Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 3 Issue 11 November 2020

Case Report

Spleen Preserving Total Pancreatectomy in a Case of Multiple Pancreatic Neuroendocrine Tumour

Urmila Basu[1], Renu Saini[1], Devmalya Banerjee[2], Gaurav Kumar[3] and Shubhayu Banerjee[4]*

[1]DNB Resident, Department of General Surgery, Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata, West Bengal, India

[2]MD Pathology, Consultant Oncopathologist, Narayana Superspeciality Hospital, Kolkata, West Bengal, India

[3]DNB General Surgery, Consultant General Surgeon, Narayana Superspeciality Hospital, Kolkata, West Bengal, India

[4]Consultant Laparoscopic and Gastrointestinal Surgeon, Narayana Superspeciality Hospital, Kolkata, West Bengal, India

***Corresponding Author:** Shubhayu Banerjee, Consultant Laparoscopic and Gastrointestinal Surgeon, Narayana Superspeciality Hospital, Kolkata, West Bengal, India.

Received: July 24, 2020

Published: October 29, 2020

Abstract

One of the most common sites of gastrointestinal neuroendocrine tumour is the pancreas. They are known as Pancreatic neuroendocrine tumour (PNET). The previous incidence rate of 0.43/100,000 has more than doubled in last few decades. Most of the PNETs are clinically silent and show slight male preponderance. 10% of PNETs are functional, associated with genetic syndromes and represent as cystic lesion on radiology. Proper pre-operative work up including endocrine testing, tumour marker study and imaging is necessary to establish the diagnosis. Since they have malignant potential, surgery is the treatment of choice for resectable tumours among the various treatment modalities available. We are presenting a case of 50 years old lady having multiple soft tissue lesions involving distal CBD, head, body and tail of pancreas. She underwent spleen preserving total pancreatectomy with Roux-en-Y hepaticojejunostomy and gastrojejunostomy. Post-operative recovery was uneventful and glycaemic control was achieved with pharmacotherapy. We will discuss the various aspects of PNETs in this report.

Keywords: Pancreatic Neuroendocrine Tumour; Pancreas; Spleen Preserving; Total Pancreatectomy

Abbreviations

PNET: Pancreatic Neuroendocrine Tumour; MEN: Multiple Endocrine Neoplasia; VHL: Von Hippel Lindau, NF1: Neurofibromatosis 1; TSC: Tuberous Sclerosis Complex; WHO: World Health Organisation; LFT: Liver Function Test; CBD: Common Bile Duct, MPD: Main Pancreatic Duct; CECT: Contrast Enhanced Computed Tomography; USG: Ultrasonography; MRCP: Magnetic Resonance Cholangio Pancreaticography; GA: General Anaesthesia; SC: Subcutaneously; POD: Post-Operative Day

Introduction

PNETs were formerly known as islet cell tumours. In 2010 the WHO renamed them as PNET. The incidence of these tumours is 0.43 per 100,000. The tumour exhibits a slight male preponderance (55% males and 45% females) [1]. PNET comprises < 3% of all pancreatic tumours and 7% of NET [2].

Almost 90% of PNETs are non-functional they produce symptoms such as jaundice, pancreatitis, abdominal pain, back pain,

nausea, vomiting and weight loss due to mass effect and may mimic adenocarcinoma. They may also be diagnosed incidentally on imaging studies [3].

Surgery is the treatment of choice for resectable tumours. Although rarely performed patients with multiple lesions throughout the pancreas may need total pancreatectomy for complete oncological clearance. Pylorus and spleen preserving total pancreatectomy is based on the principles of two surgeries namely, pylorus preserving pancreaticoduodenectomy and spleen preserving distal pancreatectomy (Extended Warshaw procedure).

Case Report

A 50-year-old lady presented with a one-year history of intermittent upper abdominal pain, dyspepsia, loss of appetite and weight loss. She denied any history of fever, jaundice, hematemesis or malena. She had no medical comorbidities other than hypothyroidism for which she was not on regular medication. She denied any past surgeries and family history of malignancy. General and systemic examination was unremarkable. Routine blood investigations including LFT was within normal limit TSH was 1.43 Ca 19-9 was 60.44 U/ml.

