1130-0108/2011/103/4/184-190
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid)
Vol. 103. N.° 4, pp. 184-190, 2011

ORIGINAL PAPERS

Pancreatic endocrine tumors or apudomas

Modesto Varas[1], Joan Gornals[1], José María Ponseti[2], Antonio Alastruè[2], Cristina Durán[3], Carlos Llevaria[3], Carlos Ballesta[2], Alberto Díez-Caballero[2] and Vicente Artigas[2]

Unit of [1]Digestive echoendoscopy, [2]General and Digestive Surgery, and [3]Department of Pathology. Centro Médico Teknon. Barcelona, Spain

ABSTRACT

Introduction and objective: pancreatic endocrine tumors (PET) are difficult to diagnose. Their accurate localization using imaging techniques is intended to provide a definite cure. The goal of this retrospective study was to review a PET series from a private institution.

Patients and methods: the medical records of 19 patients with PETs were reviewed, including 4 cases of MEN-1, for a period of 17 years (1994-2010). A database was set up with ten parameters: age, sex, symptoms, imaging techniques, size and location in the pancreas, metastasis, surgery, complications, adjuvant therapies, definite diagnosis, and survival or death.

Results: a total of 19 cases were analyzed. Mean age at presentation was 51 years (range: 26-67 y) (14 males, 5 females), and tumor size was 5 to 80 mm (X: 20 mm). Metastatic disease was present in 37% (7/19). Most underwent the following imaging techniques: ultrasounds, computed tomography (CT) and magnetic resonance imaging (MRI). Fine needle aspiration punction (FNA) was performed for the primary tumor in 4 cases. Non-functioning: 7 cases (37%), insulinoma: 2 cases [1 with possible multiple endocrine neoplasia (MEN)], Zollinger-Ellison syndrome (ZES) from gastrinoma: 5 (3 with MEN-1), glucagonoma: 2 cases, 2 somatostatinomas; carcinoid: 1 case with carcinoide-like syndrome.

Most patients were operated upon: 14/19 (73%). Four (4/14: 28%) has postoperative complications following pancreatectomy: pancreatitis, pseudocyst, and abdominal collections. Some patients received chemotherapy (4), somatostatin (3) and interferon (2) before or after surgery.

Median follow-up was 48 months.

Actuarial survival during the study was 73.6% (14/19).

Conclusions: age was similar to that described in the literature. Males were predominant. Most cases were non-functioning (37%). Most patients underwent surgery (73%) with little morbidity (28%) and an actuarial survival of 73.6% at the time of the study.

Received: 21-06-10.
Accepted: 31-08-10.

Correspondence: Modesto J. Varas. Unidad de Ecoendoscopia Digestiva, Cirugía General y Digestiva. Centro Médico Teknon. C/ Marquesa de Vilallonga 12. 08017 Barcelona, Spain
e-mail: varas@dr.teknon.es

Key words: Functioning pancreatic neuroendocrine tumors (PNET). Insulinoma. Gastrinoma. Zollinger-Ellison syndrome (ZES). Glucagonoma. Somatostatinoma. Vipoma. Carcinoid. Multiple endocrine neoplasia (MEN). Multiple hormonal secretion (MHS). Non-functioning tumors. Endoscopic ultrasonography (EUS). FNAP. Somatostatin. Interferon. Chemotherapy. Pancreatic apudoma.

Varas Modesto, Gornals Joan, Ponseti José María, Alastruè Antonio, Durán Cristina, Llevaria Carlos, Ballesta Carlos, Díez Caballero Alberto, Artigas Vicente. Pancreatic endocrine tumors or apudomas. Rev Esp Enferm Dig 2011; 103: 184-190.

INTRODUCTION

Gastro-entero-pancreatic neuroendocrine tumors (GEPETs) originate in the diffuse endocrine cell system (APUD system); 60-70% are digestive tract carcinoids, and 20-40% are located in the pancreas (PETs).

The incidence of PETs is on the rise as it had been estimated in fewer than 1 case/100,000 (0.2/100,000/year) (1-7) but has been presently reported as 4.4 cases/100,000 population and year, with non-functioning tumors predominating (8). Insulinomas and gastrinomas account for 1 case per million population.

These tumors may be sporadic or associated with multiple endocrine neopasia (MEN) (5). They may be benign or malignant according to the presence of metastasis.

