurrences rate was 18.9% with a mean time of 10-year overall survival was excellent (90.9% and 79.1%, resp.). Second, mainly patients factors are related to a better long-term survival in patients affected by well-differentiated PETs who underwent R0 pancreatic resection, confirming the indolent biologic behavior of these tumors; third, WHO classification is a very useful prognostic tool for well-differentiated PETs.

Table 3: Multivariate analysis of factors influencing overall survival in the 74 patients who underwent R0 pancreatic resection for well-differentiated pancreatic endocrine tumors.

| Variables         | HR (C.I. 95%) | P value |
|-------------------|---------------|---------|
| Sex               |               |         |
| M                 | 1.0           | 0.006   |
| F                 | 0.2 (0.4–0.6) |         |
| Comorbidity       |               |         |
| None              | 1.0           | 0.033   |
| One or more       | 4.8 (1.1–20.6)|         |
| WHO classification |               |         |
| WDT-B             | 1.0           |         |
| WDT-UB            | 25.3 (2.3–280)| 0.008   |
| WDEC              | 45.6 (4.1–500)| 0.002   |

WDT-B: well-differentiated tumor-benign; WDT-UB: well-differentiated tumor-uncertain behaviour; WDEC: well-differentiated carcinomas.

In conclusion, our study suggests, first, that R0 pancreatic resection of well-differentiated PETs is the treatment of choice because of its good long-term results; second, mainly patients factors are related to a better long-term survival in patients affected by well-differentiated PETs who underwent R0 pancreatic resection, confirming the indolent biologic behavior of these tumors; third, WHO classification is a very useful prognostic tool for well-differentiated PETs.

References

[1] K. Y. Bilimoria, J. S. Tomlinson, R. P. Merkow et al., “Clinicopathologic features and treatment trends of pancreatic neuroendocrine tumors: Analysis of 9,821 patients,” Journal of Gastrointestinal Surgery, vol. 11, no. 11, pp. 1460–1469, 2007.
[2] E. Solcia, G. Kloppel, and L. Sobin, Histological Typing of Endocrine Tumours, World Health Organization International Histological classification of Tumours, Springer, Berlin, Germany, 2nd edition, 2000.
[3] J. Y. Scoazec and A. Couvelard, “The new WHO classification of digestive neuroendocrine tumors,” Annales de Pathologie, vol. 31, no. 2, pp. 88–92, 2011.
[4] G. Rindi, G. Kloppel, H. Alhman et al., “TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system,” Virchows Archiv, vol. 449, no. 4, pp. 395–401, 2006.
[5] A. Scarpa, W. Mantovani, P. Capelli et al., “Pancreatic endocrine tumors: Improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients,” Modern Pathology, vol. 23, no. 6, pp. 824–833, 2010.
[6] P. Tomassetti, D. Campana, L. Piscitelli et al., “Endocrine pancreatic tumors: factors correlated with survival,” Annals of Oncology, vol. 16, no. 11, pp. 1806–1810, 2005.
[7] L. Fischer, J. Kleeff, I. Esposito et al., “Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas,” British Journal of Surgery, vol. 95, no. 5, pp. 627–635, 2008.
[8] R. Casadei, C. Ricci, R. Pezzilli et al., “Value of both WHO and TNM classification systems for patients with pancreatic endocrine tumors: results of a single-center series,” World Journal of Surgery, vol. 33, no. 11, pp. 2458–2463, 2009.
[9] R. Casadei, C. Ricci, D. Rega et al., “Pancreatic endocrine tumors less than 4 cm in diameter: resect or enucleate? A single-center experience,” Pancreas, vol. 39, no. 6, pp. 825–828, 2010.
[10] T. Franko, W. Feng, L. Yip, E. Genovese, and A. J. Moser, “Non-functional neuroendocrine carcinoma of the pancreas: Incidence, tumor biology, and outcomes in 2,158 patients,” Journal of Gastrointestinal Surgery, vol. 14, no. 3, pp. 541–548, 2010.
[11] R. Casadei, C. Ricci, R. Pezzilli et al., “Are there prognostic factors related to recurrence in pancreatic endocrine tumors?” Pancreatology, vol. 10, no. 1, pp. 33–38, 2010.

[12] K. Y. Bilimoria, M. S. Talamonti, J. S. Tomlinson et al., “Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients,” Annals of surgery, vol. 247, no. 3, pp. 490–500, 2008.
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