Various modes of radiological imaging were used to arrive at the final diagnosis USG done on 27/4/19 revealed an isoechoic solid SOL (37 X 27 mm) in the body of the pancreas. The MPD was however not dilated. MRCP done on 15/9/19 confirmed a 29 x 23 x 22 mm hypo enhancing mass lesion in the body of pancreas and a further 16 x 13 mm lesion in the body distal to the aforesaid mass.

CECT whole abdomen done on 29/9/2019 revealed 10 X 11 mm soft tissue lesion involving the distal CBD and ampullary region causing upstream dilatation of the CBD and MPD. The maximum diameter of CBD and MPD were 8 mm and 8.5 mm respectively. Lobulated arterial phase enhancing lesions measuring 27 X 27 mm was seen at the junction of neck and body and another 7 X 7 mm lesion at the junction of body and tail. The larger lesion showed cystic changes and was involving the MPD. The was no significant peripancreatic or periportal lympthadenopathy.

Tumor marker CA 19-9 was 60.44U/ml. All preanesthetic investigations were within normal limit. She was investigated for thyroid and parathyroid diseases but no such abnormality was detected. Spleen preserving total pancreatectomy with Roun-en-Y hepaticojejunostomy and gastrojejunostomy was performed under GA on 31/9/2019.

Figure 1: CT scan image of mass lesions involving head and body of pancreas.

Figure 2: CT scan image showing bulky tail of pancreas and dilated MPD.

Figure 3: Post-operative specimen of spleen preserving total pancreaticoduodenectomy showing mass lesion at the junction of head and body with a bulky tail. (anterior and posterior view respectively).

Post operatively glycemic control was achieved with IV insulin infusion and multiple episodes hypoglycemia was effectively managed. She was discharged on POD 11 with good glycemic control with 20 mg teneligliptin before breakfast and 6 units insulin Glargine SC at bedtime. Pancreatin 25000 U was given orally every day.

Histopathological examination of the operative specimen had the following findings. Two separate tumours were identified, the larger one measuring 4.5 x 2.0 x 1.0 cm and the smaller one measuring 0.1 x 0.5 x 0.5 cm. the primary tumour was at least 0.1 mm away from the closest pancreatic surface. There was a small nodule at the tail as well.

(a) On microscopic examination the tumor showed nests, cords, trabeculae and ribbons of monomorphic cells.

(b) Cells showing stippled chromatin, inconspicuous nucleoli and scanty cytoplasm.

Figure 4: Haematoxylin Eosin images of PNET.

The separate nodule in the tail also shows a tumour of similar morphology. No lymphovascular emboli was seen.

IHC confirmed that the cells were positive for CK (Perinulear dot like) synaptophysin, chromogranin and negative for betacatenin and TFE3. Ki67 LI is <2. All these findings were confirmatory of grade 1 multifocal Neuroendocrine tumour of pancreas.

She was followed up in the surgical and endocrinology clinic. Her FBS on 31/10/19 one month after surgery was 169.2 mg/dl. On follow up her hypogycaemic medications were changed to Huminsulin (Regular human insulin 30%+ Isophane insulin 70%) 12 U SC 20 minutes before breakfast and 1 g Metformin at bed time. Her fasting and post prandial sugars on 24/12/19 3 months after surgery were 212 mg/dl and 264.9 mg/dl respectively. She did not complain of steatorrhea or features of malabsorption. On the contrary she had satisfactory weight gain.

Discussion

pNETs forms one end of a spectrum of a diverse group of tumors referred to as pancreatic neuroendocrine neoplasms pancreatic neuroendocrine carcinomas forms the other end of the spectrum. According to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) there has been a 2-fold increase in incidence in the last 2 - 3 decades which is attributable to increased awareness amongst surgeons and advances in radiological imaging studies [3,4].

Majority of pNETS are sporadic in nature, only 10% arise in association with genetic syndromes such as Multiple endocrine neoplasia type I (MEN1) and type IV (MEN4), Von Hippel-Lindau disease (VHL), Neurofibromatosis type I (NF1), or Tuberous sclerosis complex (TSC). The most common type of pNET in MEN1 is a non-functional tumour [5-8]. PNETs are the most common underlying cause of MEN1 associated mortality, and these patients have a reduced life expectancy of 69 years compared to 77 years for MEN1 patients without a pNET [5,9,10].