They are categorized as functioning (with specific hormonal syndromes: Zollinger-Ellison syndrome (ZES) or ZES from gastrinoma, etc.) (5), and non-functioning, which are most common (8).

The frequency of non-functioning tumors (NFPETs) is 15 to 75%, reaching 91% in some series (8). Their mean incidence may be around 55-60%.

When functioning (around 40%), these tumors may result in multiple hormone secretion (MHS) or be associated with MEN-1, Von Hippel-Landau disease, Von Recklinghausen disease (neurofibromatosis 1), and tuberous sclerosis (1,5).

In an early series (84 patients with PET) mean age at presentation was 53 years with no clear gender predominance; most were located in the tail of the pancreas (41%) and were malignant (70%). Non-functioning tumors represented 24%, whereas gastrinomas (30%) and insulinomas (27%) were most common. Vipomas, glucagonomas and somatostatinomas were a minority (9).

Relevant series have been subsequently described (10-13) that detail the individual characteristics of these fascinating, uncommon tumor types (5).

Overall survival varies according to tumor type and functional status, stage, and treatment.

OBJECTIVE

The goal of this retrospective research was to review a private institution's series of PET, and to compare it with an updated review of the literature.

PATIENTS AND METHODS

When the matter was theoretically reviewed in 2008 (5) 14 cases were recorded in our site. A data base was set up and the medical records of 19 patients followed up for 17 years at one private institution were retrospectively reviewed (1994-2010). Two patients with MEN-1 had each one child affected.

Demographic parameters were studied by setting up a database with ten parameters (age and sex, symptoms, imaging techniques, size and location in the pancreas, metastasis, surgery, complications, complementary therapies, definite diagnosis, and survival), which were compared to those in the literature.

Mean, median, standard deviation, and percentage values were estimated using specific formulas.

RESULTS

Mean age at presentation was 51 years (range: 26-67 years); 73% (14/19) were males.

Mean tumor size: 20 mm (5-80 mm). They were located in the head of the pancreas: 8 (47%), uncinated process: 1, pancreas body: 3, tail: 5 cases (30%). Nearly one half were located in the head and the other half in the body-tail of the pancreas. Most were non-functioning tumors (37%) in addition to gastrinomas (26%), insulinomas (10%), somatostatinomas (10%), glucagonomas (10%) (1 with MHS), and carcinoids (5%).

Table I. Imaging techniques used in this series of 19 cases

Arteriography: 0/1	
US:	10/12 (83%)
CT:	15/17 (88%)
Octreoscan:	4/5 (80%)
PET-CT:	1/1 (100%)
EUS:	6/6 (100%)
EUS-FNAP:	3/4 (75%)

Imaging techniques used for diagnosis and localization: most cases underwent US/CT/MRI. Octreoscan for five cases and EUS for six, half of which further underwent EUS-FNAP. One underwent PET. One case had an arteriogram performed, which was negative (Table I).

Metastasis: 37% (7/19), most to the liver.

Surgery was performed for 73% of cases without operative mortality.

Morbidity: 28% (two acute pancreatitis cases, one pseudocyst, and two abdominal collections). All complications occurred in pancreatectomized patients. No postoperative complications occurred in two patients (insulinomas) who underwent enucleation.

Median follow-up was 48 m.

Actuarial survival: 73.6%.

Deceased patients presented with obstructive jaundice or had metastasis.

DISCUSSION

Of all GEPETs, 60-70% are digestive tract carcinoids, and 20-40% are located in the pancreas.

In a series (14) of 86 GEPETs seen over 10 years, most were located in the stomach, mean age was 52 years, male:female ratio was 0.87, and 35% were malignant. While women predominate in some series, there is no clear preference for either gender.

Regarding 907 cases in the Spanish national registry for endocrine cancer (15) 55% were carcinoids, 32% PET (20% non-functioning, 8% insulinomas, 4% gastrinomas), with 44% malignancies. Overall 5-year survival was 75.4%. Independent predictors of survival only included stage and Ki 67 index.

In our patients mean age was 51 years, most were males, 37% were NF tumors, and 37% also had metastases, with actuarial survival being estimated at 73.6%.

In an early reported series (9) with 84 PETs mean age was 53 years, most were located in the tail (41%) and were malignant (70%).

In our series most were located in the head of the pancreas.

