Pancreatic Neuroendocrine Neoplasms

Practical Approach to Diagnosis, Classification, and Therapy

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Preface

Since the early 2000s, the advances in imaging technologies and the wide diffusion of endoscopic ultrasound-guided fine needle aspiration have led to an increased detection of pancreatic neuroendocrine neoplasms compelling radiologists, pathologists, and nuclear medicine physicians to manage these diseases at an earlier stage. The increased surgical expertise together with new pharmacological options has also changed the therapeutic approach. At the same time, the refined WHO classification of 2010, increased experience of pathologists in this field, better knowledge of the clinicopathological features, and the availability of new molecular technologies have all increased our understanding of the pathogenesis and progression of such neoplasms. For all these reasons, the field of pancreatic neuroendocrine neoplasms has rapidly grown in the last 10 years and the aim of this book is to capture these dynamic changes providing a broad overview of this topic.

After a historical and epidemiological overview, four chapters attempt to capture the technical advances in diagnostic procedures providing insights for a critical evaluation of the new diagnostic options. The chapters on the immunohistochemical approach to diagnosis and on the criteria now used to classify pancreatic neuroendocrine neoplasm in different prognostic categories represent the bridge between the diagnostic step and the full characterization of the different entities. These are treated in 11 chapters which cover the epidemiology, diagnosis, morphology, and prognosis of each tumor type. A specific chapter is also dedicated to hyperplastic and microadenomatous neuroendocrine lesions, which may represent a diagnostic challenge for pathologists and clinicians.

Careful consideration is given to the molecular features of various tumors and a specific chapter gives a critical overview of the most important knowledge which has contributed to our understanding of the pathogenesis of such neoplasms and may have potential implications for new therapeutic pathways. The final chapters consider the surgical and medical approaches to therapy, providing a practical and analytical overview of the available options.

The book is written by a multidisciplinary team of worldwide-recognized experts and is addressed to radiologists, nuclear medicine physicians,

endocrinologists, pathologists, surgeons, and oncologists interested in endocrine tumors of the pancreas.

The editors wish to thank the contributing authors and hope the readers will find all the information they need for their daily practice.

Varese, Italy — Stefano La Rosa
Varese, Italy — Fausto Sessa

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Historical Background and Epidemiology

1

Fausto Sessa and Roberta Maragliano

1.1 Historical Background

The pancreas is a deeply located organ, which had been neglected for centuries until 1543 when the anatomist Andries van Wesel, better known *as Andreas Vesalius* (1514–1564), gave his description in the fifth book of "De Humani Corporis Fabrica Libri Septem." However, Rufus of Ephesus (circa 100 A.D.) first gave the name pancreas to the organ, which had previously been described by Herophilus of Chalcedon (circa 300 B.C.). For several centuries, this organ was forgotten probably because the canons of ancient medicine had not linked the theories of body fluids to any pancreatic diseases.

In 1642, Johann Georg Wirsung (1589–1643) described the main pancreatic duct when he was a prosector in Padua, Italy, where he performed autopsies under the guidance of his mentor, Ioannes Veslingius (Johann Vesling, 1598–1649). In 1720, the German anatomist Abraham Vater described the site of conjunction between the bile duct and the pancreatic duct, now known as the ampulla of Vater. The physiologist Albrecht Von Haller (1708–1777) noted that the pancreatic duct entered the small bowel in conjunction with the bile duct and suggested that the pancreatic juice could act by diluting and softening the bile. Thomas Wharton observed the similarity between the structure of the pancreas and that of the submaxillary gland from which Samuel Thomas *von* Sömmerring (1755–1830) employed the term "Bauchspeicheldrüse" or "abdominal salivary gland." This terminology was used until the beginning of the last century [1–4].

In February 1869, Paul Langerhans (1847–1888) first described the pancreatic islets, which make up the 1–2 % of the mass of the pancreas (average weight 70–100 g) (Fig. 1.1a). At the end of his medical studies, he presented a thesis entitled "Contributions to the microscopic anatomy of the pancreas," in which he refers to *islands of clear cells* throughout the gland, staining differently than the surrounding tissue (Fig. 1.1b) [5].

