Endocrine pancreatic tumors: factors correlated with survival

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Background: The aim of this study was to evaluate the survival rate of patients with endocrine tumors of the pancreas, functioning or non-functioning, associated or not with MEN 1 syndrome.

Patients and methods: Eighty-three patients with pancreatic endocrine tumors diagnosed in our department from 1978 to 2003 were studied.

Results: The study included 37 men (44.6%) and 46 women (55.4%). The median age of patients at diagnosis was 55 years (range 19–81 years). Fifty-two patients (62.7%) had non-functioning endocrine tumors, 16 (19.3%) had functioning endocrine tumors and 15 (18.1%) had MEN 1 disease with pancreatic involvement. Twenty-seven patients (32.5%) had liver metastases at the time of diagnosis, involvement of the lymph nodes was found in 47 out of 79 patients (59.5%). Forty patients (48.2%) had radical surgery, 20 (24.1%) had palliative surgery and 53 were treated medically. The survival rate was significantly related to the presence of metastases, lymph node involvement, and the type of tumor and treatment.

Conclusions: Tumor resection, the absence of liver and lymph node metastases, and the presence of MEN 1 syndrome are related to a better survival rate. Radical surgery continues to have a central role in the therapeutic approach to endocrine tumors of the pancreas.

Key words: endocrine pancreatic tumor, gastrinoma, multiple endocrine neoplasia, octreotide, surgical procedure

Introduction

Pancreatic endocrine tumors (PETs) are a heterogenous group of rare neoplasms, occurring in fewer than one in 100 000 people per year [1–3]. Pancreatic adenocarcinomas are much more common than their endocrine counterparts, with a ratio of pancreatic adenocarcinomas to PETs of approximately 125:1 [4]. These tumors have attracted considerable attention in recent years, both because they are relatively easy to palliate and because they demonstrate the chronic effect of the particular hormone whose level is elevated. In about 10%–48% of cases, the tumor is not associated with obvious signs or symptoms of hormone hypersecretion; these are called non-functioning tumors [5–7]. Surgery is generally considered the treatment of choice and, for patients with localized disease, it can be curative. However, in patients with metastatic disease, the role of surgery is not clearly established. Moreover, the treatment is particularly controversial in patients affected by MEN-1 with pancreatic involvement; hence, other therapies should also be considered [8, 9]. Pharmacological therapy, e.g. with proton pump inhibitors (PPIs) and somatostatin analogs, has dramatically improved symptom control, and radiolabeled somatostatin analogs offer targeted therapy for metastatic or inoperable disease [9].

The aim of this study was to evaluate the survival rate of patients with endocrine tumors of the pancreas, functioning or non-functioning, as well as associated or not with MEN 1 syndrome. We also evaluated which clinical, radiological and histological variables are associated with the survival rate of these patients. Finally, we evaluated which of the different treatment modalities are associated with the survival rate of patients with pancreatic endocrine tumors.

Patients and methods

This study included a total of 83 consecutive patients having endocrine tumors of the pancreas, admitted to our unit from 1978 to 2003. All patients underwent physical examination, laboratory and radiological investigations. To localize and stage the tumor, all patients underwent ultrasonography (US) and computed tomography (CT) and, in addition, some patients also underwent endoscopic ultrasonography (EUS) and magnetic resonance (MR). All had histopathologic confirmation of endocrine tumors. Ki-67 determination was performed only in the last 29 patients studied; it was not performed earlier because it was not available in our department. Endocrine tumors were classified as functioning on the basis of clinical symptoms of hormonal excess associated with increased serum peptide levels. Tumors without clinical symptoms were classified as non-functioning. In particular, in gastrinoma patients, we evaluated basal gastrin levels associated with basal acid output (BAO) and, when necessary to confirm the diagnosis, a secretin test was performed. In patients with insulinomas, the diagnosis was carried out
using plasma determination of insulin, C-peptide eventually associated with fasting test.

The patients enrolled in the study underwent a clinical check-up and abdominal US every 3 months. A CT scan was performed in all patients every 6 months during the first year after diagnosis and every 12 months thereafter. Surgical and medical procedures and survival rates were recorded in the follow-up period.

Statistics

Mean, median, standard deviation, range and frequencies were used as descriptive statistics. Survival curves were computed by using the Kaplan–Meier method, whereas the Mantel–Cox model was applied in order to identify factors significantly related to survival; the hazard ratios (HR), together with their respective 95% confidence intervals (CI), were also computed. The Wilcoxon signed ranks test was also applied. Statistical significance was defined as two-tailed P values less than 0.05. Statistical analyses were performed by means of the SPSS (Version 8.0 for Windows) statistical package.