The most extensive American study (16) with 168 PETs in one same center mean age was 56 years; 51%

Table II. NFPET series

Author and year	*No. cases*	*Metastasis*	*Survival at 3, 5, 10 & 20 years*			
			3 years	*5 years*	*10 years*	*20 years*
Kent, 1981 (18)	25	18/25 (72%)	60%	44%		
Evans, 1993	73	(51%)		50%		
La Rosa, 1996	61	(56%)		NR		
Solórzano, 2001	163 28% Op.	(62%)		43%		
Gullo, 2003	184 67% Op.	(38%)	77 vs. 29%	60%		
Guo, 2004	41 Op.	(41%)		NR		
Liang, 2004	43 91% Op.	(65%)		58%	29%	
Hung, 2007	13 Op.	(38%)	85%	NR		
Chung, 2007	25 88% Op	NR		53%		
Bettini, 2008	180 52% Op.	(33%)		67%	44%	
Franko, 2010	2,158	(60%)		33%	17%	10%
Falconi, 2010	50 Op.	(32%)				
X:		50%		49%	30%	10%

NR: Not recorded; Op.: Operated on; X: arithmetic mean.

women, 76% benign, 24% malignant, 57.7% NF, and 33% insulinomas; 63% were located in the body or tail of the pancreas. Survival at 5-10 years was 77 and 62%, respectively.

In a recent Italian multicenter study (17) of 297 PETs mean age was 58 years: 51% women, 57% malignant, 24.6% functioning, and 75.4% non-functioning. Mean tumor size was 20 mm (2-150 mm), similar to ours, 20 mm (5-80 mm).

NFPETs (18-38) are usually most common, oscillating from 15-52% to 70-85-91%, with survival according to tumor size and malignity (metastasis); 70% are greater than 5 cm, and half are malignant (50%). In a series (23) of 43 cases (65% malignant) mainly in younger women, good results were obtained after surgery with curative intent, including cases of liver metastases (24) (Table II).

Insulinomas are usually pancreatic, benign, small, and multiple; nearly 90% (28) may be healed with surgical enucleation or resection (5), and survival is thus very high (almost 100%).

Gastrinomas are malignant in around 50% of cases, and 90% are located in the so-called "gastrinoma triangle" -in order of frequency, pancreas (45%), duodenum (20%) , and others (2%); 75% are sporadic and 25% have MEN-1.

When operated on with curative intent gastrinomas have a 1-year survival of 98% versus 74% (39) for non-surgical patients; 29% of non-surgical patients developed liver metastases (primary concern when caring for ZES). Vipomas (15%) (10-11), glucagonomas (7%) (12), pancreatic somatostatinomas (4%) (13), and carcinoids (1% of all carcinoids) (40) are much less common.

The most relevant issue to achieve a definite cure is assessing their exact location (41-43). Combined US/CT had a sensitivity of 84% (28). Of all imaging techniques EUS with or without FNAP in association with CT (100%) is the best approach, particularly for insulinomas (5,41,43). Most of our cases were localized using US/CT/EUS.

The best approach for gastrinomas is likely a combination of EUS and Octreoscan (41) or PET-CT (Fig. 1).

EUS localizes up to 93% of PETs (44), and 87% of insulinomas (45) with a sensitivity of 89.5% (46). EUS-FNAP reaches a diagnosis in 90-100% of cases (47-49) (Fig. 2).

Once localized and staged, the best option -when possible- is surgery with curative intent: enucleation *versus* resection or partial pancreatectomy (50) after careful palpation and intraoperative US (IUS), which localizes 93% of insulinomas (52).

In a national surgical series (32) with 48 cases (22 years' experience: 2 cases per year approximately), 39 of them benign (81%) and with predominant insulinomas (28 cases), with a mean age of 49 years (22 males/27 females: 0.81), 20 tumors were enucleated. Morbidity: 6 fistulas (22%), 3 abdominal collections, 1 pancreatitis, 1 pseudocyst.

In our series of 19 cases with 14 patients operated upon (73%), morbidity was 28% at the expense of pancreatitis and abdominal collections in patients undergoing pancreatectomy. In other series (34) morbidity was intermediate -25% (Table IV).