In 1893, E. Laguesse named these clusters of clear cells "Islands of Langerhans" and suggested that they were the pancreatic units involved in diabetes mellitus [6]. In 1902, he described in detail the histological characteristics of the islets in dogs after ligation of the duct. After that, E. Lindsay Opie (1873–1971) described the hyaline changes of pancreatic islets in diabetic patients. At the beginning of the last century, F.G. Banting and C.H. Best, working at the University of Toronto under the supervision of the physiologist J.J. R. Macleod, obtained "isletin" from Ringer's solution containing pancreatic juice from dogs (Fig. 1.2). Insulin was not

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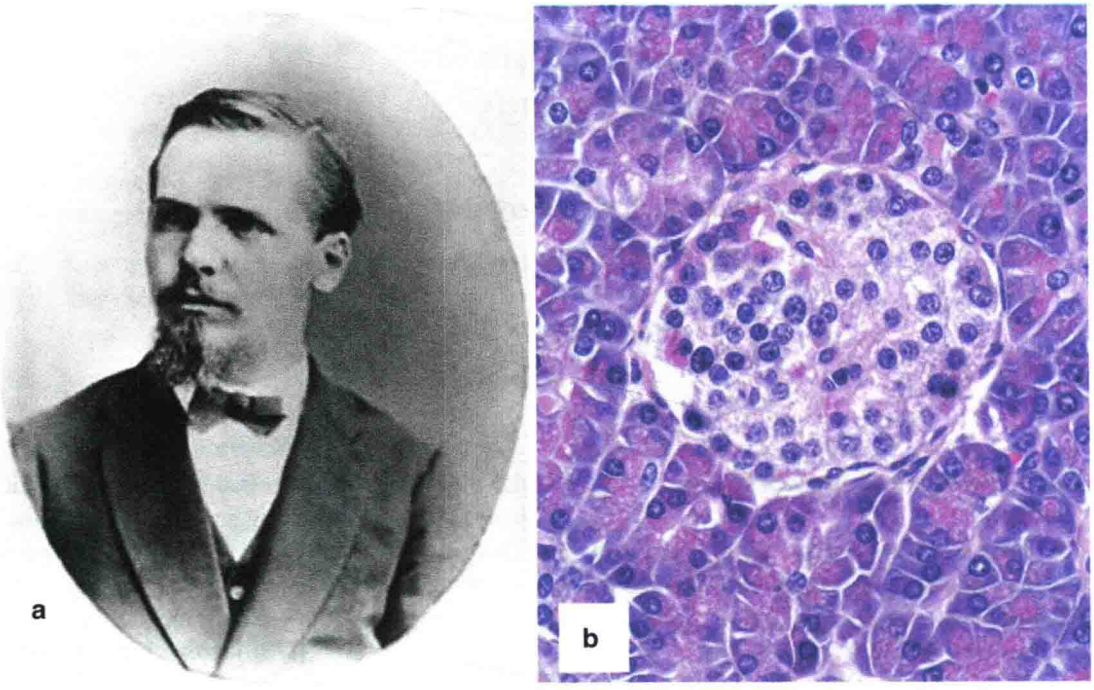

Fig. 1.1 (**a**) Paul Langerhans (1847–1888) in 1873 (© Bildarchiv Preußischer Kulturbesitz, Berlin, 1873, Photographer: Ruf und Dilger [85]) (**b**) Histological appearance of the islet of Langerhans (hematoxylin-eosin)

Fig. 1.2 Frederick Grant Banting (1891–1941) (*right*) and Charles Herbert Best (1899–1978) (*left*) in 1924 (Courtesy of the Thomas Fisher Rare Book Library, University of Toronto)

successfully isolated until December 1921 with the aid of the biochemist, J. B. Collip [7].