Results

There were 37 men (44.6%) and 46 women (55.4%). The median age of patients at diagnosis was 55 years (range 19–81 years) and the median age at their last observation was 60 years (range 29–82 years); the median follow-up period was 30 months (range 3–264 months). Fifty-two patients (62.7%) had non-functioning tumors, 16 patients (19.3%) had functioning tumors (seven gastrinomas, four insulinomas, two VIPomas, two somatostatinomas, one glucagonoma) and 15 patients (18.1%) were affected by MEN 1 with pancreatic involvement (11 non-functioning tumors, three insulinomas, one gastrinoma). The tumor was localized in the head of the pancreas in 31 patients (37.3%), in the body in 24 patients (28.9%), in the tail in 21 patients (25.3%) and, in seven patients (8.4%), the tumor was diffuse throughout the pancreas. In Table 1, we report the size of tumors taken as a whole and also the size of each subtype. No significant differences in the size of the tumor were found between radiological and surgical exploration. Twenty-seven patients (32.5%) had liver metastases at diagnosis and 43 patients (51.8%) developed metastases during the follow-up period. Involvement of lymph nodes was found in 47 out of 79 patients (59.5%); in four patients, it was not possible to obtain these data. The median Ki-67 evaluated on 29 histological specimens was 2.9% (range 1.0%–84.1%). Forty patients (48.2%) had radical surgery, 20 (24.1%) had palliative surgery and 53 (63.8%) were treated medically. Of the latter, 53 underwent medical treatment with somatostatin analogues (63.8%), 10 had chemotherapy (12%), nine chemoembolization (10.8%) and six had treatment with alpha interferon (7.2%). None of the patients underwent neoadjuvant therapy.

Forty-nine patients (59.0%) were still alive at the time of the study; the median survival time was 90 months (95% CI 29–151 months) and the 5-year survival rate was 55.3% (Figure 1). Table 2 reports the effect of various clinical, radiological and histological findings on the survival. The survival rate was significantly related to the presence of liver metastases at diagnosis ($P <0.001$) (Figure 2), the presence of lymph node involvement ($P = 0.001$) (Figure 3), the type of tumor (overall $P = 0.033$; functioning versus MEN $P = 0.010$; non-functioning versus MEN $P = 0.010$; not operated versus radical surgery $P = 0.001$; palliative surgery versus radical surgery $P = 0.001$; not operated versus palliative surgery $P = 0.026$; treatment with somatostatin analogues $P = 0.072$).

Table 1. Median size of the endocrine tumors of the pancreas at imaging techniques and at surgery. Data are reported as median and range (in brackets)

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Size at imaging (cm)</th>
<th>Size at surgery (cm)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-functioning</td>
<td>4.1 (1.3–11.3)</td>
<td>4.5 (1.0–13.0)</td>
<td>0.120</td>
</tr>
<tr>
<td>Functioning</td>
<td>5.4 (1.4–8.0)</td>
<td>3.5 (1.8–5.5)</td>
<td>0.276</td>
</tr>
<tr>
<td>MEN 1</td>
<td>3.8 (1.0–10.0)</td>
<td>5.5 (1.5–10.0)</td>
<td>0.599</td>
</tr>
<tr>
<td>All endocrine tumors</td>
<td>4.1 (1.0–11.3)</td>
<td>5.0 (1.0–13.0)</td>
<td>0.403</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative survival (Kaplan–Meier) among 83 patients with pancreatic endocrine tumors.

Table 2. Effect of various clinical, radiological and histological findings on the survival in the 83 patients with endocrine tumors

<table>
<thead>
<tr>
<th>Effect</th>
<th>HR</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functioning versus MEN 1</td>
<td>7.63</td>
<td>1.64–35.51</td>
<td>0.010</td>
</tr>
<tr>
<td>Non-functioning versus MEN 1</td>
<td>4.65</td>
<td>1.07–20.13</td>
<td>0.040</td>
</tr>
<tr>
<td>Functioning versus non-functioning</td>
<td>0.228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of treatment</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not operated versus radical surgery</td>
<td>5.20</td>
<td>2.12–12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palliative surgery versus radical surgery</td>
<td>4.29</td>
<td>1.76–10.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Not operated versus palliative surgery</td>
<td>0.626</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with somatostatin analogues</td>
<td>1.17</td>
<td>0.56–2.46</td>
<td>0.672</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval.
MEN $P = 0.040$) (Figure 4) and the type of treatment (overall $P < 0.001$; not operated versus radical surgery: $P < 0.001$; palliative surgery versus radical surgery $P = 0.001$) (Figure 5). On the other hand, the survival rate was not significantly related to sex ($P = 0.151$), the patient’s age ($P = 0.965$), the localization of the tumor ($P = 0.646$), the size of the tumor both at imaging techniques ($P = 0.222$) and at surgery ($P = 0.325$), Ki-67 determination ($P = 0.341$) and treatment with somatostatin analogues ($P = 0.672$).

