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Comparison of phenotypes and outcomes following resection of incidental versus symptomatic pancreatic neuroendocrine tumors

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Disclosure statement

The authors declare no conflicts of interest.

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Abstract

Background/Aim

Fifty to 70 percent of pancreatic neuroendocrine tumors are diagnosed incidentally. The objective of this study is to compare the phenotype and oncological outcomes of incidental versus symptomatic pancreatic neuroendocrine tumors.

Methods

A retrospective study was conducted identifying all incidental and symptomatic tumors resected between 2000 and 2019. Baseline characteristics, symptoms, operative variables and pathological stage were all recorded. In both groups, patterns of recurrence and overall and disease-free survival were analyzed.

Results

Fifty-one incidental and 45 symptomatic pancreatic tumor resections were performed. Symptomatic tumors were more frequent in women (29 vs 17; p=0.005), in younger patients (median years; 50 vs 58; p=0.012) and were detected at a more advanced stage (p=0.027).

There were no differences in location and most resections (n= 49; 51%) were performed laparoscopically. There were no operative mortalities and 17 (17.7%) severe complications (≥IIIb on the Clavien-Dindo classification) were recorded with no differences between the two groups. With a median follow-up of 64.4 months (range 13.5 – 90), overall survival at 5 and 10 years was 89.7% and 72.8% for the non-incidental tumors, and 80.9% and 54.6% for the incidental tumors (p=ns). Disease-free survival in both groups (excluding M1a) was 71.2% and 47.5%, and 93.7% and 78.1%, respectively (p= ns).

Conclusions

Symptomatic tumors are more frequent in women and present at higher pathological stages. There were no significant differences in overall and disease-free survival between the two groups. Resection of incidental tumors ≥1.5 – 2 cm seems advisable, although each case should assessed on an individual basis.

Keywords: Pancreas. Neuroendocrine tumor. Surgery. Incidental. Outcomes.

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INTRODUCTION

"Neuroendocrine tumors of the pancreas (PanNETs) comprise a very heterogeneous group of neoplasias whose incidence has very significantly increased over the last two decades (0.45 cases per 100.000 in 2008 to 0.82 per 100.000 in 2012) (1, 2).

Although in 2019 the World Health Organization updated the classification of PanNETs into three grades depending on the Ki-67 proliferation index and the mitotic index, at present controversy surrounds the appropriate treatment of non-symptomatic tumors of < 2 cm in diameter(1, 3).

With the more widespread use of more sensitive imaging techniques including computed tomography (CT), nuclear magnetic resonance imaging(MRI), 50-70% of such tumors are diagnosed incidentally, which further complicates the decisions on therapeutic choices in tumors of < 2 cm (1–6).

The primary objective of the study was to analyze and compare oncologic outcomes – disease-free survival, patterns of recurrence – in resected tumors diagnosed incidentally and symptomatic tumors.

The secondary objectives were to analyze the differences in the clinical and histologic phenotypes between both groups as well as operative morbidity and mortality."

MATERIAL AND METHODS

Study design

A retrospective study of all pancreatic resections for pancreatic neuroendocrine tumors (PanNETs) performed between 2000 and 2019 was carried out. The study was approved by the center's Research Ethics Committee (ref 2020.255) and was conducted following the STROBE norms and the latest version of the Declaration of Helsinki.

Patient selection and data collection

From the center's prospective database, all pancreatic resections performed for symptomatic and incidentally detected pancreatic tumors were identified. Incidental tumors were defined as those diagnosed casually as a result of abdominal radiological

tests in the absence of digestive or hormonal symptoms. Two authors (JAC, LHP) confirmed the incidental nature of the tumors in all cases.

Prior to surgery, all patients had undergone one or two imaging tests: ultrasound (US), CT or MRI. In most cases a preoperative cytological study was performed using endoscopic ultrasound- (EUS) or CT-guided fine needle aspiration (FNA).

As from 2002, enucleations and central and distal pancreatectomies were performed laparoscopically using a technique as previously described(7, 8) . In the distal pancreatectomies efforts were made to preserve the spleen and the splenic vessels using the technique developed by Kimura(9). In all cases, intraoperative ultrasound scanning was used to evaluate the distance of the tumor from the main pancreatic duct and its relation to the splenic vessels.

