

Pancreas Neuroendocrine Tumors: An Introduction

Yasunaru Sakuma, Naohiro Sata, Alan Kawarai Lefor

Department of Gastroenterological Surgery, Jichi Medical University, Tochigi, Japan

ABSTRACT

Neuroendocrine tumors are rare, however their incidence is increasing. Details of the clinical aspects of these unusual tumors are gradually being revealed all over the world. Pancreas neuroendocrine tumors are a heterogeneous group of tumors with diverse morphologies and behaviors. However, as their character is being revealed, new treatment options have been developed in recent years. This introduction presents an overview of Pancreas Neuroendocrine Tumors, with a focus on their origin, character, epidemiology and biology.

Origin of Neuroendocrine Tumors of the Pancreas

"Neuroendocrine tumors (NET)" are considered to arise from "neuroendocrine cells" located in various parts of the body. Since neuroendocrine cells are located throughout the body, these tumors can originate in many organs of the body including the pancreas, gastrointestinal tract, lung, etc. [1]. The origin of the cells from which neuroendocrine tumor cells arise is not well understood. However, neuroendocrine cells can be divided into two systems, namely aggregations of cells that constitute glands (pituitary, thyroid, parathyroid, ganglia, thymus and adrenal medulla) and diffusely distributed dispersed cells that constitute a disseminated system which is now referred to as the diffuse neuroendocrine system (DNES) [2]. Embryologically, these systems are different, because the former is derived from ectodermal tissue and the latter is from endodermal tissue.

Compensating for these embryological differences, Pearse *et al.* identified these diverse cells more reliably by using Grimelius staining which applies a redox reaction of silver, and described a peptide hormone secreting cells in the body which have a common morphological characteristic, a new Amine and Precursor Uptake and Decarboxylation (APUD) cell concept [3]. APUD cells are recognized by the presence of neurosecretory granules and have autocrine, paracrine and neuromodulatory functions, in accordance with their endocrine function. These cells are also found not only in the gland they constitute, but

also throughout the body as if supporting the DNES concept, and are thought to originate in the embryologic neural crest [4]. This APUD cell concept cleverly explains the origin of Multiple Endocrine Neoplasms (MEN) which produce multiple peptide hormone, and synchronous and/or metachronous tumors which occur also in multiple organs. While the pituitary and adrenal glands, target organs for MEN, are known to be derived from ectodermal tissue, the pancreas is originally from endoderm. The APUD cell concept overcomes this embryological antinomy.

However, to add to the confusion, it is still believed that pancreas neuroendocrine cells arise not from the neural crest but from the endoderm, meaning that these cells should come from the epithelial cells of the pancreas itself or the proximal small intestine. Histologically, pancreas NET (PNET) seems to arise in tissues adjacent to the pancreas, as well as within the pancreas itself [5]. PNETs thus originate from islet cells or the islets of Langerhans, hence they were previously known as islet cell tumors. Islet cells are the endocrine cells of the pancreas and distinct from the exocrine cells, from which pancreatic ductal adenocarcinomas arise.

When focusing on PNET, there are still other probable origins as well as these anatomical aspects. In addition to mature endocrine cells in the pancreas, there are also multipotent stem cells that can differentiate into endocrine cells in the pancreas and malignant cells such as adenocarcinomas or squamous cell carcinomas which have the potential to be trans-differentiated into neuroendocrine cells. Furthermore, intraductal papillary neoplasm also considered having a common neoplastic progenitor or they may be transdifferentiation into PNET. Isolated endocrine cell which exist in acinar cells may also serve as the origin of these tumors [6, 7, 8, 9]. Finally, when considering the origin of PNET, the APUD cell concept is still reasonable, however there is other evidence to support the origin of these cells from endoderm and/or the trans-differentiation from stem cells in the pancreas [10, 11].