Previously it was thought that pNETS arose from hormone secreting pockets of cells of the pancreas called islets of Langerhans. However recent studies suggest that pluripotent stem cells of the pancreatic ductal or acinar system give rise to pNETS [11]. These tumors exhibit genetic differences from pancreatic adenocarcinoma. KRAS gene mutation which is seen in adenocarcinoma is absent in pNETs. PNETS exhibit MEN1 in 44% of tumours, DAXX in 25% of tumours, ATRX in 18% of tumours, and mTOR pathway genes in 16% of tumors [12].

In the last 10 - 15 years the classification and staging system of pNETS has undergone a number of changes. Presently the WHO, European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) have each suggested staging system for pNETS. (Table 1 shows the AJCC Staging system) [13-15].

2010 AJCC staging system for pNETs

Stage	Tumor	Node	Metastasis	Stage specific 5-year survival	
IA	T1	N0	M0	Stage IA	96%
IB	T2	N0	M0	Stage IB	92%
IIA	T3	N0	M0	Stage IIA	76%
IIB	T1-3	N1	M0	Stage IIB	73%
III	T4	Any N	M0	Stage III	-
IV	Any T	Any N	M1	Stage IV	56%

Table 1: Survival data from Ellison TA., *et al*. SMA: Superior Mesenteric Artery; AJCC: American Joint Committee on Cancer; pNETs: Pancreatic Neuroendocrine Tumors. T1: < 2 cm But Limited to the Pancreas; T2: > 2 cm but Limited to the Pancreas; T3: Tumor Extends Beyond the Pancreas But Not Involving the celiac axis or SMA; T4: Tumor Involves Celiac Axis or SMA; N0: No Regional Lymph Node Metastases; N1: Regional Lymph Node Metastases; M0: No Distant Metastases; M1: Distant Metastases.

90% of pNET nonfunctional. Patients generally present with compression symptoms such as jaundice, weight loss, abdominal pain, palpable mass, nausea/emesis, pancreatitis, or back pain. A differential diagnosis of pancreatic adenocarcinoma must be borne in mind. Some asymptomatic tumors are detected incidentally cross sectional imaging. Almost 60% patients present with metastatic or while 21% have locally advanced disease [1]. 10% of pNETs are functional. The presenting symptoms of functional tumors depend on hormone hypersecretion (Table 1 showing common functional PNETS and their symptoms).

Tumor markers play a key role in the diagnosis and prognostication of nonfunctional pNETS. These are chromogranin A (CgA), neuron-specific enolase (NSE), pancreatic polypeptide, pancreastatin and human chorionic gonadotropin. CgA is the most sensitive of these, with elevated levels present in 72 - 100% of patients but it has limited specificity of 50 - 80% [16-18]. Use of proton-pump inhibitor, impaired renal function, liver disease, and inflammatory bowel disease can all increase CgA leading to false positive results. CgA increases in patients with metastatic disease. Elevated CgA levels are hence more useful in assessing response to therapy. The sensitivity of NSE is low at 30 - 40%, but its specificity is almost 100%. Hence a combination of CgA and NSE levels yields better results [19].

Name of tumor (syndrome)	Hormone causing syndrome	Signs or symptoms	Percentage of all functional pNETs
Insulinoma	Insulin	Symptoms of hypoglycemia (weakness, sweating, tremors, palpitations, confusion, visual changes, etc.)	35 - 40%
Gastrinoma (Zollinger-Ellison)	Gastrin	Abdominal pain, refractory peptic ulcer disease, secretory diarrhea	16 - 30%
Glucagonoma	Glucagon	Dermatitis (migratory necrolytic erythema), diabetes mellitus, diarrhea, DVT (4D syndrome	< 10%
VIPoma (Verner-Morrison)	VIP	Profuse watery diarrhea, dehydration, hypokalemia, achlorhydria (WDHA syndrome)	< 10%
Somatostatinoma	Somatostatin	Diabetes mellitus, cholelithiasis, steatorrhea, anemia, weight loss	< 5%

Table 2: Common functional pNETs and their syndromes.

Computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy (SRS), positron-emission tomography (PET), and endoscopic ultrasonography (EUS)aid in diagnosis of pNETS. In case of failure of these modalities angiography with selective arterial stimulation and venous sampling may be used. If the tumor cannot be located prior to surgery, surgeons have to depend on bimanual palpation with intra-operative ultrasound to locate the tumour.