Two authors (JAC, LHP) recorded all postoperative complications and rated their severity using the Clavien-Dindo classification(10). All complications equal or greater than IIIb were considered severe. Pancreatic fistula, postoperative bleeding and delay in gastric emptying were all defined according to the norms of the International Study group for pancreatic surgery (ISGPS)(11–13). A minimum margin width of >1 mm was defined as an R0 margin; an R1 was designated as the presence of tumor at the margin or a minimum margin length of <1 mm.

The anatomical and pathological analyses were performed according to the criteria of the World Health Organization and pathology staging was established using the European neuroendocrine Tumor Society (ENETS) criteria (14–16).

Other data collected included age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), American Society of Anesthesiologists physical status classification (ASA)(17) , presence of diabetes according to the American Diabetes Association (ADA(18)), location (head, body or tail), size of tumor, type of surgery (open/laparoscopic), and duration of surgery and hospital stay.

Study outcomes

Overall survival (OS) was defined as the time between surgery and time of death or last contact with the patient. Disease-free survival (DFS) (excluding M1a patients; n=16) was defined as the time elapsing up to the first tumor recurrence (local or distant), last contact, or death of the patient from any cause. Local recurrence was defined as radiological evidence of recurrent disease in the surgical bed or in local/regional nodes. Distant recurrence was defined as radiological evidence of relapse outside these areas and was stratified by the organ of recurrence.

Postoperative mortality was defined death as a result of any cause-in-hospital-or within 90 days following the resection.

Statistical analysis

Data were analyzed using the R programming language (https://www.r-project.org/). Categorical values are reported as total counts and percentages and were compared using Pearson's Chi Squared test. Continuous variables are expressed as medians with interquartile ranges (IQR). Normality was assessed using the Shapiro-Wilk test and comparisons made using the Mann-Whitney U test. For these exploratory tests, a p value <0.05 was considered significant. Survival data were compared using Kaplan-Meier curves and the log rank test.

RESULTS

During the study period, 96 pancreatectomies were performed for PanNETs. The cohort comprised 46 females (47.9%) and 50 males (52%), with a median age and BMI of 55 (46-64) and 26.5 (23.1-29.1) respectively Fifty-one (53.1%) were diagnosed incidentally and 45 (46.8%) were symptomatic. Of the 45 non-incidental tumors 19 (42.2%) were functional, 10 insulinomas (22.2%), 6 gastrinomas (13.3%), 2 glucagonomas (4.4%) and one VIPoma (2.2%), while the remaining 26 were symptomatic and non-functional.

Baseline characteristics, operative variables and pathological stages are shown in Table 1. Compared to patients with incidental tumors, the proportion of women was higher

(64.4% vs 33.3%; p= 0.005) and age was lower (50 years [39-62] vs 58 years [52-67]; p= 0-012) among patients with symptomatic tumors.

The most frequent location in both groups was the tail of the pancreas, which explains why most of the resections (n=49, 51%) were performed laparoscopically. In 53.4% (n=25) of the distal pancreatectomies the spleen and splenic vessels were conserved (58.6% incidental vs 47% non-incidental). Thirteen (13.5%) enucleations (5 laparoscopic), 17 (17.7%) pancreato duodenectomies, 11 (11.5%) corporocaudal pancreatectomies, 9 (9.4%) central pancreatectomies (8 laparoscopic) and 46 (47.9%) distal pancreatectomies (36 laparoscopic; of which 3l (53.4%) involved sparing of the thymus and splenic vessels) were performed.

In neither group were there any cases of conversion to open surgery. Table 2 summarizes the postoperative complications following the Clavien-Dindo classification. There were no differences in the incidence or specific type of complication across the two groups, including complications such as pancreatic fistula, delayed gastric emptying, postoperative bleeding. Hospital stay averaged 7 days in length (range 5-12).

