ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 04, pp.2850-2854, April, 2019

DOI: https://doi.org/10.24941/ijcr.34766.04.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

PANCREATIC NEUROENDOCRINE NEOPLASMS- A SERIES OF SIX CASES

***Zubaida Rasool, Dr. Iqbal Lone, M., Huzaifa Tak, Nazia Bhat, Nuzhat Samoon and Kanika Gupta**

Department of Pathology, SKIMS Soura Jammu and Kashmir India

ARTICLE INFO

Article History:
Received 06th January, 2019
Received in revised form
02nd February, 2019
Accepted 11th March, 2019
Published online 29th April, 2019

Key Words:
Neuroendocrine, Pancreas, Histopathology, Ki67, Insulinoma.

Abbreviations

Panen- Pancreatic Neuroendocrine Neoplasms.

ABSTRACT

Background: Pancreatic neuroendocrine tumors (PNETs) are a rare subgroup of NETs with unique tumor biology, natural history, and clinical management. They account for about 1-2% PNETs with incidence 1/100,000. There is an increase by 5 times in the detection rate of NET′s in the last two decades, partly due to improved radiological diagnostic techniques. Histopathology provides an important prognostic information about these tumors **Objectives:** We present here six cases of pancreatic neuroendocrine neoplasms **Results:** Of these 5 were non functional and 1 was functional (insulinoma).

***Citation: Rosero, R.J. and Polanco, J.P.,* 2019.** "Pancreatic neuroendocrine neoplasms- A series of six cases", *International Journal of Current Research*, 11, (04), 2850-2854.

INTRODUCTION

Pancreatic neuroendocrine neoplasms are a highly heterogeneous mixture of tumors that originate from pluripotent stem cells (Yao *et al*., 2008; Modlin *et al*., 2008). Their biological behavior varies widely from nearly benign tumors to malignant ones that give rise to metastasis and local invasion. panNENs are classified as two general categories- functional and nonfunctional. Patients with functional panNENs are diagnosed earlier than patients with nonfunctional pan NENs (Halfdanarson, 2008). The nonfunctional pan NENs account for 40-90% pan NENs (Valle *et al*., 2014; Kuo *et al*., 2014). The optimal treatment strategy of these patients is not known but surgery, chemotherapy, radiotherapy can be used alone or as a multidisciplinary approach (Öberg, 1998) Histopathological examination provides relevant postoperative prognostic information, including tumour size, local invasion, pancreatic capsular penetration and the mitotic rate (Fasanella *et al*., 2009). Ki67 is a well-recognized prognostic factor, and is used in the WHO grading of these tumours. One study found the risk of progression increases 2% for every Ki67 unit increase (Panzuto *et al*., 2011).

****Corresponding author:*** **Huzaifa Tak,**
Senior Residents, Department of pathology, SKIMS Soura Jammu and Kashmir India.

MATERIALS AND METHODS

The study was carried out in the Department Of Pathology at Sheri-i-Kashmir Institute of Medical Sciences, Kashmir India. A total of 30 cases of resected specimens of pancreas (including pancreatico duodenectomy specimen) collected over a period of 2 years from 1st January 2016 to 31st Dec 2018 were included in the study. Of these 6 cases were found to be neuroendocrine tumors including a biopsy specimen. The age, sex, relevant clinical and radiological details were recorded for each case. The specimen was processed as per standard procedure. 4-5m thick sections were cut on microtome and stained by hematoxylin and eosin stain. The stained slides were studied in detail microscopically; and Immunohistochemistry was done for confirmation.

RESULTS

Of 6 cases, 4were females and 2males. Male to female ratio was 1:2.Age ranged from 24 years to 55 yrs. Majority of lesions were seen in the head of the pancreas (Table1 and 2) Only 1 lesion was seen in the tail of pancreas. (Fig1) Pancreatic duodenectomy was done in 4 cases. limited pancreatic resection was done in one case. In one case pancreatic biopsy was done. Grossly 3 cases presented as grayish /brown lesion centered in the head of the pancreas (Fig2). In one case cystic degeneration was seen. On microscopic examination tumor was present in nests and sheets.