C.P. Kimball and J.R. Murlin first postulated the existence of a second pancreatic hormone in 1923, when they found that acetone precipitated a fraction of aqueous extracts of the pancreas soluble in 95 % alcohol, allowing the separation of an unknown substance from insulin. The

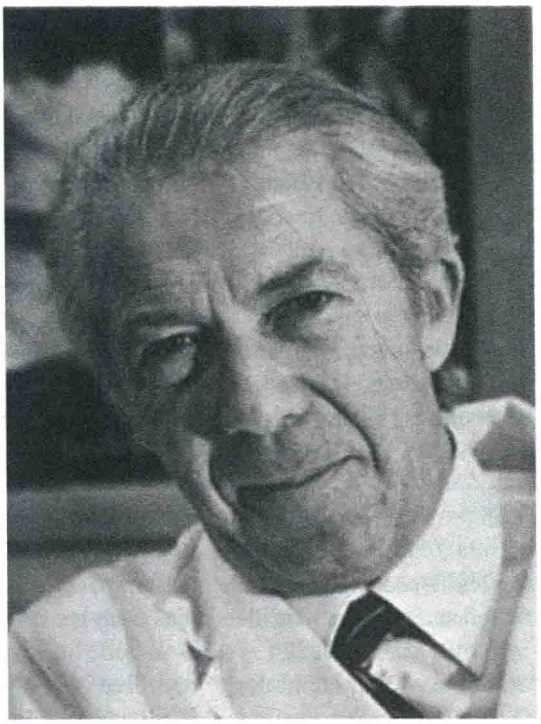

Fig. 1.3 Christian René de Duve (1917–2013) in 1974 [86]

injection of this fraction into dogs and rabbits caused a rapid rise in blood glucose levels. They inferred from these results that the preparation contained a second pancreatic hormone and named it "*gluc*ose *agon*ist," hence the term glucagon also known as the H-G or hyperglycemic-glycogenolytic factor. The H-G factor was subsequently dismissed as a contaminant [8]. However, E. Sutherland and C. de Duve who found the H-G factor in the pancreas and gastric mucosa of the dog (Fig. 1.3) speculated that the new factor might be a second hormone involved in glucose metabolism, so the name glucagon was reintroduced, probably by de Duve, to replace that of the H-G factor [9].

Nonetheless, E. Laguesse was the first to suggest the endocrine function of islet cells, while V. Diamare distinguished two types of endocrine cells that M. Lane, in 1907, had called A cells and beta cells, defined B cells by Bensley in 1911 [10, 11]. W. Bloom described the third cell type in 1931, and then J.F. Deconinck identified type IV and type V cells, using electron microscopy [12–14].

The use of immunohistochemistry has allowed the localization of glucagon in A cells, insulin in B cells, somatostatin in D cells, and pancreatic polypeptide (PP) in type V cells, in addition to recognizing the topography of endocrine cells within the islets (see Fig. 7.1).

In 1902, A.G. Nicholls described the first adenoma arising from islet cells, while performing an autopsy. The tumor was small, round, encapsulated, and probably represented the first non-functioning pancreatic neuroendocrine tumor (PanNET) [15]. In 1927, 5 years after the discovery of insulin, R. M. Wilder reported the first case of hyperinsulinism associated with an islet cell tumor that was metastatic to the liver and lymph node [16]. The alcoholic extracts from the neoplastic tissue of the liver that looked like pancreatic islet cells acted like insulin when injected into rabbits. R. R. Graham (1890–1948) first removed an insulinoma at the Toronto General Hospital in 1929. In 1938, A.O. Whipple (1881–1963) described for the first time the classical triad (shakiness, syncope, and sweating) associated with an insulin-producing islet cell tumor alias insulinoma [17].

In 1955, R.M. Zollinger and E.H. Ellison suggested that a non-beta cell pancreatic adenoma might have a functional role in producing an ulcerogenic factor, which was isolated by R.A. Gregory and named "gastrin" [18, 19]. Subsequently, in 1958, J.V. Verner and A.B. Morrison described a diarrheogenic syndrome due to a non-beta cell tumor (WDHA syndrome: water diarrhea, hypokalemia, and achlorhydria) (see Chap. 11). In addition, PanNETs have been reported in association with other types of endocrine tumors. In 1927, H.W. Cushing and then C.W. Lloyd described an association between PanNETs and parathyroid and pituitary tumors. In 1953, L.O. Underdahl and M.P. Moldawer both described multiple endocrine adenomas involving the pancreas, parathyroid, and pituitary [20, 21]. A year later, P. Wermer suggested a genetic basis of inheritance for the syndrome now called MEN1. However, PanNETs have also been observed, although less frequently, in von Hippel-Lindau (VHL) disease and in association with the

type 1 neurofibromatosis (NF-1) and tuberous sclerosis complex (TSC).