Seventeen (17.7%) severe complications (Clavien-Dindo ≥IIIb) were recorded but no hospital deaths

“With regard to pathologic stage, symptomatic (non-incidental) tumors presented at more advanced stages than incidental tumors (p=0.02)- Of the incidental tumors (n=51), 25 were stage I, 13 IIa, 7 IIIb and 5 stage IV. In contrast, for the symptomatic tumors (n=45), 15 were stage I, 7 IIa, 3 IIb, 4 IIIb and 12 stage IV, figure 1. **The median maximum diameter of the tumor (mm) was similar in both groups - 20 (range 13-25) vs 20 (range** 13-40); p=0.412

With a median follow-up of 64.4 months (range 13.5-90), a higher incidence of liver metastases was observed in the non-incidental tumors (7.1% vs 23.7%; p= 0.039).

Overall survival for the entire cohort at 5 and 10 years was 89.7% and 72.8% in patients with non-incidental tumors, and 80.9% and 54.6% in incidental cases, with no statistically significant differences (p=0.56), figure 2A. Disease-free survival at 5 and 10 years was 71.2% and 47.5% for the non-incidental group, and 93.7% and 78.1% for the incidental group respectively (p=0.079), figure 2B.

DISCUSSION

The increasingly use of more sensitive cross-sectioned imaging techniques (CT, MRI) has led to a great increase in the diagnosis of PanNETs, 50-70% of which are diagnosed incidentally(1–5).

For this reason, we compared the surgical and oncological findings for neuroendocrine tumors diagnosed incidentally with those of symptomatic tumors. In our study we found that incidental tumors presented in older patients (p=0.01) and at significantly less advanced clinical stages (p=0.027; figure 1) than symptomatic tumors, a finding that is in line with several other studies(19, 20).

The laparoscopic procedures were performed by the same surgeon (FR), who has extensive experience in laparoscopic hepato-biliary-pancreatic surgery, which explains why there were no conversions to open surgery when the incidence of conversions is around 30-40% in central pancreatectomies and 20% in distal pancreatectomies (21)

In our series more laparoscopic resections were performed in incidental tumors because most tumors were located in the body and tail of the pancreas. This could reflect a surgical bias towards more readily treating lesions located in the tail of the pancreas, as distal pancreatectomies cause less morbidity than central pancreatectomies or duodenopancreatectomies(22, 23)

In our analysis we found no significant differences in overall 5- and 10-year survival even though the symptomatic tumors presented more advanced pathological stages, which is consistent with findings from recent series in which the resection of incidental tumors larger than 1.5 cm is recommended whereas patients with tumors <1.5 cm are

identified as candidates for surveillance(1, 8, 24, 25) . Interestingly, among patients who relapsed, the pattern of recurrence was similar comparing patients with incidental and symptomatic tumors.

There are many explanations for these findings. Firstly, 46.9% of the symptomatic tumors were functional – that is, producing hormones leading to hypoglycemia, diabetes, and ulcer syndrome – and these were diagnosed earlier than incidental tumors. We are aware that 10 of the 19 functional tumors were insulinomas, which have better prognosis, although 9 of them have an aggressive behavior (6 gastrinomas, 2 glucagonomas and 1 VIPoma)(1, 15)

Furthermore, incidental tumors grow more slowly with a greater latency period, a phenomenon known as the length time bias which leads to overestimations of survival.(26, 27)

Several recent studies have confirmed that in tumors with a diameter of between 1.5 and 2 cm, 3- and 5-year survival is significantly greater in patients who undergo resection as compared to those merely being observed and monitored.(24, 28).

“Given the heterogeneity in the biologic behavior of neuroendocrine tumors of the pancreas, some discrepancies exist in the clinical guidelines regarding what therapeutic measures to adopt in asymptomatic (incidental) tumors of <2 cm in diameter (1.5-2 cm) (1, 3). The ENETS and NCCN guidelines recommend watchful waiting while the North American Neuroendocrine Tumor Society (NANETS) and other authors recommend individualizing treatment in tumors between 1-2 cm depending on various factors such as age of the patient, location of the tumor, surgical experience of the center (low morbidity and minimum mortality), patient preference and the possibility of ensuring exhaustive follow-up for at least 5 years (1, 4, 15, 29).

Currently, ENETS is conducting a prospective study of 1000 patients with tumors smaller than 2 cm in diameter comparing those undergoing surgery with those who receive only observation and follow-up (NCT 03084770, ASPEN) (30). The study is in the patient recruiting phase and is expected to complete this phase in 2023.