Table 1. Clinicoradiological details

Age	Sex	Clinical details	CT Findings	Site of tumor
24	F	Pain abdomen	Hypodense lesion in head of pancreas	Head of pancreas
55	F	Pain abdomen,anorexia	Hyperenhancing mass	Head
50	F	Obstructive jaundice	Enhancing mass	Head
40	M	HYPOGLYCEMIA	Well defined enhancing lesion	TAIL
55	M	Pain abdomen,weight loss	Hypodense lesion	Head
48	F	Non specific	Enhancing mass	Head

Table 2. Pathological findings

S No	Gross	Size of Lesion	Microscopy	Ki67 index
1	G/W MASS 2X2 cms	2X2 cms	NET Grade I	<2/10HPF
2	Grey /white mass	2.1x1.9cms	NET Grade I	<2/10HPF
3	SOLID CYSTIC LESION	4.5CMSX3cms	NET Grade I	<2/10HPF
4	G/W SOLID	2.5x2cms	NET Grade 1	<2/10HPF
5	Grey/Brown hemorragic	3.5X3 cms	NET Grade II	12/10HPF

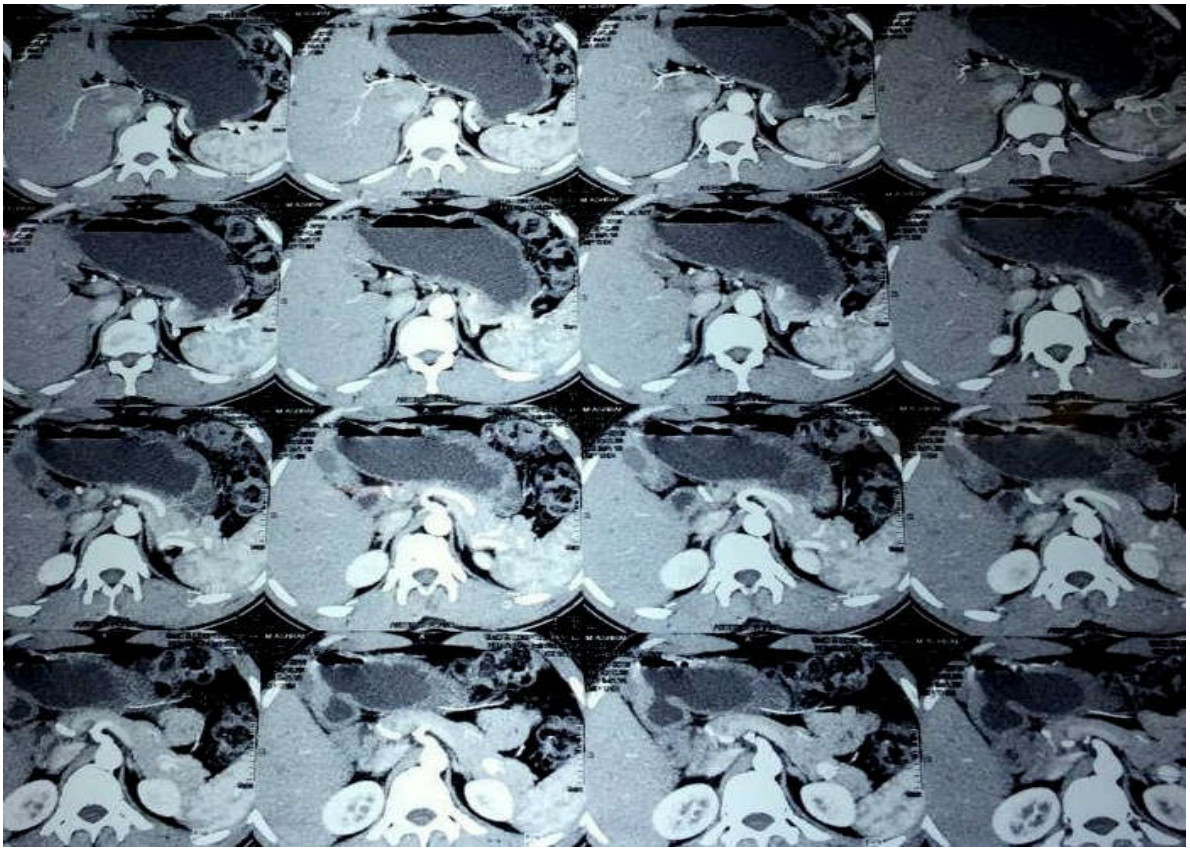

Figure 1. Contrast enhanced CT showing small enhancing mass in tail of pancreas

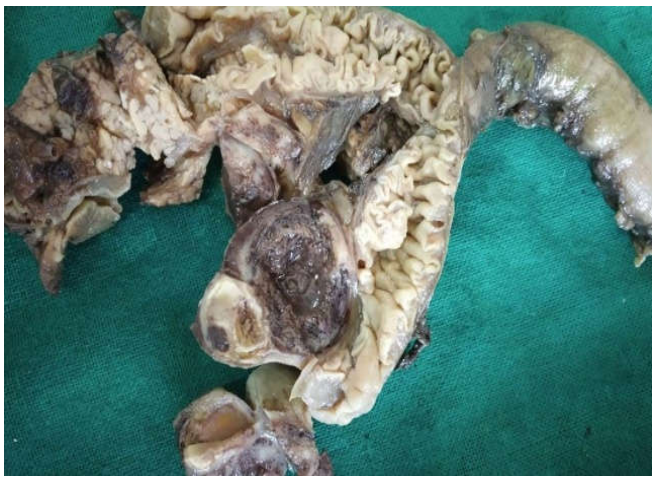