Over the years, the terminology and classification of PanNETs have undergone multiple changes. In 1938, G. F. Laidlaw proposed the term "nesidioblastoma" and "nesiodioblasts" for cells that differentiate from the secretory duct epithelium to form islets. R.F. Weichert and L.M. Roth instead suggested "carcinoid-islet cell tumor" to stress the morphological similarity of islet tumors to intestinal carcinoids that were described for the first time in September 1907, by S. Oberndorfer, who then published his seminal paper entitled "Carcinoid tumors of the small intestine" in the *Frankfurt Journal of Pathology*. He described and characterized the tumor that had previously been referred to as a "benign carcinoma." Successively, I. Sziji introduced the term "apudomas," in 1969, to refer to APUD characteristic of pancreatic endocrine cells. Nonetheless, the term "islet cell tumors" was used most often [22–25].

From the 2000 WHO Histological Typing of Endocrine Tumours to the 2004 WHO Classifications of Tumours of the Endocrine Organs, PanNETs have been divided into two main categories: well- and poorly differentiated neuroendocrine tumors. Well-differentiated tumors were subsequently divided into benign neuroendocrine tumors, neuroendocrine tumors of uncertain malignant potential, and well-differentiated neuroendocrine carcinomas [26, 27]. The last WHO Classification of Tumours of the Digestive System, published in 2010, introduced a three-tiered classification separating Grade 1 and Grade 2 PanNETs and Grade 3 pancreatic neuroendocrine carcinomas (PanNECs) of large cell and small cell type [28].

In 2011 the complete exomes of ten PanNETs were sequenced, followed by the screening for mutations of the most commonly found altered genes in a cohort of 58 tumors. MEN1 was found to be the most frequently mutated gene as it was altered in 44 % of PanNETs, but the most striking discovery was the identification of additional somatic mutations in 43 % of PanNETs. They harbored mutations in two subunits of a transcription/chromatin remodeling complex, the death domain-associated protein (DAXX) and the thalassemia/mental retardation syndrome X-linked (ATRX), while 14 % harbored mutations in the mammalian target of the rapamycin (mTOR) pathway. In addition, PanNETs seem to have a degree of genetic complexity lower than that of ductal adenocarcinomas (DAC) because they harbor a median of 16 somatic mutations versus 66 somatic mutations in DAC. This may explain the different behavior of the two pancreatic entities [29, 30].

1.2 Epidemiology

PanNETs account for less than 3 % of pancreatic neoplasms, but their incidence has been increasing over the past 20 years. Based on the Surveillance, Epidemiology, and End Results (SEER) data, the incidence of all neuroendocrine tumors (NETs) in the USA increased nearly fivefold over the past three decades from 1.09 per 100,000 in 1973 to 5.25 per 100,000 in 2004. The same data suggest a sex and race difference in the site of origin (gastrointestinal tract, pancreas, lung, thyroid, adrenal gland, adenohypophysis, parathyroid) and in the incidence of these tumors. Male patients are more likely to develop PanNETs (0.38 per 100,000) than female ones (0.27 per 100,000), and African-Americans (0.36 per 100,000) are more susceptible than American Indians/Alaskan Natives (0.20 per 100,000) [31]. Nevertheless, SEER data show that PanNETs represent about 7 % of all gastroenteropancreatic (GEP)-NETs and have an incidence of 0.43 per 100,000 in 2007, a twofold increase in the incidence since 1980 [32]. In addition, SEER data showed that exocrine pancreatic cancers tended to decrease over time, whereas the incidence rates of endocrine neoplasms increased. From the period 1977–1981 to 2002–2005, the incidence of exocrine cancers decreased by approximately 11 %, while the incidence of endocrine cancers rose 90 % for younger adults (<60 years) and 149 % in older adults (>60 years) [33].

Although most PanNETs occur sporadically, nearly 10 % are associated with genetic syndromes. These include MEN1, VHL, NF-1, and TSC.