Received August 12th, 2017 - Accepted October 10th, 2017

Keywords Biology; Embryology; Epidemiology; Neuroendocrine Cells; neuroendocrine tumor; Pancreas

Abbreviations APUD Amine and Precursor Uptake and Decarboxylation; DNES diffuse neuroendocrine system; NET neuroendocrine tumors

Correspondence Yasunaru Sakuma

Department of Surgery
Jichi Medical University
3311-1 Yakushiji Shimotsuke, Tochigi, Japan 3290427
Tel +81(285) 58-7371
Fax +81 (285) 44-3234
E-mail naruchan@jichi.ac.jp

NETs are classified according to their site of origin in the embryological gut, and divided into foregut, midgut and hindgut tumors. These are reasonable classifications which only include cells of endodermal origins. Foregut tumors develop in the thymus, esophagus, respiratory tract, stomach, duodenum, and pancreas. Midgut tumors develop in the appendix, small bowel, cecum and ascending colon. Hindgut tumors develop in the transverse colon, descending colon, sigmoid colon and rectum. PNET were previously classified within foregut tumors, with at least five functional and other non-functional tumors [12] (Figure 1).

To investigate the origin of these tumors, the genesis of the cells is important to understand their nature. However in the clinical setting, the ideal situation is to detect these tumors before they grow significantly, which may make it difficult to fully evaluate their pathology and morphology. At the present stage, wherever from and how the neuroendocrine cells arise, there remains a difference between the clinical importance and the many theories to explain their origin.

Characteristics of Neuroendocrine Cells

The term “neuroendocrine” reflects the fact that these cells exhibit both the morphological and physiological attributes of the neural and endocrine regulatory systems, and the “neuroendocrine cell” means the type of cell which synthesizes hormones in the cytoplasm with transport to the axon, and finally secreting into the blood vessels from the nerve endings [13]. As an example, the hypothalamus is connecting the nervous system to the endocrine system via the pituitary gland, thus vasopressin and oxytocin are released into the capillaries of the posterior lobe of the

pituitary gland from its neuroendocrine cells [14]. The phenotype sometimes does not relate to their histogenesis and hormones at each site. With more “neural-like” differentiation, there are neuroendocrine cells in the larynx, lung, thymus, and thyroid. With a more “epithelial-like” differentiation, there are neuroendocrine cells in the gastroenteropancreatic NET (GEP-NET) system, and interplay seems to exist between these neuroendocrine cells and neural crest-derived nerve endings [15].

Not only neuroendocrine cells, but also NETs, expressing general markers of neuroendocrine differentiation such as chromogranin, synaptophysin and neuron-specific enolase. These are peptide hormones, and can be employed in the clinical and morphological diagnosis of GEP-NET, because they are independent of cell-specific hormone production. These peptide hormones share a neural-endocrine phenotype [16]. Synaptophysin is a small synaptic vesicle, and Chromogranin A (CgA) is a membrane protein of neurosecretory granules. These molecules can serve as tumor markers, including serum tumor markers and immunohistochemical tumor markers [17]. These peptide hormones are useful for establishing the diagnosis of NET. Furthermore, serum CgA levels, a widely used serum marker and member of the chromogranin family, are often elevated in the serum of patients with PNET especially those with non-functioning tumors [18]. Serum CgA is now considered to be the best available biomarker for the diagnosis of NET, and an elevated CgA level may correlate with tumor progression. In neuroendocrine cells, CgA is usually secreted into the serum with the hormones inside, however the real reason for the elevation of CgA in patients with NET and its relation to tumor growth are unknown. Enolase is a glycolytic enzyme with five subtypes, and two types are expressed in neuroendocrine cells, called