Triple-phase contrast CT is the most commonly used imaging modality. PNETs are best visualized during the arterial phase. They usually appear as spherical, hyper-dense, and hyper-vascular mass that rarely obstruct the pancreatic duct. Almost 10% pNETS present as a cystic lesion with smooth margins and peripheral enhancement on both arterial and portal phases [21,22].

PNETs are usually well visualized on MR. Again, pNETs are best visualized during the arterial contrast phase. MR is useful when lesions are too small to be detected on CT. In detecting and following liver metastases, MR has been suggested to be superior to CT [22-24].

Functional pNETs other than insulinoma and nonfunctional pNETs express somatostatin receptors hence radiolabeled somatostatin analogs are used to locate these tumors when imaging modalities fail. SRS is also useful in evaluating the burden of metastatic disease [22,25].

PNETS are usually well differentiated with low metabolic rate hence not well visualized by standard PET imaging with ^{18}F-Fluorodeoxyglucose (FDG) [26,27]. However poorly differentiated pNETs can be detected. Combination of PET with CT images yields better results with sensitivities of 94 - 100% [28].

EUS is an invaluable tool in the evaluation of pancreatic head lesions. But it has limited use for lesions in the tail and results are operator dependent. However, EUS guided biopsies aid in tissue diagnosis EUS has the added benefit of being able to tattoo smaller lesions for easier intraoperative identification, facilitating laparoscopic resection [29-31].

The first total pancreatectomy was performed on a dog in 1898 in Breslau, Germany by Minkowski [32]. but only after the discovery of insulin in 1921 it could be performed safely on humans. Arthur William Mayo-Robson stated in his speech at a medical congress in Paris in 1901 [33]. that Theodore Billroth from Vienna performed the first total or near total pancreatectomy in 1884 with good results. The first true elective total pancreatectomy is reported to be performed in 1942 by Eugene Rocky of Portland, Oregon but unfortunately the patient did not survive beyond 15 days due to CBD leakage leading to biliary peritonitis [32]. Three weeks from this event, James Priestly, while operating on a patient who was suffering from recurrent hypogycaemic episodes could not locate the tumor and hence performed total pancreatectomy [34]. The patient lived for 29 years after the surgery and later died of cholangitis.

The major complications of this procedure included severe metabolic problems such as brittle insulin dependent diabetes mellitus and loss of pancreatic exocrine function leading to malabsorption. The resultant diarrhea and weight loss lead to cachexia, which compromised quality of life and restricted normal physical activity. Carbohydrate absorption could not be estimated due to steatorrhea and short transit time thus making the titration of the dosage of insulin more challenging. The patients often suffered from hypogylcaemia and hypoglycaemic coma. Steatorrhea also lead to malabsorption of fat-soluble vitamins, vitamin D deficiency caused osteopathy and osteoporosis. Due to these intractable complications total pancreatectomy started losing is popularity as a viable option for the treatment of pancreatectomy.

Several recent studies have however proved beyond doubt that total pancreatectomy bears same morbidity and mortality as partial pancreatectomy provided the operative time is comparable. According to a study conducted by Muller., *et al*. on 147 patients the morbidity and mortality of elective total pancreatectomy were 36% and 4.8% respectively. They did not find any statistical difference in comparison to partial pancreatectomy [35]. Another retrospective study by Epelboym., *et al*. on 77 patients also had similar results [36].

Indications of total pancreatectomy

- Malignant tumors of the head of pancreas encroaching onto the left pancreas in which is difficult to secure a tumor free resection margin in spite of extended resection.
- Recurrent malignancy in the remnant pancreas.
- Cancer surgery with resection of celiac trunk.
- Leaking pancreatico-jejunostomy following Whipples or similar surgery. The surgery is then known as rescue pancreatectomy.
- Multifocal potentially malignant IPMN throughout the pancreas.
- Multifocal neuroendocrine tumor which are mostly a component of MEN.
- Multiple metastatic deposits of multiple melanoma and renal cell carcinoma.
- Pancreatic cancers with high grade of penetration, such as hereditary pancreatic cancers.