Complementary or alternative therapies (1,5) include somatostatin analogues, interferon, angiogenesis inhibitors, palliative chemotherapy and radiation therapy,

Table III. PET series

Author and year	*No. cases*	*X age*	*M*	*NFPET*	*Status*	*S at 5 years*
Eriksson, 1989 (9)	84 74% Op.	53 y.	70%	24%	Tail: 41%	?
Phan, 1998 (26)	125	51 y.	52%	48%		65%
Kazanjian, 2006	70		53%	71%		77%M
Vagefi, 2006	168	56 y.	26%	58%	C-C: 63%	77%
Liu, 2007	36	47 y.		19%		92 vs. 50%
Schurr, 2007	62 78% Op.	55 y.	31%	NR		80% vs. 64%
Bilimoria, 2007	9,821 40% Op.	60 y.	56%	85%		59%
Halfdanarson, 2008	1,483	58 y.	60%	91%		48 vs. 31%
Ekeblad, 2008	324	NR				64%
Ruiz-Tovar, 2008	48 46% Op.	49 y.	21%	17%		
Jagad, 2008	54 39% Op.		57%			
Bonney, 2008	20 M y Op.	54 y.				70%
Strosberg, 2009	90 M					56%
Nissen, 2009	46		52%	70%		
Isailovic, 2009	45 58% Op.	52 y.	42%		56%	64%
Hill, 2009	728 43% Op.	57 y.			> 80%	
Yildiz, 2009	86 in 10 y.	52 y.	35%			
Figueiredo, 2009	86 35% Op.	58 y.		80%		60%
Zerbi, 2010	297 85% Op.	58 y.	57%	75%		
Botsis, 2010 (58)	98 85% Op.	60 y.		81%	B-T: 48%	61%
Pais, 2010 (59)	92 63% Op.	55 y		66%	Ca: 46%	
X:		53 y.	45%	59%		65%

M: Metastasis or malignity; B-T: body-tail of the pancreas. Op.: operated on; X: arithmetic mean.

etc. Most of our patients were treated with chemotherapy and somatostatin analogues.

Survival at 5 years among 70 operated patients (23% insulinomas, 71% non-functioning and 53% malignant) was 77% (27). In shorter series (28,34), with 36 (19% non-functioning) and 20 cases, survival was 92 *versus* 50% for malignancies, and 70% at 5 years. In larger series (31) survival at 5 years was 59.3%, and at 10 years 37.7%. In the multivariate analysis, age, stage, metastasis, functionality, and type of resection were all independent predictors of survival following resection.

The Swedish Uppsala team (53) studies prognostic factors in 324 patients with PET, with survival at 5 and 10 years of 64 and 44%, respectively. In the univariate analysis, stage, radical surgery, functional status, high Ki 67 index and Cg-A (highly sensitive and specific for PET), tumor size, and sporadic (rather than familial) nature are significant prognostic factors; in the multivariate analysis only stage, radical surgery, and Ki 67 above 2% were relevant. Non-functioning tumors were an independent marker of poorer prognosis.

Bettini et al. (54) study 180 cases of NFPET with survival at 5, 10 and 15 years of 67, 49 and 33%, respective-

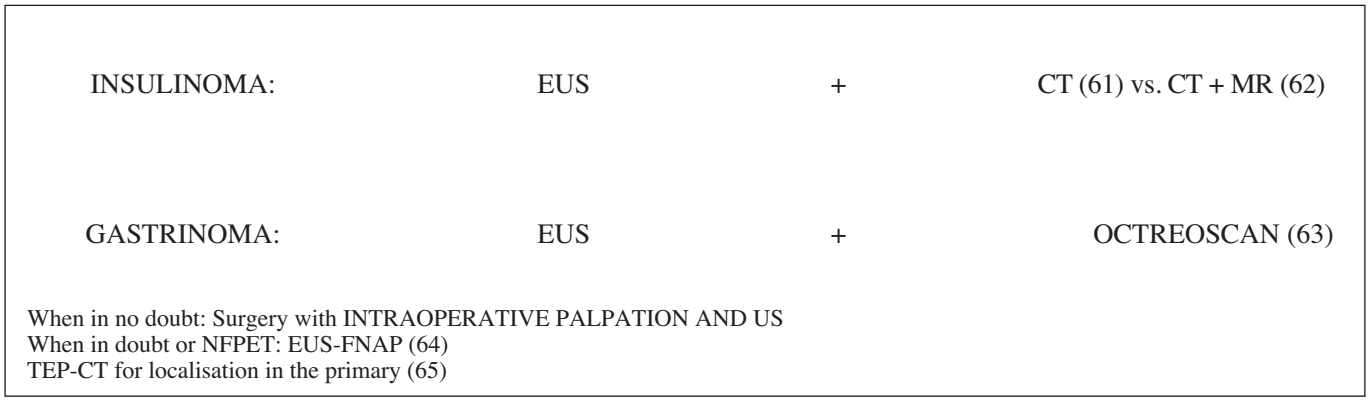

Fig. 1. An algorithm for most common PETs.