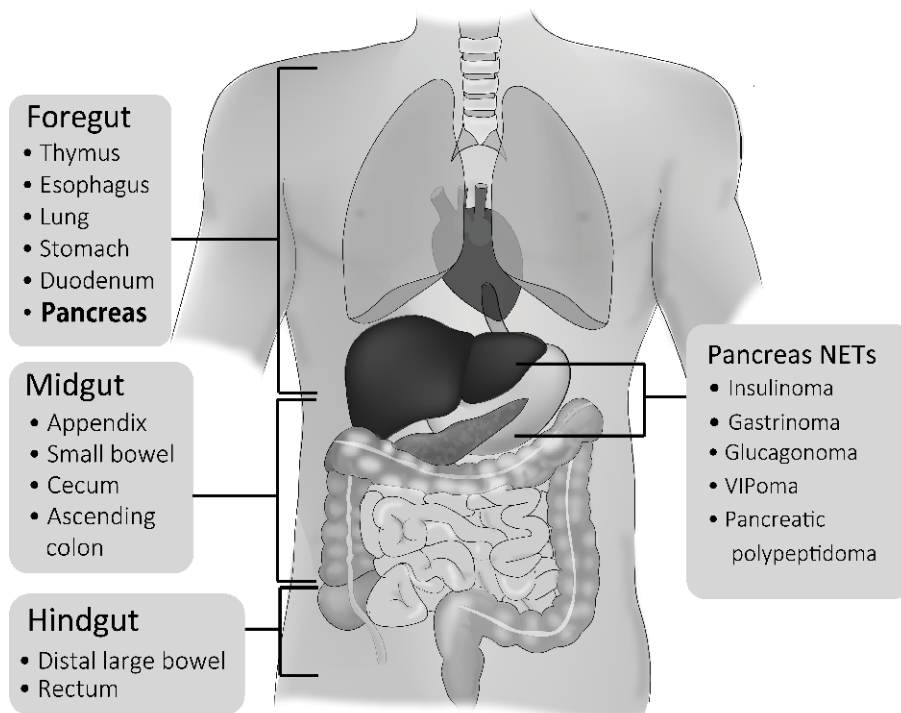


Figure 1. Neuroendocrine tumors are generally classified as foregut, midgut, or hindgut depending on their embryonic origin, and the pancreas are having at least 5 different types of functional tumors.

neuron specific enolase (NSE). If cells containing NSE are lysed due to rapid proliferation and/or treatment of the tumor, the serum level of NSE is elevated [19]. Not only neuroendocrine cells but also NET cells express at least two subtypes of somatostatin receptors (SSTRs) which are important for the regulation of hormones. SSTRs are analyzed using various procedures, including immunohistochemistry (IHC) for especially SSTR2 [20]. Neural cell adhesion molecules (NCAM) which contribute to cell proliferation are also specific markers (**Figure 2**). The NET cells contain the same specific markers as neuroendocrine cells, and it is important to comprehend the character of neuroendocrine cells.

Overview of Neuroendocrine Tumors

Oberndorfer coined the term “karzinoide” in 1907, which means “carcinoma like”, implying that the tumors are “benign carcinomas”, because these tumors were evaluated as carcinomas based on pathological findings but the clinical course was benign at the beginning [21]. However, this is an unfortunate misnomer for the majority of NETs. After World War II, along with long-term survivors, some NETs were revealed to have malignant potential and metastasize, generally to the liver. Referring to any NET, the term “carcinoid” should only be used in reference to carcinoid syndrome. The symptoms of carcinoid syndrome include flushing, abdominal cramps, and diarrhea, and most cases are associated with tumors of the gastrointestinal tract [22]. Carcinoid syndrome occurs in approximately 8% to 35% of patients with NETs and occurs mostly in patients with hepatic metastases. These symptoms are a consequence of vasoactive peptides such as serotonin, histamine, or tachykinins being released into the circulation [23, 24].

At least 17 different entities are described arising in different organs only in GEP-NET, and different terminologies have increased the level of confusion. Moreover, NETs are generally characterized by their ability to produce peptides that lead to the associated syndromes, and named their ability based on the production of these hormones. These different characteristics are not common to every NET which over time has led to confusion, which gradually became fixed in the medical literature. In 2000, the World Health Organization (WHO) for the first time updated its classification of NETs based on site of origin, clinical syndrome, and degree of differentiation [25]. Finally, NETs are now regarded as malignant neoplasms that can cause multiple symptoms and are a potentially life-threatening disease.

Epidemiology of Neuroendocrine Tumors

NETs are rare tumors. However, the number of patients is increasing every year originating not only in the pancreas, but also other sites referred to as GEP-NET [26]. A review of the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database showed an increased incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000), with an estimated prevalence of 103,312 cases in the United States [27]. The age-adjusted incidence rate amazingly increased 6.4 fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000). This tendency is found not only in the United States but all over the world, and the incidence of NETs has markedly increased over the past three decades.