With advent of newer pharmacological agents, it is now possible to handle complications of total pancreatectomy much more efficiently. Treatment of pancreatic exocrine insufficiency aims at providing adequate lipase in the duodenal lumen at the time of gastric emptying. This is achieved by administration of enzymes in the form of enteric coated microspheres which prevents inactivation of lipase by gastric acid. Steatorrhea is now effectively controlled with such drugs [37]. Barbiet., *et al*. studied 56 patients for

the short- and long-term effects of total pancreatectomy of which 30 patients had weight loss with an average of 9 kg (2 - 14). Four of them had a median weight gain of 13 kg (4 - 22 kg). Majority of patients passed stool twice daily. Day to day activity of 7 patients was hampered by night time stool and of 5 patients by persistent diarrhea. The average daily intake of pancreatic enzymes was 6 capsules (3-18) each containing 25,000 units and 5 patients took other medications such as loperamide and diosmectite for intestinal transit [38].

Diabetes Mellitus occurring after total pancreatectomy differs considerably from type 1 and 2 diabetes. Ketoacidosis and severe hyperglycemia are rarely encountered unlike type 1 DM. Pancreatogenic diabetes is highly insulin sensitive unlike type 2 DM which is insulin resistant and exhibits relative insulin deficiency. Large proportion of absorbed glucose undergoes insulin independent metabolism making pancreatogenic DM distinct from Type 1 and 2 DM. These patients may suffer from unexpected hypoglycemia unrelated to food intake or physical activity. This type of diabetes is often referred to as 'brittle diabetes'. Pancreatic exocrine deficiency causing malabsorption and slow transit also affects glycemic control. Deficient pancreatic glucagon secretion in these patients leads to elevated levels of gluconeogenic precursors such as lactate and alanine in such patients [37]. In contrast to type 1 diabetes these patients have elevated serum insulin level with minimal or no response to food intake. Glucagon deficiency and increased sensitivity to insulin results in hypoglycemia in response to exogenous insulin administration. Such an iatrogenic hypoglycemia may require hospitalization, can cause irreparable brain damage and can even cause death [39,40]. In recent times better understanding of pathophysiology of T3cDM has led to more effective control of this complication. Comparable Hba1c levels have been recorded between Type 1 Diabetes and pancreatectomized patient.

Conclusion

As we have discussed, PNETs are most common neuroendocrine tumours having a better survival rate and lower recurrence rate following adequate treatment. Since, 90% PNETs are sporadic and non-functional, proper assessment and management is required due to malignant potential of the tumour. An approach including multi-disciplinary therapy is suggested for post-operative management. With the help of surgical expertise and advanced pharmacotherapy we can expect better outcome in terms of quality of life and survival benefit.

Bibliography

1. Halfdanarson TR., *et al*. "Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival". *Annuals of Oncology* 19 (2008): 1727-1733.

2. Lawrence B., *et al*. "The epidemiology of gastroenteropancreatic neuroendocrine tumors". *Endocrinology and Metabolism Clinics of North America* 40 (2011): 1-18.

3. Halfdanarson TR., *et al*. "Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors". *Endocrine-Related Cancer* 15 (2008): 409-427.

4. Fraenkel M., *et al*. "Epidemiology of gastroenteropancreatic neuroendocrine tumours". *Best Practice and Research: Clinical Gastroenterology* 26 (2012): 691-703.

5. Triponez F., *et al*. "Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas". *Annals of Surgery* 243 (2006): 265-72.

6. Perren A., *et al*. "Multiple endocrine neoplasia type 1 (MEN1): loss of one MEN1 allele in tumors and monohormonal endocrine cell clusters but not in islet hyperplasia of the pancreas". *The Journal of Clinical Endocrinology and Metabolism* 92 (2007): 1118-1128.

7. Jensen RT., *et al*. "Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies". *Cancer* 113 (2008): 1807-1843.

8. Pipeleers-Marichal M., *et al*. "Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome". *The New England Journal of Medicine* 322 (1990): 723-727.

9. Dean PG., *et al*. "Are patients with multiple endocrine neoplasia type I prone to premature death?". *World Journal of Surgery* 24 (2000): 1437-1441.

10. de Wilde RF., *et al*. "Well differentiated pancreatic neuroendocrine tumors: from genetics to therapy". *Nature Reviews Gastroenterology and Hepatology* 9 (2012): 199-208.

11. Vortmeyer AO., *et al*. "Nonislet origin of pancreatic islet cell tumors". *The Journal of Clinical Endocrinology and Metabolism* 89 (2004): 1934-1938.

12. Jiao Y., *et al*. "DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors". *Science* 331 (2011): 1199-1203.

13. Klimsta DS., *et al*. "Neuroendocrine neoplasms of the pancreas". In: Bosman F, Carneiro F, Hruban RH., *et al.* eds. WHO Classification of Tumours of the Digestive System. Lyon: IARC Press (2010): 322-326.