Figure 2. Gross picture of pancreatic neuroendocrine tumor showing well circumscribed Grey/brown mass (Whipple's specimen)

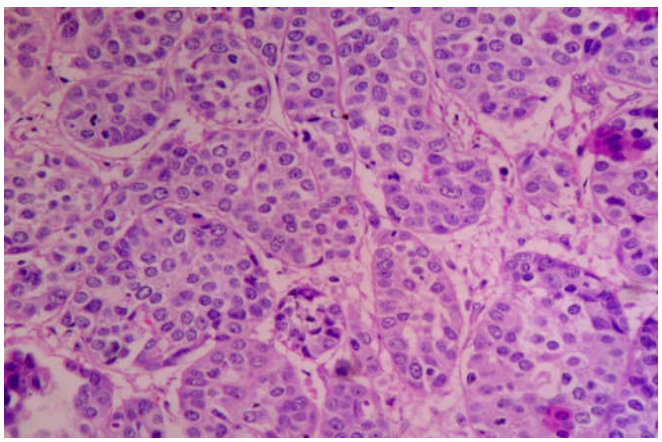

Figure 3. Microscopic appearance of a well-differentiated Pan NET, in which neoplastic cells are organized in a nested fashion and demonstrate minimal pleomorphism or mitotic activity (low-grade or G1 lesion).(H and E Stain) 40x

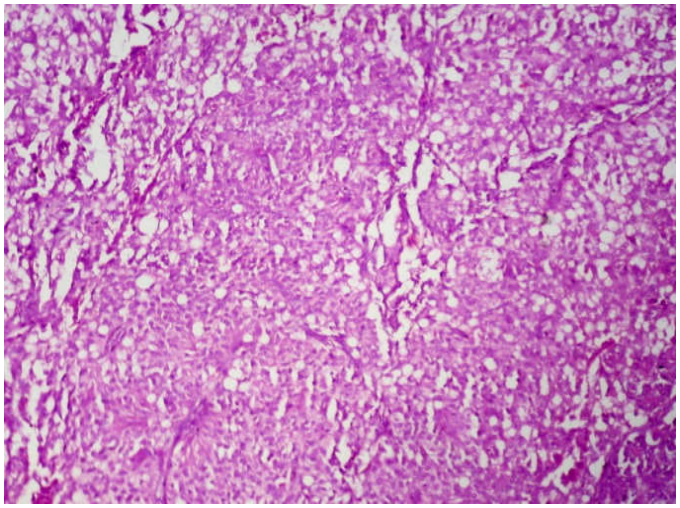

Figure 4. Photomicrograph of pancreatic neuroendocrine tumor with clear cell change

Individual cells had fine chromatin with moderate amount of eosinophilic cytoplasm (Fig3 and 4). Four of our cases were Grade 1 Neuroendocrine tumor. Two cases were Grade 2 Neuroendocrine Tumors .IHC was positive for synaptophsin and chromagranin.TNM staging was done in 5 cases, (Table 3) as one of the six cases was that of a small biopsy so no TNM staging couldn't be done in this cases.