NETs originating in the pancreas are relatively rare when compared with gastrointestinal NETs and other organs. In Europe and the United States, PNET is represents about 1-2% of the all pancreatic tumors, and less than

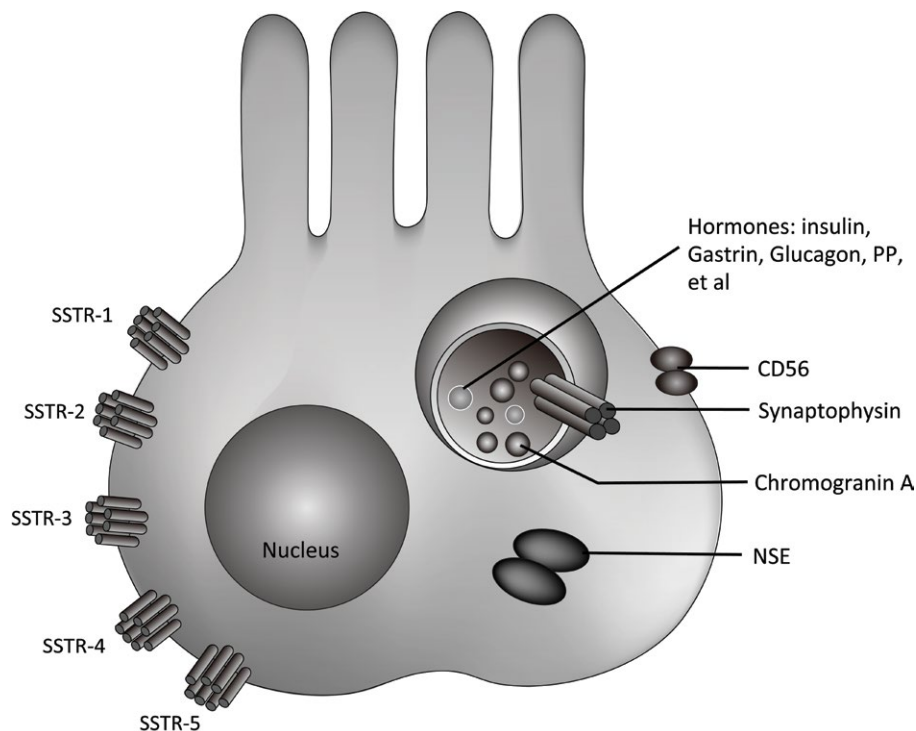


Figure 2. Common character between neuroendocrine cell and tumor especially in pancreas. CD56 neural cell adhesion molecules; NSE neuron specific enolase; PP pancreatic polypeptide; SSTR somatostatin receptors

10% among all NETs. A review of data from SEER shows that the annual PNET incidence was 0.3–0.4 per 100,000 in the United States. In Europe, the ratio for each primary site of NET is almost same as the US series and PNET is also relatively rare [28]. The pancreas is the most common primary location of NETs from a survey of the Middle East and the Asia Pacific region (Figure 3). Although PNETs are not always the majority in Asian countries, they have a higher incidence when compared with Western countries [29, 30, 31].

Data from the SEER registry shows that the digestive system is the most common location of primary NETs and they represent over half of all NETs. In Europe, the digestive system is also reported to be the most common location of primary NETs, and the relative incidence is the same as in US series. When considering racial differences, the lung was the primary site more often among white patients (30%) than among patients in other racial groups. Additionally, jejunal/ileal NETs were more common in white (17%) and African American (15%) patients than in Asian/Pacific Islander and American Indian/Alaskan native patients. In contrast, rectal NETs occurred at a markedly higher frequency among Asian/Pacific Islanders (41%), American Indian/Alaskan Natives (32%), and African American (26%) patients than among white (12%) patients. Interestingly, in this US survey, the incidence of PNETs is not so different in each racial group, and different from the previously described Asian data. It is very difficult to explain the differences in the occurrence of PNETs comparing the data from the United States and the results from Asian countries [27]. However, the fact that the ratio of PNETs in Asian countries is relatively higher may be significant and suggests racial difference in the epidemiology of PNETs. In summary, foregut NETs except in the pancreas have a higher tendency in Western

countries, while hindgut NETs are more common in Asian countries (Figure 4).