**Discussion**

The main aim of this study was to determine which clinical, radiological and histological variables are associated with survival by examining a large number of patients coming from a single center and having this disease. Regarding gender, we found a slight prevalence of women compared to men; this finding has been recently reported in a Multicenter Italian Study [10]. The average age at the time of diagnosis was 55 years, which is similar to that reported in previous studies [10, 11]. In our series, the percentage of patients with non-functioning tumors of the pancreas (62.7%) was higher than that referred to in the literature in which the percentage varies between 10% and 58% [7, 12, 13]. This difference may be explained by a more accurate diagnosis of pancreatic endocrine tumors according to the WHO classification [14]. The median dimension of the tumors at imaging (4.1 cm) and at surgery (5.0 cm) overlaps those of other authors [13, 15]. Specifically, in the present study, the median dimension of functioning pancreatic tumors at imaging (5.4 cm) was superior to that reported by other authors [15–17] but was in agreement with what was recently found by Chu et al. [13]. Furthermore, in our series, we did not find any significant differences in survival between patients with functioning and those with non-functioning endocrine pancreatic tumors. There is some controversy with regard to these data in the literature. Several reports have suggested a lower 5-year survival rate in patients with non-functioning tumors than in those with functioning tumors [7, 15, 18]. On the contrary, other authors found no significant differences in the survival rate between these two groups [13, 16]. These data can be explained by the wide use of PPIs, which have been available to us since the 1980s for compassionate use and which reduce the gastric acid hypersecretion due to ZES, thus delaying the diagnosis of a gastrinoma which is already metastatic when first observed [19]. It should always be kept in mind that multiple factors play a role in the evaluation of
of the survival rate and, in agreement with recent reports, functioning and non-functioning tumors should be considered equally aggressive with similar prognoses [13, 16, 17]. Patients with MEN 1 syndrome associated with pancreatic involvement showed a better survival rate than patients with sporadic pancreatic tumors. These data are not related to an earlier diagnosis, to the dimension of the tumors at diagnosis or to the type of neoplasia. In fact, according to the literature, in our series endocrine tumors of the pancreas associated with MEN 1 were mainly non-functioning [20]. The higher survival rate in these patients may be explained by the indolent clinical course of this disease [18].

In our study, the 5-year survival rate was 55.3%, which is similar to that reported by other authors (between 35% and 60%) [10, 21–23].

In our experience, sex, age of patients and localization of the tumor were not significantly related to survival [10, 13]; size was not related, this finding being in contrast with other reports at least concerning non-functioning pancreatic tumors [10, 24, 25]. One possible explanation is that we could not find an accurate definition of the tumor size that unequivocally affects patient's survival in the literature. As a rule, 3–4 cm diameter is considered the accepted limit, but there are controversial data [24, 26–28]. Moreover, in a recent study in patients with MEN-1, Lowney et al., in agreement with our results, could not find a correlation between the size of the primary tumor and its metastatic potential [29, 30]. In our opinion, this discrepancy may be explained by the heterogeneity of the tumors grouped together as NETs. Due to the long period of time considered, it was not possible to separate well- and poorly-differentiated tumors according to the histopathological classification proposed by WHO in 2000. For this reason a careful study of the natural history of each of these neoplasms is required in order to define better the relationship between the features of the tumor and patient survival.

Moreover, in our patients, we could not find a significant relationship between survival and the Ki-67 proliferative index determination which is considered by several authors as a reliable prognostic factor [26, 27, 31]. We determined the Ki-67 index only in the last 29 patients studied. The limited number of determinations can affect the relevance of statistical significance.

Regarding patients with metastases, survival was also significantly better in patients without metastases at diagnosis compared with those with metastases at diagnosis and this finding is in agreement with other recent reports. At present, metastases, and in particular liver metastases, are considered the factors that are more highly correlated with the survival rate [10, 13, 24].

The overall survival rate in patients who underwent radical surgery was significantly better than in those not operated on and in patients who underwent palliative surgery; our data agree with those of other authors [10, 17, 21, 24]. In addition, patients who underwent palliative surgery did not show a better survival rate with respect to patients not operated on. Moreover, recent reports suggest that conventional contraindications to surgical resection, such as nodal or distant metastases, the hallmarks of advanced malignancy, should be redefined, giving further support to surgical options [32].

Regarding medical treatment, available data did not show any statistical significance between patients treated with somatostatin analogues and those not treated. However, we have noticed a positive trend concerning survival in treated patients. It is important to stress that medical treatment with somatostatin analogues, available since the 1990s, has produced a rapid disappearance of symptoms due to hormonal hypersecretion in patients with functioning endocrine tumors and an improvement in the quality of life in those with non-functioning ones.

In conclusion, we can suggest that radical surgery continues to have a central role in the therapeutic approach to NETs of the pancreas. The crucial point is an early diagnosis that allows radical surgery when the tumor has not yet metastasized. Of course, our data cannot be proposed as a prognostic model for the treatment of endocrine tumors of the pancreas; we only report our experience on this topic even if we believe that a wider approach to surgical criteria can give better opportunities to patients.

Medical treatment has a precise role in functioning endocrine tumors while, as far as non-functioning tumors are concerned, further studies on a larger number of patients are necessary.

References