Table IV. A comparison of series with small n

Author & year	*No. cases surgery*	*Metastasis*	*NFPET*	*Survival*
Hung, 2007 (24)	7 y.: 13 Op. with no deaths	38% M	100% N-F	11/13 (85%)
Varas et al.	17 y.: 6/7 Op. with no deaths	50% M	100% N-F	4/6 (66%)
Varas et al.	17 y.: 19 73% Op. 51 y. (26-67)			
Morbi: 28%	37% M	37% N-F	(73%)	
Bonney, 2008 (34)	7 y.: 20 M & Op. 54 y. (24-79)			
Morbi: 25%	100% M		(70%)	
Ruiz, 2008 (32)	22 y.: 48 46% Op. 9 y.			
Morbi: 22%	21% M	17% N-F	13.5 y of S	
Isailovic, 2009 (37)	45 58% Op. 51.8 y (35-71)	42% M	56% N-F	(64%)
Nomura, 2009 (60)	17 94% Op.	41% M	100% N-F	Over 3 y.

Op.: Operated on; Morbi: operative morbidity; M: metastasis.

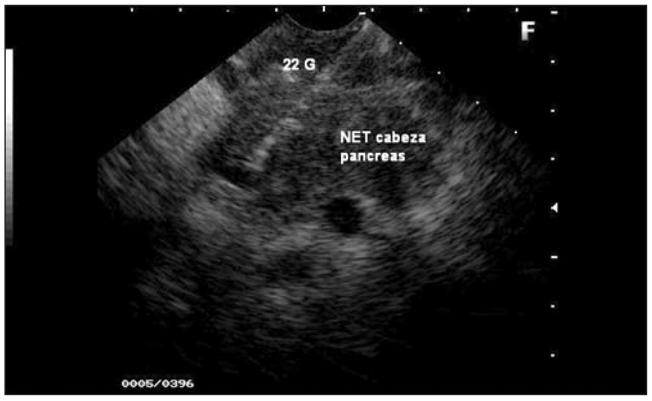

Fig. 2. EUS-FNAP for a NFPET.

ly, which confirms that metastases (to nodes and liver), poor differentiation, Ki 67 index, and weight loss are prognostic factors regarding survival.

In a recent study by the Verona team (55) of 137 NF cases the authors claim that primary tumor size is correlated to malignity and survival, thus defining surgery extent -1 cm excludes a carcinoma, 2 cm is the most widely used limit in clinical practice.

However, NF tumors usually show a mean size of 5 cm (21,56) *versus* 2 cm for functioning growths (21); 70% are greater than 5 cm at diagnosis, hence surgical treatment is an issue. Nevertheless, early detection and treatment with enucleation or pancreatic resection have been attempted, as for insulinomas, with very good results (57); no death occurred after a mean follow-up of 58 months.

Mean 5-year survival for all PETs is 65%, lower for NF tumors (49%) (Tables II-IV).

Our actuarial survival was 73.6%; the presence of obstructive jaundice and metastasis were associated with a poorer prognosis.