Literatures evaluating the ratio of pancreas NET in autopsy series present interesting histologic information. Eleven “endocrine adenomas” were found among 1366 Swedish autopsy cases (0.8%), and none of the patients carried the diagnosis of a pancreatic tumor in life or had evidence of symptoms from hormone overproduction [32]. Twenty pancreas NETs were found among 800 consecutive patients (2.5%) undergoing autopsy in a Japanese geriatric hospital. None of these patients had symptoms of excessive hormone secretion prior to their death and only one patient had a prior history of a resected gastrinoma. A randomly selected subset of 60 patients who had 5 mm thick sections of the pancreas were examined thoroughly and six (10%) were found to have an occult PNET [33]. Considering these results, PNETs may be much more common than previously thought. The patients are frequently asymptomatic. Finally, the increasing incidence of PNETs is likely to be pluralistic, attributed to an aging population, improved detection with advanced imaging and diagnostic endoscopy and an increased awareness of the disease, among both the medical community and the public [34].

At the time of diagnosis, distant metastases are reported in 21% of patients with PNETs, and the non-functioning PNETs represent 32% of lesions. Among functional PNETs, gastrinoma has a high rate of distant metastases (30%). It has also been reported that distant metastasis are found in 64% of patients at the time of diagnosis. Interestingly, non-functional PNETs have a significant correlation with more than 2cm tumors and distant metastases. Earlier resection is recommended to limit the development of distant metastases. Overall mean survival of patients

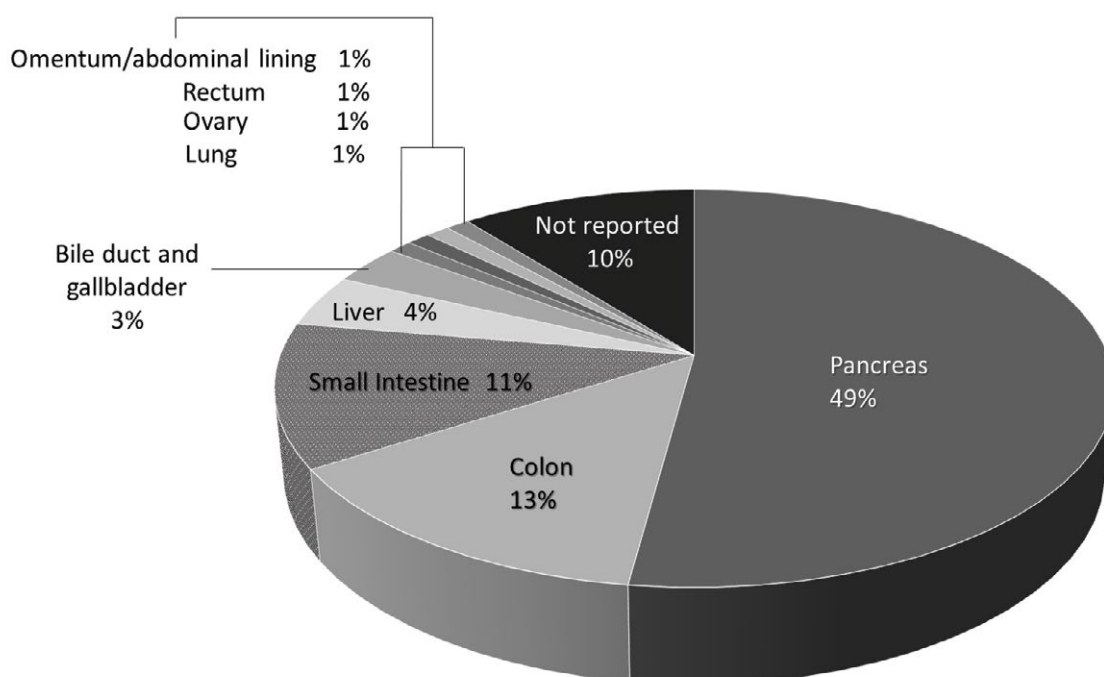


Figure 3. The pancreas is the most common primary location of neuroendocrine tumor in Middle East and Asia Pacific region survey.