Limitations

We are aware of the limitations of the study given its retrospective nature even though the data were collected prospectively and the period of study was extensive. Due to missing KI-67 index on several patients, we decided not to include this variable in the analysis, although ENETS grading and staging system was utilized.

As a control group matched for observation and follow-up was not available, we cannot provide a categorical answer to the controversial issue regarding what therapy to follow for tumors smaller than 1 cm which are discovered incidentally.

CONCLUSIONS

Symptomatic pancreatic neuroendocrine tumors are more frequent in women, younger patients and present higher pathological stages than incidental tumors.

Surgical resection of incidental pancreatic neuroendocrine tumors larger than 1.5 cm yields excellent results. Survival and patterns of recurrence are similar to those of symptomatic tumors.

Given the lack of prospective comparative studies, treatment for tumors smaller than 1.5 cm and which are asymptomatic continues to be a dilemma. Incidental tumors larger than 1.5 cm should be resected in centers with the appropriate experience, ideally using laparoscopic techniques.

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The Spanish Journal of Gastroenterology

TABLE 1. Comparison of clinical, surgical details and tumor characteristics.

Characteristics	Overall n=96	Incidental n=51	Non-incidental n=45	P-value
Sex (women), n (%)	46 (47.9)	17 (33.3)	29 (64.4)	0.005
Age, median (IQR)	55 (46-64)	58 (52-67)	50 (39-62)	0.012
Diabetes, n (%)	14 (14.6)	9 (17.6)	5 (11.1)	0.538
BMI, median (IQR)	26.5 (23.1-29.1)	26.8 (23.4-29.1)	25.1 (21.8-29.5)	0.172
ASA class on admission, n (%)				0.374
I (no disturbance)	6 (6.3)	3 (6.1)	3 (6.7)	
II (mild disturbance)	48 (50)	22 (44.9)	26 (57.8)	
III (severe disturbance)	38 (39.6)	24 (48.9)	14 (31.1)	
Missing data	4 (4.2)	2 (3.9)	2(4.4)	
Tumour location, n (%)				0.212
Head/uncinated process	26 (27.1)	10 (19.6)	16 (35.6)	
Body	20 (20.8)	12 (23.5)	8 (17.8)	
Tail	50 (52.1)	29 (56.9)	21 (46.7)	
Surgical procedure, n (%)				0.196
Enucleation	13 (13.5)	5 (9.8)	8 (17.8)	
Pancreatico-duodenectomy	17 (17.7)	6 (11.7)	11 (24.4)	
Corporocaudal pancreatectomy	11 (11.5)	5 (9.8)	6 (13.3)	
Central pancreatectomy	9 (9.4)	6 (11.7)	3 (6.7)	
Distal pancreatectomy	46 (47.9)	29 (56.9)	17 (37.8)	
Splenectomy, n (%)	29 (30.2)	15 (29.4)	14 (31.1)	1
Total hospital stay (days), median (IQR)	7 (12-5)	7 (12-4)	7 (12-5)	0.297
Max diameter of tumour (mm), median (IQR)	20 (13-35)	20 (13-25)	20 (13-40)	0.412
Resection state, n (%)				0.528
R0	76 (79.2)	41 (80.4)	35 (77.8)	
R1	4 (4.2)	1 (1.9)	3 (6.7)	
R2	16 (16.7)	9 (17.6)	7 (15.6)	
Follow up time (months), median (IQR)	43 (13.5-96)	38 (10-73)	61 (24-99)	0.104

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ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

TABLE 2. Comparison of postoperative complications.