Table3. TNM Staging

	TNM Staging	Stage
1	PT2NOMO	IB
2	PT2NOMO	IB
3	PT3NICMO	IIB
4	PT1NOMO	IA
5	PT2NOMO	IB

DISCUSSION

Pancreatic Neuroendocrine Neoplasms (PanNENs) are relatively uncommon tumors that account for 1% to 2% of all pancreatic neoplasms. They typically occur in adults, with a peak incidence from age 30 to 60 years, but cases have been described at all ages (Florian, 2009). A neuroendocrine tumour arises in any organ derived from primitive endoderm, including pancreatic islet cells, or diffuse neuroendocrine cells of the gut, thyroid gland, respiratory system, or thymus (Ochiai, 2011). As such, PNETs were originally believed to arise from the islets of Langerhans (Asa, 2011). An alternative theory which is gaining acceptance suggests PNETs are derived from the ductal epithelial stem cells. In this theory, precursor pluripotent stem cells from the neural crest mature and secrete one or multiple hormones (Lodish, 2008) Pan NETs are divided into functional and nonfunctional tumors. Functional tumors are classified based upon the hormones they produce and the associated endocrine syndrome (Wendy, 2006; Jian, 2017). The most common PNET, comprising 20% - 30%, secreting insulin is the insulinoma (Goldin, 2008). These are single lesions, measuring less than two cm in 90% of cases (Low, 2011). Insulinomas are benign in 90% of cases (Metz, 2018). The 8% - 10% of lesions over 2 cm are at a higher risk of malignancy .In our study we had a single case of insulinoma who presented with symptoms of hypoglycemia. Glucagonoma, VIPomas, and somatostatinomas are rarer PanNETs, and other rare functional PanNETs also exist (Reid, 2014). The nonfunctional pNENs account for 40-90% pNENs (Kuo, 2014). Nonfunctioning tumors are either an incidental finding or are associated with an expanding mass rather than a hormonal syndrome. However, serologic or immunohistochemical evidence for elevated hormones may be identified (Kuo, 2014; Li, 2011). Because of lacking specific symptoms, non-functional pancreatic NENs tend to be diagnosed at more advanced stages of disease compared with functional pancreatic NENs such as insulinoma and gastrinoma. Five of our cases were non functional neuroendocrine tumors, with only one tumor presenting as functional tumors ie insulinoma. Rest of our cases presented with non specific symptoms like abdominal pain. due to pressure effects caused by tumor. Several radiological imaging techniques can be used for PNEN detection, characterization, and staging (Niina *et al*., 2012). These radiological interventions can be divided by their use into the "anatomic techniques" that determine the location and extent of the tumour, which include CT, MRI and EUS, and the "functional techniques" that define metastatic spread and biological behaviour, which includes scintigraphy (Octreoscan) and PET (Ranvier, 2016). Functional PNENs are more difficult to diagnose radiologically than non-functional, as these tumors are small and seldom alter the pancreatic contour (Goldin, 2008). The most common radiological tools used in the work-up of PNETs are computed tomography (CT) and magnetic resonance imaging (MRI), and all patients should have at least one of these to localize the tumour, determine its respectability and assess metastatic spread (Goldin, 2008).

The sensitivity of these modalities has been reported to range from 14% - 77% (Niina, 2012). Surgical resection remains the only curative treatment for PNETs and alleviates symptoms associated with hormone secretion and mass effect. Surgical options include radical excision with a curative intent, palliative excision aimed at symptomatic relief, and surgical treatment of complications (Ranvier, 2016). The 5-year overall survival rate of resected PNETs is significantly greater than unresected ones, from 77% to 46% (The *et al*., 2017). Complete excision with a curative intent plays a central role for patients with localized tumours at presentation. Major aggressive resection, including either pancreaticoduodenectomy or distal pancreatectomy, may effectively treat tumour-related endocrinopathies and local symptoms due to mass effect (The, 2007). Some authors suggest that sporadic malignant tumours, or tumors over 3cm, are best managed with Whipple's resection or distal pancreatectomy, with resection of adjacent organs and vasculature as indicated in relation to tumor size and its localization. In our study 4 of our patients were managed with Whipples resection and distal pancreatic resection was done in one case. Studies have showed higher rates of lymph node metastases among large tumors (>1.5 cm), tumors involving the pancreatic head, tumors with a high (>20%) Ki67 index, and tumors with vascular invasion; lymph node metastases was associated with a shorter disease free survival (4.5 years vs. 14.6 years without nodal involvement). These authors concluded that lymph node metastases are predictive of poor outcome (Hashim, 2014). While some authors have also reported a relationship between tumor size and lymphadenopathy, others have failed to show this correlation. Recommendations from the National Comprehensive Cancer Network suggest lymph node resection is indicated for tumors between 1 - 2 cm in size (Clancy, 2016). The exact extent of lymph node resection, whether regional, radical, extended or lymph node "picking" is still unclear. The presence of