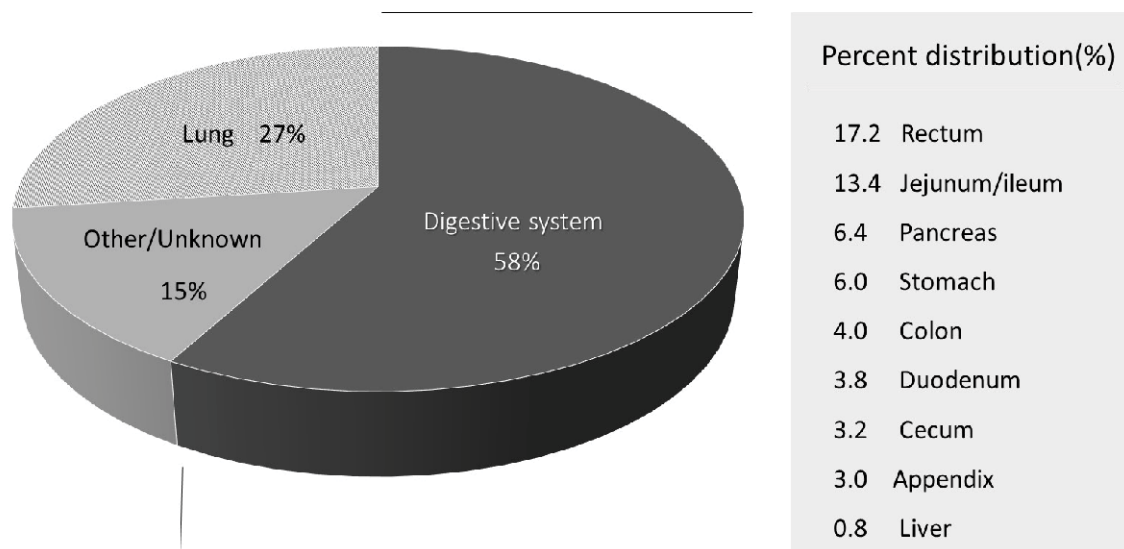


Figure 4. The digestive system is the most common primary location of neuroendocrine tumor in US SEER data, and the lung was the second target organ. In digestive system, the midgut tumor is also the common primary location in US and the ratio is different from Asian report compared with figure 3.

with PNET is reported to be 99 months. The 5-year survival rate is estimated to be 60–100% for patients with localized disease, 40% with regional disease and 25% with metastatic disease. However, in dedicated centers the 5-year survival in patients with metastatic disease has been reported at over 60%, highlighting the importance of specialized care for patients with this rare tumor [35, 36].

Biology of PNETs

PNETs are a heterogeneous group of tumors with diverse morphologies and behavior. Non-functioning tumors which are considered sporadic comprise a substantial proportion of all PNETs comprising 25–100% [37]. The frequency of various subtypes of functional PNETs has been described in several studies and insulinoma is the most frequently encountered functional NET. Insulinomas are usually benign and almost always located in the pancreas [38]. Gastrinoma is the second most commonly encountered functional PNET but gastrinoma frequently presents outside the pancreas, in contrast to insulinoma. Moreover, up to 30% of gastrinomas are associated with MEN type 1 [39]. MEN1, known as a tumor suppressor gene, is widely distributed patients with MEN type 1 while NETs occur only in target organs (e.g. hypothalamus, parathyroid and pancreas). The mechanism of this organ specificity is still unknown. Clinically, MEN type 1 and 2 are considered as similar diseases, but there actually many differences include their background.

In patients with sporadic PNETs, 20–40% express a somatic mutation of MEN1 and the mutation is frequently associated with gastrinoma or glucagonoma. Additionally, the most frequently mutated genes in sporadic PNET appear to be involved in the remodeling of chromatin, and its novel tumor suppressor genes ATRX (alpha thalassemia/mental retardation syndrome X-linked) and DAXX (death-domain associated protein) were mutated in 43% of a cohort of 58 PNETs [40]. These mutations can be associated with hereditary diseases, such as MEN

1, Von Hippel Lindau (VHL) and Neurofibromatosis type 1 (NF-1). The MEN1 mutation is thought to be an early event in PNET tumorigenesis [41, 42], and mutations in MEN1 promote the proliferation of cells and DAXX mutations result in uncontrolled cell proliferation [41, 42]. Furthermore, mutations in ATRX and mTOR are involved in de-differentiation, invasion and metastasis [43]. More recently, PHLDA3 was introduced as a novel tumor suppressor of PNETs, and this genetic change is correlated with disease progression and poor prognosis [44].