However, published epidemiological studies on PanNETs are poorly comparable for several reasons:

(a) In the past, there was no consensus among pathologists on the diagnostic criteria of PanNETs or the criteria to establish their malignant potential.
(b) PanNETs may be functioning or nonfunctioning, depending on the cell type and hormone hypersecretion and on the lack of clinical syndromes.
(c) PanNETs have been included in several epidemiological studies together with gastrointestinal neuroendocrine tumors (GI-NETs), or studies only reported data from single referral centers.
(d) The national registries of tumors started at different times in different countries, for example, 1953 in Norway and 1973 in the USA. This means that they utilize different histological criteria and different tools for diagnoses.
(e) Tumor registries generally only recorded malignant tumors. This explains why they do not reflect the real incidence of PanNETs, since "benign" tumors were omitted from many national registries.
(f) Healthcare systems could affect the incidence results because not all the people could benefit from them; hence, the tumor registry may include only the records of a fraction of the population.

In addition, the widespread use of abdominal imaging, like computer tomography (CT) and ultrasound scans in the last 20 years, is altering the time of discovery and has increased the number of pancreatic lesions in asymptomatic patients with an increase of the so-called pancreatic incidentalomas. This may in part explain the different incidence of PanNETs between countries with public or private healthcare services. In a series of 475 pancreatectomies (January 1995–June 2007), 64 out of 475 (13.5 %) were performed for lesions found incidentally ("pancreatic incidentalomas"), 10 of which (15,6 %) were diagnosed as PanNETs. In the remaining 411 pancreatectomies performed for symptomatic patients, only 23 cases were PanNETs (5,6 %) ($p<0.05$). Interestingly, more than 90 % of the incidentally found PanNETs were observed after the year 2000 [34]. Crippa et al. in a series of 355 nonfunctioning PanNETs (NF-PanNETs) (124 incidentally found and 235 detected because of symptoms) reported that the frequency of incidental NF-PanNETs increased from 9 % during the period 1992–1996 to 40 % in the period 2002–2006. They also reclassified all cases according to the WHO 2010 criteria and found that most of the incidentally found NF-PanNETs were G1 (73 %) and had a lower tumor stage, smaller size, and better survival, whereas only 42 % of symptomatic NF-PanNETs were G1 [35].

1.2.1 Autopsy Studies

In the first part of the last century, the epidemiological studies were based on autopsy findings, frequently reporting "incidentalomas" which probably represented NF-PanNETs. A.G. Nicholls reported the first case of a PanNET detected among 1,514 autopsies [15]. In a series of 34,079 autopsies focusing on a search for PanNETs, 170 cases were reported, corresponding to a frequency of 0.5 %. The studies were not always informative regarding the patients' status and the symptoms of excessive hormone secretion. However the autopsy series showed a PanNET frequency ranging from 0.1 % to 2.5 %. For instance, B. Korpassy found four cases (0.8 %) of macroscopically evident PanNETs among 500 autopsies [36]. Twenty-four cases (0.3 %) of "benign islet cell neoplasms" were observed by V.K. Frantz in a series of 9,158 consecutive autopsies [37]. S. Warren et al. reported 42 PanNETs that they defined "islet cell tumors" among 4,666 autopsies corresponding to a frequency of 0.9 % [38]. V. Becker who observed 62 PanNETs in his autopsy series reported a similar frequency of 1.4 % [39]. In two studies performed by L. Grimelius and W. Kimura [40, 41], 11 PanNETs were found among 1,366 Swedish

autopsy cases (0.8 %) and 20 PanNETs were found among 800 consecutive Japanese autopsies (2.5 %). Furthermore, K.Y. Lam and C.Y. Lo described 13 PanNETs in a series of 11,472 Chinese autopsies (0.11 %) where only 4 patients were endocrinologically symptomatic [42]. The last autopsy series in which the presence of PanNETs had systematically been investigated was reported by S. Kishi et al. who identified 6 (1.2 %) cases in a series of 413 autopsies [43].

1.2.2 Study Population

Several studies have been performed on the incidence of GEP-NETs in defined populations [31, 32, 42, 44–54] including East Asia, North and South America, and West Europe. No or a few information is available from Africa and East Europe.