metastases is the most definitive indicator of a malignant PNET. The risk of metastatic spread depends on the functional status of the tumour and the hormone being expressed. Complete resection and/or hepatic debulking for metastases is associated with improved quality of life and survival (Panzuto *et al*., 2011). Among all PNETs, 60% - 80% will present with metastatic spread (Huang *et al*., 2007). The most common site of metastases is the liver; however, hepatic dysfunction is rare despite the large tumour mass (27). Optimal treatment of liver metastases remains controversial, with options including cytoreduction, debulking surgeries, transplantation, or observation with or without pharmaceutical interventions. Cytoreductive surgery is indicated if metastases are localized or if >90% of the tumor burden is resectable. Nonsurgical therapeutic approaches include chemotherapy, biotherapies, targeted therapies, peptide receptor radiotherapy (PRRT), local ablation and interventional therapy (Jian Sun, 2017).

Conclusion

Pancreatic neuroendocrine neoplasms are a distinct entity from other pancreatic malignancies, and from neuroendocrine tumors elsewhere in the digestive tract.Due to the heterogeneity of tumors encompassed by this diagnosis, panNENs may present with a wide spectrum of clinical features, including signs and symptoms related to hormone hypersecretion or due to mass effect or as an asymptomatic incidental radiographic finding. The incidence of panNENs is increasing and the majority of panNENs are nonfunctional. The revised version of the WHO classification published in 2017 proposed grading criteria based on both cell proliferation and morphology. Better strategies, depending on appropriate pathological evaluation, to treat and improve the outcomes of the patients with pancreatic NETs are required.

Acknowledgements: Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed

Financial Support: None

Conflict OF Interest: None

REFERENCES

Asa, S.L. 2011. Pancreatic Endocrine Tumors. Modern Pathology; 24: S66-S77.

Clancy, T.E. 2016. Surgical Management of Pancreatic Neuroendocrcine Tumors. *Hematology/Oncology Clinics of North America,* 30:103-118.

Fasanella, K.E., McGrath, K.M., Sanders, M., Brody, D., Domsic, R. and Khalid, A. 2009. Pancreatic Endocrine Tumor EUS-Guided FNA DNA Microsatellite Loss and Mortality. *Gastrointestinal Endoscopy,* 69:1074-1080.

Florian E, Hans D, Saeger C. Neuroendocrine tumors of the pancreas. The Oncologist 2009;14:456–67.

Goldin, S.B., Aston, J. and Wahi, M.M. 2008. Sporadically Occurring Functional Pancreatic Endocrine Tumors: Review of Recent Literature. Current Opinion in Oncology. 20: 25-33.

Halfdanarson TR., Rabe KG., Rubin J., Petersen GM. 2008. Pancreatic neuroendocrine tumors (PNETs): Incidence, prognosis and recent trend toward improved survival. *Ann Oncol.* 19:1727-1733.

Hashim, Y.M., Trinkaus, K.M., Linehan, D.C., Strasberg, S.S., Fields, R.C., Cao, D. and Hawkins, W.G. 2014. Regional Lymphadenectomy Is Indicated in the Surgical Treatment of Pancreatic Neuroendocrine Tumors (PNETs). *Annals of Surgery.,* 259:197-203.

Huang, J.S., Chang, M.C., Lee, P.H. and Tien, Y.W. 2007. Is Surgery Indicated for Patients with Symptomatic Nonfunctioning Pancreatic Neuroendocrine Tumor and Unresectable Hepatic Metastases? *World Journal of Surgery,* 31: 2392-2397.

Jian Sun Pancreatic neuroendocrine tumors Intractable & Rare Diseases Research. 2017; 6(1):21-28.