Common gene mutations such as p53 and K-ras which occur in other solid tumors, are rare in PNETs, but more common in neuroendocrine carcinoma (NEC), and appear to have very different molecular profiles [42]. NEC can have mutated p53, but not DAXX/ATRX, so the transcriptional modification might be important in gene expression and activity. These considerations may partially explain why the clinical course of patients with PNETs and PNECs are noticeably different. The mean 5-year survival of patients with PNEC is about 10%, while for those with PNET, it is over 50% [45]. Interestingly, based on clinical observations, it is quite rare that the character and malignant potential of PNETs change over the clinical course. Further investigation of these biological differences might reveal the reasons for the differences in character.

Conflict of Interest

The authors have no financial conflicts of interest concerning the manuscript to disclose.

References

1. Montuenga LM, Guembe L, Burrell MA, Bodegas ME, Calvo A, Sola JJ, et al. The diffuse endocrine system: from embryogenesis to carcinogenesis. *Prog Histochem Cytochem* 2003; 38: 155–272. [PMID: 12756892]

2. Simon S, Bernhard S, Benjamin L, Mark K, Irvin M. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg* 2011; 396: 273-298. [PMID: 21274559]
3. Pearse AGE. 5-hydroxytryptophan uptake by dog thyroid C cells and its possible significance in polypeptide hormone production. *Nature* 1966; 211: 598-600. [PMID: 5298184]
4. Pearse AGE. The diffuse neuroendocrine system and APUD concept: Related peptide in brain, intestine, pituitary, placenta and anuran cutaneous glands. *Med Biol* 1977; 55:115-125. [PMID: 330966]
5. Andrew A, Kramer B, Rawdon B. The origin of gut and pancreatic neuroendocrine (APUD) cells – the last word? *J Pathol* 1998; 186:117-118. [PMID: 9924424]
6. Marrache F, Cazals-Hatem D, Kianmanesh R, Palazzo L, Couvelard A, O'Toole D, et al. Endocrine tumor and intraductal papillary mucinous neoplasm of the pancreas: a fortuitous association? *Pancreas* 2005; 31:79-83. [PMID: 15968252]
7. Laidlaw GF. Nesidioblastoma, the islet tumor of the pancreas. *Am J Pathol* 1938; 14:125-134. [PMID: 19970380]
8. Creutzfeldt W, Creutzfeldt C, Frerichs H, Track NS, Arnold R. Pathomorphologic, biochemical, and diagnostic aspects of gastrinoma (Zollinger-Ellison syndrome). *Hum Pathol* 1975; 6:47-76. [PMID: 179934]
9. Le Douarin NM. On the origin of pancreatic endocrine cell. *Cell* 1988; 53:169-171. [PMID: 3282672]
10. Rosai J. The origin of neuroendocrine tumors and the neural crest saga. *Mod Pathol* 2011; 24(Suppl 2):53-7. [PMID:21455201]
11. Paris M, Turrel-Cuzin C, Plachot C, Ktorza A. Review: pancreatic beta-cell neogenesis revisited. *Exp Diabetes Res* 2004; 5:111-121. [PMID:15203882]
12. Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet* 1963; 1:238-9. [PMID:14000847]
13. Gann DS. Endocrine control of plasma protein and volume. *Surg Clin North Am* 1976; 56:1135-45. [PMID:185730]
14. Bisset GW, Chowdrey HS. Control of release of vasopressin by neuroendocrine reflexes. *Q J Exp Physiol* 1988; 73:811-72. [PMID:2907166]
15. Tischler AS, Dichter MA, Biales B, DeLellis RA, Wolfe H. Neural properties of cultured human endocrine tumor cells of proposed neural crest origin. *Science* 1976; 192:902-4. [PMID: 179139]
16. Bishop AE, Power RF, Polak JM. Markers for neuroendocrine differentiation. *Pathol Res Pract* 1988; 183:119-28. [PMID:2968544]
17. Wiedenmann B, Huttner WB. Synaptophysin and chromogranins/secretogranins--widespread constituents of distinct types of neuroendocrine vesicles and new tools in tumor diagnosis. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1989; 58:95-121. [PMID:2575822]
18. Panzuto F, Severi C, Cannizzaro R, Falconi M, Angeletti S, Pasquali A, et al. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. *J Endocrinol Invest* 2004; 27:6-11. [PMID:15053236]