REFERENCES

1. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008;135:1469-92.
2. O´Grady HL, Conlon KC. Pancreatic neuroendocrine tumours. EJSO 2008;34:324-32.
3. Davis K, Conlon KC. Neuroendocrine tumors of the pancreas. Current Gastroenterol Reports 2009;11:119-27.
4. Ong SL, Garcea G, Pollard CA, et al. A fuller understanding of pancreatic neuroendocrine tumours combined with aggressive management improves outcome. Pancreatology 2009;9:583-600.
5. Varas MJ. Neuroendocrine tumors –fascination and infrequency. Rev Esp Enferm Dig 2009;101:195-208.
6. Ehehalt F, Saeger HD, Schmidt CM, et al. Neuroendocrine tumors of the pancreas. Oncologist 2009;14:456-67.
7. Fendrich V, Waldmann J, Bartsch DK, et al. Surgical management of pancreatic endocrine tumors. Nature Reviews Clin Oncol 2009; 6:419-28.
8. Halfdanarson T, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent toward improved survival. Ann Oncol 2008;19:1727-33.
9. Erikson B, Oberg K, Skogseid B. Neuroendocrine pancreatic tumors. Clinical finding in a prospective study 84 patients. Acta Oncol 1989;28:373-7.
10. Nikou GC, Toubanakis C, Nikolaou P, et al. Vipomas: an update in diagnosis and management in a series of 11 patients. Hepatogastroenterology 2005;52:1259-65.
11. Muñoz-Guijosa C, Moral A, Hernández A, et al. Vipoma pancreático: aportación de dos casos con diferente malignidad. Cir Esp 2003;74:239-41.
12. Kindmark H, Sundin A, Granberg D, et al. Endocrine pancreatic tumors with glucagon hypersecretion: a retrospective study of 23 cases during 20 years. Med Oncol 2007;24:330-7.
13. Garbrect N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. Endocr Relat Cancer 2008;15:229-41.
14. Yildiz O, Ozguroglu M, Yanmaz T, et al. Gastroenteropancreatic neuroendocrine tumors: 10-year experience in a single center. Med Oncol 2009; On line.
15. García Carbonero R, Capdevila J, Crespo Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer registry of Spain (RGRTNE). Ann Oncol 2010;21:195-8.
16. Vagefi PA, Razo O, Deshpande V, et al. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachussets General Hospital experience from 1977 to 2005. Arch Surg 2007;142:347.