Kuo JH., Lee JA., Chabot JA. 2014. Nonfunctional pancreatic neuroendocrine tumors. *Surg Clin North Am.,* 94:689-708.

Li J, Luo G, Fu D, *et al*., 2011. Preoperative diagnosis of nonfunctioning pancreatic neuroendocrine tumors. *Med Oncol.,* 28(4):1027

Lodish, M.B., Powell, A.C., Abu-Asab, M., Cochran, C., Lenz, P., Libutti, S.K., Pingpank, J.F., Tsokos, M. and Gorden, P. 2008. Insulinoma and Gastrinoma Syndromes from a Single Intrapancreatic Neuroendocrine Tumor. *The Journal of Clinical Endocrinology & Metabolism*. 93; 1123-1128.

Low, G., Panu, A., Millo, N. and Leen, E. 2011. Multimodality Imaging of Neoplastic and Non-Neoplastic Solid Lesions of the Pancreas. Radiographics : 31, 993-1015.

Metz DC., Jensen RT. 2008. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*., 135(5):1469.

Modlin IM., Oberg K., Chung DC., Jensen RT., de Herder WW., Thakker RV. *et al*., 2008. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.,* 9:61-72

Niina, Y., Fujimori, N., Nakamura, T., Igarashi, H., Oono, T., Nakamura, K., Kato, M., Jensen, R.T., Ito, T. and Takayanagi, R. 2012. The Current Strategy for Managing

Öberg, K. 1998. "Carcinoid Tumors: Current Concepts in Diagnosis and Treatment". *The Oncologist.,* 3 (5): 339–45..

Ochiai, T., Masuda, T., Nishizawa, M., Ito, H., Igari, K., Aihara, A., Kumagai, Y., Iida, M., Odajima, H., Arii, S. and Yamazaki, S. Curative Resection of a Huge Malignant Pancreatic Endocrine Tumor by Pancreatoduodenectomy with Portal and Superior Mesenteric Vein Resection and Reconstruction Using the Right Ovarian

Pancreatic Neuroendocrine Tumors in Multiple Neuroendocrine Neoplasia Type *I. Gut and Liver.,* 6: 287-294.

Panzuto, F., Boninsegna, L., Fazio, N., Campana, D., Brizzi, M.P., Capurso, G., Scarpa, A., de Braud, F., Dogliotti, L., Tomassetti, P., Face, G.D. and Falconi, M. Metastatic and Locally Advanced Pancreatic Endocrine Carcinomas: Analysis of Factors Associated with Disease Progression. Journal of Clinical Oncology. 2011; 29: 2372-2377.

Panzuto, F., Boninsegna, L., Fazio, N., Campana, D., Brizzi, M.P., Capurso, G., Scarpa, A., de Braud, F., Dogliotti, L., Tomassetti, P., Face, G.D. and Falconi, M. 2011. Metastatic and Locally Advanced Pancreatic Endocrine Carcinomas: Analysis of Factors Associated with Disease Progression. *Journal of Clinical Oncology.* 29: 2372-2377

Ranvier, G.G.F., Shouhed, D. and Inabnet III, W.B. 2016. Minimally Invasive Techniques for Resection of Pancreatic Neuroendocrine Tumors. *Surgical Oncology Clinics*., 25: 195-215.

Reid, M.D., Balci, S., Saka, B. and Adsay, N.V. 2014. Neuroendocrine Tumors of the Pancreas: Current Concepts and Controversies. *Endocrine Pathology.,* 25: 65-79.

Teh, S.H., Deveney, C. and Sheppard, B.C. 2007. Aggressive Pancreatic Resection for Primary Pancreatic Neuroendocrine Tumor: Is It Justifiable? *The American Journal of Surger*. 193:610-613.

Valle JW., Eatock M., Clueit B., Gabriel Z., Ferdinand R., Mitchell S. 2014. A systematic review of non-surgical treatments for pancreatic neuroendocrine tumours. *Cancer Treat Rev.,* 40:376-389.

Vein: Report of a Case. Surgery Today (2011):; 41, 1260-1265.

Wendy L. Frankel, MD. 2006. Update on Pancreatic Endocrine Tumors Arch Pathol Lab Med. July., 130: 963-67.

Yao JC., Hassan M., Phan A., Dagohoy C., Leary C., Mares JE. *et al*., 2008. One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.,* 26:3063-72.

****