19. Lamberts SW, Hofland LJ, Nobels FR. Neuroendocrine tumor markers. *Front Neuroendocrinol* 2001;22:09-339. [PMID:1158755]
20. Papotti M, Bongiovanni M, Volante M, Allia E, Landolfi S, Helboe L, et al. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. *Virchows Arch* 2002; 440:461-75. [PMID: 12021920]
21. Oberndorfer S. Karzinoide tumoren des dunndarms. *Frankfurter Zeitschrift fur Pathologie* 1907; 1:424-432.
22. Bhattacharyya S, Gujral DM, Toumpanakis C, Dreyfus G, Davidson BR, Davar J, et al. A stepwise approach to the management of metastatic midgut carcinoid tumor. *Nat Rev Clin Oncol* 2000; 6:429-433. [PMID:19561636]
23. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol* 2005; 89:151-60. [PMID:15719376]
24. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. The molecular genetics of gastroenteropancreatic neuroendocrine tumors. *Gastroenterology* 2005; 128:1717-1751. [PMID:16258976]
25. Solcia E, Kloppel G, Sobin LH. *Histological typing of endocrine tumors*, 2nd, Springer-Verlag, Berlin, Heidelberg, 2000.
26. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934-959. [PMID:12569593]
27. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; 26:3063-3072. [PMID:18585694]
28. Taal BG, Visser O. Epidemiology of neuroendocrine tumours. *Neuroendocrinology* 2004; 80:3-7. [PMID:15477707]
29. Tsai HJ, Wu CC, Tsai CR, Lin SF, Chen LT, Chang JS. The epidemiology of neuroendocrine tumors in Taiwan: a nation-wide cancer registry-based study. *PLoS One* 2013; 8:e62487. [PMID:23614051]
30. Wang YH, Lin Y, Xue L, Wang JH, Chen MH, Chen J. Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995-2012) in South China. *BMC Endocr Disord* 2012; 12:30. [PMID:23194346]
31. Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. *J Gastroenterol* 2010; 45:234-43. [PMID:20058030]
32. Grimelius L, Hultquist GT, Stenkvist B. Cytological differentiation of asymptomatic pancreatic islet cell tumours in autopsy material. *Virchows Arch A Pathol Anat Histol* 1975; 365:275-288. [PMID:46649]
33. Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci* 1991; 36:933-942. [PMID:2070707]
34. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; 121:589-97. [PMID:25312765]
35. Ehehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. *Oncologist* 2009; 14:456-67. [PMID:19411317]
36. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; 19:1727-33. 7. [PMID:18515795]
37. Eriksson B, Öberg K, Skogseid B. Neuroendocrine pancreatic tumors. Clinical findings in a prospective study of 84 patients. *Acta Oncol* 1989; 28:373-377. [PMID:2472825]
38. Öberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol* 2005; 19:753-781. [PMID:16253899]
39. Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, et al. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. *Medicine (Baltimore)* 2000; 79:379-411. [PMID:11144036]
40. Reid MD, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. *Endocr Pathol* 2004; 25:65-79. [PMID:24430597]
41. Zhang J, Francois R, Iyer R, Seshadri M, Zajac-Kaye M, Hochwald SN. Current understanding of the molecular biology of pancreatic neuroendocrine tumors. *J Natl Cancer Inst* 2013; 105:1005-17. [PMID: 23840053]
42. Perren A, Anlauf M, Komminoth P. Molecular profiles of gastroenteropancreatic endocrine tumors. *Virchows Arch* 2007; 451:S39-S4.
43. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, et al. DAXX/ATRAX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 2011; 331:1199-203. [PMID: 21251325]

44. Ohki R, Saito K, Chen Y, Kawase T, Hiraoka N, Saigawa R, et al. PHLDA3 is a novel tumor suppressor of pancreatic neuroendocrine tumors. *Proc Natl Acad Sci U S A* 2014; 111:E2404-13. [PMID: 2491292]

45. Pape UF, Jann H, Müller-Nordhorn J, Bockelbrink A, Berndt U, Willich SN, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer* 2008; 113:256-65. PMID: [18506737]