17. Zerbi A, Falconi M, Rindi G, et al. Clinicopathological features of pancreatic endocrine tumors: A prospective multicenter study in Italy of 297 sporadic cases. Am J Gastroenterol 2010;105:237-8.
18. Kent RB, van Heerden JA, Weiland IH. Nonfunctioning islet cell tumors. Ann Surg 1981;193:185-90.
19. La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumors. Virchows Archiv 1996;429: 323-33.
20. Solórzano CC, Lee JE, Pisters PWT, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. Surgery 2001;130:1078-85.
21. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol 2003;98:2435-39.
22. Guo KJ, Liao HH, Thian YL, et al. Surgical treatment of nonfunctioning islet cell tumor: report 41 cases. Hepatobiliary and Pancreatic Dis Int 2004;3:469-72.
23. Liang H, Wang P, Wang X-N, et al. Management of nonfunctioning islet cell tumors. World J Gastroenterol 2004;10:1806-9.
24. Hung J-S, Chang M-C, Lee P-H, et al. Is surgery indicated for patients with symptomatic nonfunctioning pancreatic neuroendocrine tumor and unresectable hepatic metastases? World J Surg 2007;31: 2392-7.
25. Chung J, Choi D, Jo S, et al. Malignant nonfunctioning endocrine tumors of the pancreas: predictive factors for survival after surgical treatment. World J Surg 2007;31:579-85.
26. Phan GQ, Yeo CJ, Hruban RH, lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg 1998;2:472-82.
27. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. Arch Surg 2006;141:765-70.
28. Liu H, Zhang SZ, Wu YL, et al. Diagnosis and surgical treatment of pancreatic endocrine tumors in 36 patients: a single-center report. Chin Med J 2007;120:1487-90.
29. Schurr PG, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors. An institutional experience. Ann Surg 2007;245:273-81.
30. Bilimoria KY, Tomlinson JS, Merkow RP, et al. Clinicopathologic features and treatment trends of pancreatic neuroendocrine tumors: analysis of 9821 patients. J Gastrointest Surg 2007;11:1460-7.
31. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008;247:490-500.
32. Ruiz-Tovar J, Priego P, Martinez E, et al. Pancreatic neuroendocrine tumours. Clin Transl Oncol 2008;10:493-7.
33. Jagad R, Koshariya M, Kawamoto J, et al. Pancreatic neuroendocrine tumors: our approach. Hepato-Gastroenterology 2008;55:275-81.
34. Bonney GK, Gomez D, Arman SH, et al. Results following surgical resection for malignant pancreatic neuroendocrine tumors. A single institutional experience. JOP 2008;9:19-25.
35. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. Pancreas 2009;38:255-8.
36. Nissen NN, Kim AS, Yu R, et al. Pancreatic neuroendocrine tumors: presentation, management, and outcomes. Am Surgery 2009;75: 1025-9.
37. Isailovic T, Popovic B, Petakov M, et al. Pancreatic neuroendocrine tumors: a national survey. Endocrine Abstracts 2009;20:P212.
38. Hill JS, McPhee JT, McDade TP, et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009;115: 741-51.
39. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. Ann Surg 2006;244:3.
40. Varas MJ, Miquel JM, Maluenda MD, et al. Preoperative detection of gastrointestinal neuroendocrine tumors using endoscopic ultrasonography. Rev Esp Enferm Dig 2006;98:828-36.
41. McLean AM, Fairclough PD. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. Best Pract Res Clin Endocrinol Metab 2005;19:177-93.
42. Patel KK, Kim MK. Neuroendocrine tumors of the pancreas: endoscopic diagnosis. Current Opinion Gastroenterology 2008;24:638-42.
43. Varas Lorenzo MJ. Ultrasonografía Endoscópica. Aplicaciones diagnósticas y terapéuticas. Madrid: Ed. Médica Panamericana; 2008. p.159-69.
44. Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs managements in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000;95: 2271-7.
45. De Angelis C. Echoendoscopy for the diagnosis of pancreatic endocrine tumors. Endocrine Abstracts 2007;14:S9.4.
46. Sotoudehmanesh R, Hedayat A, Shirazian N, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine 2007;31:238-41.
47. Santo E, Kariv R, Monges G, et al. The role of linear array endoscopic ultrasound with fine-needle aspiration in the diagnosis and preoperative evaluation of pancreatic neuroendocrine tumors –experience with 76 cases. Gastrointest Endosc 2002;56:S118.
48. Kongkam P, Al-Haddad M, Attasaranya S, et al. EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. Endoscopy 2008;40:602-5.
49. Figueiredo F, Giovannini M, Monges G, et al. Pancreatic endocrine tumors: A large single-center experience. Pancreas 2009;38:947-53.
50. Pitt SC, Pitt HA, Baker MS, et al. Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? J Gastrointest Surg 2009;13:1692-98.
51. Ponseti JM, Fort JM, Armengol M. Insulinoma (21 pacientes). En: Varas MJ, editor. Endocrinologia gastroentero-pancreática. Smar SL; 1997.p.207-29.
52. Diaz AG, Lucas S, Ferraina P, et al. Experiencia clínica sobre 37 casos de insulinoma. Medicina (Buenos Aires) 2006;66:499-504.
53. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008;14:7798-803.
54. Bettini R, Boninsegna L, Mantovani W, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. Ann Oncol 2008;19:903-8.
55. Bettini R, Boninsegna L, Partelli S, et al. Non-functioning pancreatic endocrine tumors: any correlation of tumor size with malignancy? JOP 2009;10:606-7.
56. Franko J, Teng W, Yip Genovese E, et al. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2158 patients. J Gastrointest Surg 2010;14:541-8.
57. Falconi M, Zerbi A, Crippa S, et al. Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. Ann Surg Oncol 2010;17:1624-27.
58. Botsis T, Anagnostou VK, Hartvigsen G, et al. Developing a multivariable prognostic model for pancreatic endocrine tumors using the clinical data warehouse resources of a single institution. Appl Clin Inf 2010;1:38-49.
59. Pais SA, Al-Haddad M, Mohamadnejad M, et al. EUS for pancreatic neuroendocrine tumors: a single-center, 11-year experience. Gastrointest Endosc 2010;71:1185-93.
60. Nomura N, Fujii T, Kanazumi N, et al. Nonfunctioning neuroendocrine pancreatic tumors: our experience and management. J Hepato-Biliary-Pancreatic Surg 2009;16:639-47.
61. Varas MJ. Diagnostic evaluation of pancreatic insulinoma. Rev Esp Enferm Dig 2008;100:183-4.
62. Druce MR, Muthupalaniappan VM, O´Leary B, et al. Diagnosis and localisation of insulinoma: the value of modern magnetic resonance imaging in conjuction with calcium stimulation catheterisation. Eur J Endocrinol 2010;162(5):971-8.
63. Varas MJ. Preoperative diagnostic approach for gastrinoma associated to Zollinger-Ellison syndrome. Rev Esp Enferm Dig 2008;100: 307-9.
64. Gornals J, Varas M, Catalá I, et al. Definitive Diagnosis of neuroendocrine tumors using fine-needle aspiration-punction guided by endoscopic ultrasonography. Rev Esp Enferm Dig 2011;103(3):123-8.
65. Kuiper P, Verspaget HW, Overbeek LI, et al. An overview of the current diagnosis and recent developments in neuroendocrine tumours of the gastroenteropancreatic tract: the diagnostic approach. Neth J Med 2011;69(1):14-20.