In 2014, Ito reported a second nationwide survey analysis of GEP-NETs in Japan which had been performed in 2010. The results were compared with the first nationwide survey analysis performed in 2005. The incidence of PanNETs was 1.27 per 100,000, and the prevalence was 2.69 per 100,000. A total of 3,379 PanNETs were treated in 2010 compared to 2,845 treated in 2005, a 1.2-fold increase. NF-PanNETs comprised 65.5 % of cases followed by insulinomas (20.9 %) and gastrinomas (8.2 %) [54]. In 2005, NF-PanNETs were 47.4 % followed by insulinomas (38.2 %) and gastrinomas (7.9 %) [50]. The study by Ito et al. reported for the first time the grading of PanNETs according to the 2010 WHO classification and showed that NECs represented 7.5 % of pancreatic neuroendocrine neoplasms (PanNENs). The frequency of NECs among NF-PanNENs was 9.7 % compared with 3.2 % among functioning ones. In Taiwan, a nationwide cancer registry-based study on NETs was performed from January 1996 to December 2008. The annual incidence increased from 0.30 per 100,000 in 1996 to 0.55 per 100,000 in 2000 to 1.51 per 100,000 in 2008 signifying the incidence rate increased by 83 % from 1996 to 2000 and by 175 % from 2000 to 2008. The pancreas was the fourth primary site, representing 6 % of all the NETs. The incidence of PanNETs increased from 0.02 per 100,000 in 1996 to 0.13 per 100,000 in 2008, which is lower than the Japanese data, probably because only malignant PanNETs were recorded as in the SEER database [55].

From South America, O'Connor reported an observational study on GEP and bronchial NETs in Argentina. A total of 532 NETs were found, which included 71 bronchial NETs and 461 GEP-NETs, 116 of which were pancreatic (25.2 %). In this PanNET series, the lymph node involvement was detected in 44 (37.9 %) cases and liver metastases in 74 (63.8 %) cases. In this study the 2010 WHO grading system was applied independently of the site of origin to 457 GEP-NENs with NEC representing the 9 %. In Brazil, a study published in 2011 by Estrozi et al. reported 773 GEP-NETs that included 126 PanNETs (16.4 %) found in *Consultoria em Patologia* from January 1997 to December 2009. The grading in this study was also done according to the 2010 WHO classification criteria and reported that the majority (64.5 %) were G1 PanNETs, followed by G2 PanNETs (27.5 %) and NECs (8 %). In these two South American studies, no data about the incidence was given although Estrozi noted an increase in the percentage of GEP-NETs out of the total number of surgical pathology cases from 0.18 % to 0.50 %.

In Spain, a national registry of GEP-NETs started in 2001, thanks to GETNE (Spanish Society of Neuroendocrine Tumors). From January 2001 to December 2008, 837 NETs with follow-up were registered, including 288 PanNETs (33.7 %), 171 of which were NF-PanNETs and 67 insulinomas. No information about incidence was given in relationship to the population of this multi-institutional academic and community registry [51].

In 2013, a study by Scherübl et al. reported that the number of GEP-NETs increased about fivefold between 1976 and 2006 in Germany [52]. A total of 2,821 GEP-NETs were documented with an incidence of 4.65 per 100,000 in comparison to 0.3 per 100,000 in 1976. The incidence of PanNETs was 0.11 per 100,000 in 1976 and 0.5 per 100,000 in 2006. At the same time, the authors reported that the survival of GEP-

NETs patients had improved significantly. A prospective study was done in Austria from May 2004 to April 2005 documenting 285 GEP-NETs, which means an incidence of 2.3 per 100,000 inhabitants. The age-specific incidence rate was highest between 50 and 70 years. In this series, there were 33 (11.6 %) PanNETs, and the overall annual incidence was 0.25 per 100,000 [56].

A Swedish study reported an annual incidence of 0.4 per 100,000 [45], and a study from Northern Ireland found an annual incidence of 0.18 per 100,000 [44]. The latter study was later updated reporting an incidence of 0.23 per 100,000 [46]. A Norwegian study on NETs of different sites made with data obtained from the Norwegian Registry of Cancer showed that the incidence of PanNETs was 0.23 per 100,000 with a male predominance (0.29 in males compared to 0.17 in females, per 100,000). However, the prognosis of PanNETs of this series was among the poorest of NET subtypes, probably reflecting the late diagnosis of malignant PanNETs and because well-differentiated G1 and G2 PanNETs were excluded from the two registries [57].