14. Rindi G., *et al*. "TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system". *Virchows Archives* 449 (2006): 395-401.

15. Exocrine and Endocrine Pancreas. AJCC Cancer Staging Manual. New York, NY: Springer (2010): 241-249.

16. Paik WH., *et al*. "Clinical usefulness of plasma chromogranin A in pancreatic neuroendocrine neoplasm". *Journal of Korean Medical Science* 28 (2013): 750-754.

17. Singh S and Law C. "Chromogranin A: a sensitive biomarker for the detection and post-treatment monitoring of gastroenteropancreatic neuroendocrine tumors". *Expert Review of Gastroenterology and Hepatology* 6 (2012): 313-334.

18. Vinik AI., *et al*. "Biochemical testing for neuroendocrine tumors". *Pancreas* 38 (2009): 876-889.

19. Oberg K. "Circulating biomarkers in gastroenteropancreatic neuroendocrine tumours". *Endocrine Relation Cancer* 18 (2011): S17-25.

20. Anders S. "Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumors". *Best Practice and Research: Clinical Gastroenterology* 26 (2012): 803-818.

21. Herwick S., *et al*. "MRI of islet cell tumors of the pancreas". *AJR American Journal of Roentgenology* 187 (2006): W472-480.

22. Sundin A., *et al*. "ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations". *Neuroendocrinology* 90 (2009): 167-183.

23. Oberg K. "Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors". *Clinics (Sao. Paulo)* 67 (2012): 109-112.

24. Joseph S., *et al*. "Neuroendocrine tumors: current recommendations for diagnosis and surgical management". *Endocrinology and Metabolism Clinics of North America* 40 (2011): 205-31.

25. de Herder WW., *et al*. "Neuroendocrine tumors and somatostatin: imaging techniques". *Journal of Endocrinology Investigation* 28 (2005): 132-136.

26. Garin E., *et al*. "Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors". *The Journal of Nuclear Medicine* 50 (2009): 858-864.

27. Binderup T., *et al*. "18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors". *Clinical Cancer Research* 16 (2010): 978-985.

28. Frilling A., *et al*. "Multimodal management of neuroendocrine liver metastases". *HPB (Oxford)* 12 (2010): 361-379.

29. Kim MK. "Endoscopic ultrasound in gastroenteropancreatic neuroendocrine tumors". *Gut Liver* 6 (2012): 405-410.

30. Atiq M., *et al*. "EUS-FNA for pancreatic neuroendocrine tumors: a tertiary cancer center experience". *Digestive Diseases and Sciences* 57 (2012): 791-800.

31. Lennon AM., *et al*. "EUS-guided tattooing before laparoscopic distal pancreatic resection (with video)". *Gastrointestinal Endoscopy* 72 (2010): 1089-1094.

32. Minkowski O. "De l'exirpation des pancéas chez les animoux et du diabète experimental". *Semaine Med (Paris)* 9 (1889): 175-176.

33. Rockey EW. "Total pancreatectomy for carcinoma: case report". *Annals of Surgery* 118 (1943): 603-611.

34. Priestley JT., *et al*. "Total pancreatectomy for hyperinsulinism due to an islet-cell adenoma: survival and cure at sixteen months after operation presentation of metabolic studies". *Annals of Surgery* 119 (1944): 211-221.

35. Müller MW., *et al*. "Is there still a role for total pancreatectomy?". *Annals of Surgery* 246 (2007): 966-974 discussion 974-975.

36. Epelboym I., *et al*. "Quality of life in patients after total pancreatectomy is comparable with quality of life in patients who undergo a partial pancreatic resection". *Journal of Surgery and Research* 187 (2014): 189-196.

37. Domínguez-Muñoz JE. "Pancreatic enzyme therapy for pancreatic exocrine insufficiency". *Current Gastroenterology Report* 9 (2007): 116-122.

38. Barbier L., *et al*. "Impact of total pancreatectomy: short- and long-term assessment". *HPB (Oxford)* 15 (2013): 882-892.

39. Unger RH. "Glucagon physiology and pathophysiology". *The New England Journal of Medicine* 285 (1971): 443-449.

40. Slezak LA and Andersen DK. "Pancreatic resection: effects on glucose metabolism". *World Journal of Surgery* 25 (2001): 452-460.