Characteristics	Overall n=96	Incidental n=51	Non-incidental n=45	P-value
Clavien-Dindo, n (%)				0.301
<IIIa	79 (82.3)	43 (84.3)	36 (80)	
>IIIb	17 (17.7)	8 (15.7)	9 (20)	
Infection in wound, n (%)	2 (2.1)	1 (1.9)	1 (2.2)	1
Intra-abdominal collection, n (%)	13 (13.5)	8 (15.7)	5 (11.1)	0.723
Delay in emptying, n (%)	5 (5.2)	5 (9.8)	0 (0)	0.09
Degree of fistula, n (%)				0.434
Biochemical leak	1 (1.1)	1 (1.9)	0 (0)	
B	6 (6.3)	3 (5.9)	3 (6.7)	
C	2 (2.1)	2 (3.9)	0 (0)	
Treatment of fistula, n (%)				0.268
Medical	5 (5.2)	2 (3.9)	3 (6.7)	
Endoscopic	1 (1.1)	1 (1.9)	0 (0)	
Surgical	3 (3.1)	3 (5.9)	0 (0)	
Bleeding, n (%)				0.403
Intraluminal	1 (1.1)	0 (0)	1 (2.2)	
Extraluminal	9 (9.4)	6 (11.7)	3 (6.7)	
Degree of bleeding, n (%)				0.403
Moderate	8 (8.3)	4 (7.8)	4 (8.9)	
Severe	2 (2.1)	2 (3.9)	0 (0)	

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FIGURE 1. Comparison ENET staging by incidental or non incidental tumours.

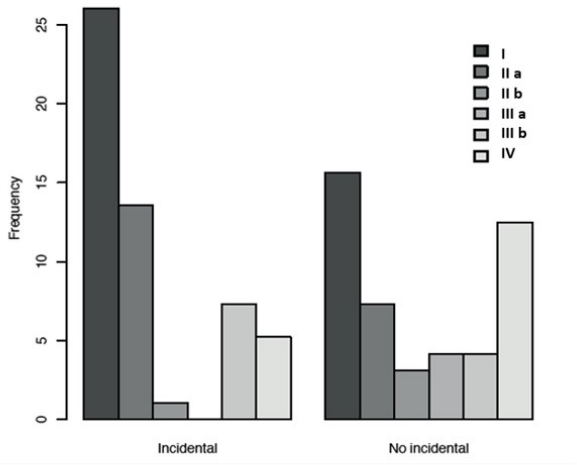

Figure 1. Comparison between Incidental and Non-incidental neuroendocrine tumours, by the European Neuroendocrine Tumor Society (ENETS)

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FIGURE 2. Kaplan-Meier overall survival (A) and disease-free survival curves (B).

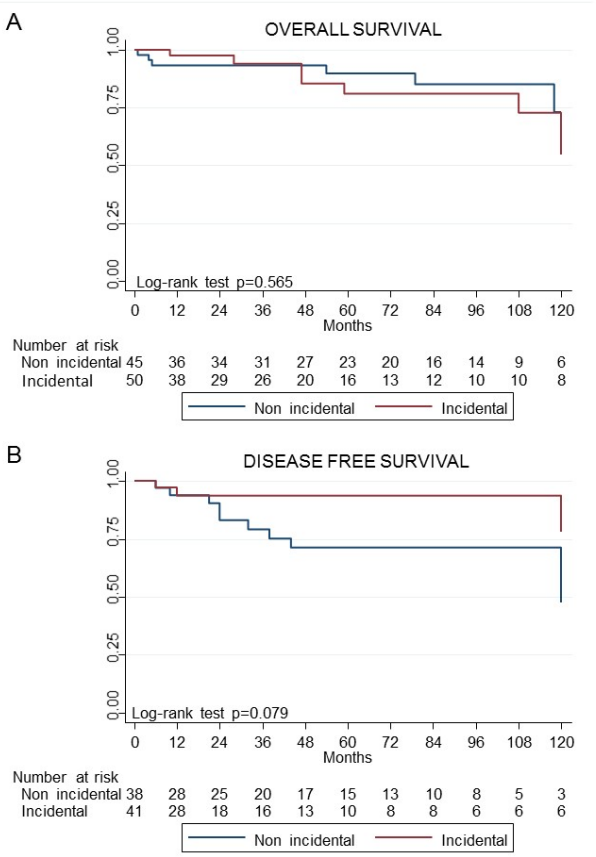

Figure 2. Kaplan-Meier estimates of survival for patients who underwent pancreas resection for pancreatic neuroendocrine tumours, comparing Incidental vs Non-incidental. 2A Overall-survival. 2B Disease-free-survival

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ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Author Contributions

Conceptualization and design LHP, JAC, CEB, FR

Collection and Data Curation L H-P, JAC

Data Analysis and interpretation L H-P, CEB, JAC, FR

Manuscript Draft JAC

Final review and approval of manuscript L H-P, JAC, CEB, FMR, FR

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