A French study using a population-based cancer registry found the overall annual crude incidence of malignant digestive endocrine tumors (MDETs) to be 2.16 per 100,000 inhabitants. PanNETs accounted for 20.5 % of all tumors in this cohort. The age-standardized incidence rate of PanNETs was 0.31 per 100,000, with a male-to-female ratio of 1.6 [48]. They observed that incidence rates were low in people under 40 years of age but increased with age, reaching a peak at the age of 75 for men and 65 for women. In England and Wales, a similar study on MDETs was done by using data from a National Cancer Registry. The 4,102 endocrine carcinomas collected in the period 1986–1999 represented 0.6 % of all the digestive cancers. They divided MDETs into well-differentiated tumors (78.8 %) and small cell carcinomas (21.2 %). Well-differentiated tumors included insulinomas, gastrinomas, VIPomas, glucagonomas, carcinoids, insular carcinomas, and neuroendocrine carcinomas. The mean age at diagnosis was 62.8 years for patients with well-differentiated tumors and 70.6 years for small cell carcinomas. The 240 cases of PanNETs represented the 5.8 % of MDETs and included 49 insulinomas, 31 gastrinomas, 17 glucagonomas, and 1 VIPoma [58].

In the USA, a study using SEER data between 1973 and 2003 found 1,310 islet cell carcinomas among 101,046 pancreatic cancers, representing 1.3 % of all pancreatic cancers. However, due to a better outcome of islet cell carcinoma, they represent almost 10 % of pancreatic cancers in prevalence analyses. Histologically, 1,117 cases were islet cell carcinomas, carcinoids, or NF-PanNETs, while of the F-PanNETs, 73 cases were gastrinoma, 49 insulinoma, 26 glucagonoma, and 16 VIPoma [31]. Obviously, this study underestimated the total number of patients with islet cell tumors because all cases from the SEER database are malignant. Over such a long time period, PETs had been classified in different ways, and in most cases there was more significant clinical presentation than histopathology. Many small islet cell tumors that may have been considered benign or of unclear malignant potential were not recorded in the SEER database. However, in the study from E. J. Kuo, using population-based data including patients diagnosed from 1988 (when SEER initiated the data collection of tumor size) to 2009, a total of 263 out of 1,371 NF-PanNETs were reported to be less than 2 cm in size. Over the 22-year study period, the incidence of PanNETs <2 cm increased, accounting for the 20.2 % in 2009 in contrast to the 12.3 % in 1988 [59].

In a SEER registry data from 1973 to 1987, the annual incidence of PanNETs was 0.6 per 100,000 for all age groups [47]. In the series of PanNETs from 1973 to 2000, the annual incidence was 0.2 per 100,000 with the highest incidence (0.7–0.8 per 100,000) in the sixth and seventh decades and with a slight male predominance [60]. In the same series that included 1,483 PanNETs, the majority were NF-PanNETs (90.8 %), while malignant F-PanNETs included gastrinomas (4.2 %), insulinomas (2.5 %), glucagonomas (1.6 %), and VIPomas (0.9 %) [60]. The annual incidence of insulinomas and gastrinomas in the SEER registry was 0.1/million, but this may be due to a substantial underestimation

of F-PanNETs due to the fact that SEER registers only included malignant tumors and probably missed most of the insulinomas that frequently behave in a benign fashion [60]. The 5-year survival rate was 47.6 % in F-PanNETs versus 31.3 % in NF-PanNETs [60]. The SEER database was the source of 49,012 NETs recorded from 1973 to 2007. In these series, 29,664 cases were GEP-NETs and included 3,598 PanNETs which represented 7.34 % of all cases. PanNETs had the lowest 5-year survival rates (37.6 %), whereas rectal NETs showed the highest 5-year survival rates (88.5 %), reflecting the different behavior of NETs of different sites [32].

The frequency of the various subtypes of F-PanNETs has been described in several studies [49, 50, 58, 65–69]. Insulinomas (see Chap. 8) are the most frequently encountered F-PanNETs and are usually tumors with indolent behavior [54, 62, 63, 65–67]. Gastrinomas (see Chap. 12) are the second most commonly encountered F-PanNETs, but it is worth noting that gastrinomas can also arise outside of the pancreas [54, 64, 67, 70]. Pancreatic gastrinomas are generally more aggressive and frequently associated with liver metastases [71]. In a Japanese series, 30.2 % of gastrinomas had liver metastases at the time of the initial diagnosis, whereas insulinomas accounted for only 9.3 % of liver metastases [54]. Up to 30 % of gastrinomas are associated with MEN1 [68, 70]. In Denmark, the incidence of gastrinoma was estimated to be 0.5 per million per year [61]. A higher incidence of two to four per million has been found in Switzerland [68]. Other studies have reported an annual incidence of 0.5–1.2 cases per million [45, 46]. Epidemiological data on F-PanNETs other than insulinoma and gastrinoma are rare.

Functioning glucagon-secreting tumors (glucagonomas, see Chap. 9) represent <10 % of F-PanNETs and are almost exclusively found within the pancreas [72, 73]. Glucagonomas are very rare, and their annual incidence has been estimated to be around 0.1 per million [45, 46]. Functioning somatostatin-secreting PanNETs (somatostatinomas see Chap. 10) are extremely rare and account for <1 % of all F-PanNETs, and the true incidence of these tumors is not completely known. Somatostatinomas typically present in the fifth and sixth decades of life with a slight female preponderance. Up to 50 % of somatostatin-secreting tumors arise outside the pancreas, and these are not associated with a full-blown somatostatinoma syndrome [74–76].

PanNETs secreting vasoactive intestinal peptide (VIPomas, see Chap. 11) comprise <10 % of all F-PanNETs and appear to be slightly more common in females according to some but not all reports [72, 73, 77–79]. VIPomas are found in extrapancreatic locations in up to 25 % of cases [82].

Pancreatic tumors secreting other hormones are very rare. In the study by I. M. Modlin, a series of 13,715 carcinoid tumors were identified in the SEER database from January 1973 to December 1999. Seventy-nine cases were "pancreatic carcinoid" representing 0.73 % of all the carcinoids. However, the parameters utilized to distinguish pancreatic carcinoid tumors from PanNETs were not specified, and probably immunohistochemistry techniques were not applied to all the cases in these series because the antibodies were not available at the beginning of registry enrollment [80]. In the Netherlands Cancer Registry from 1989 to 1996, on a series of 2,391 patients harboring carcinoid tumor 68 (2.8 %), pancreatic carcinoids were found [81]. Fifteen cases of serotonin-producing PanNETs were reported in 2011 by La Rosa et al. who reviewed the medical literature and found 23 additional cases of nonfunctioning serotonin PanNETs and 17 cases of functional pancreatic carcinoids [82]. At present there are 71 nonfunctioning serotonin-producing PanNETs in the medical literature (see Chap. 14). There are 134 cases of adrenocorticotropin (ACTH)-secreting PanNETs (see Chap. 13) reported in the English medical literature [83] and 37 calcitonin-secreting PanNETs [84]. Growth hormone- and parathyroid hormone-related peptide F-PanNETs are extremely rare and are frequently associated with MEN1, but their incidence is unknown (see Chap. 15).

A European multicenter study collected 1,072 surgical PanNETs. There were 331 (30.9 %) F-PanNETs including 222 insulinomas (67.1 %), 37 gastrinomas (11.2 %), 22 glucagonomas

(6.5 %), and 19 VIPomas (5.7 %). There were 874 (94.6 %) sporadic PanNETs, while 36 (3.9 %) were associated with MEN1 and 14 (1.5 %) with VHL. According to the 2010 WHO classification, 488 (52.3 %) were PanNET G1, 382 (40.9 %) were PanNET G2, and lastly 63 (6.8 %) were PanNECs [65]. This study and the others that used the 2010 WHO classification show that there is good agreement in the diagnosis of PanNECs that is not always observed in NET G1 and G2.

In conclusion, there is evidence that PanNETs are a group of tumors with increasing incidence and prevalence. This is probably due to a longer life span, a widespread use of imagining, an increased awareness of physicians, and because more people benefit from a healthcare service. These tumors have a heterogeneous clinical presentation mostly with an advanced disease underscoring their malignant potential. However, F-PanNETs and incidentally discovered PanNETs have a better prognosis because of the small size and early detection. Nevertheless, to compare geographic or ethnic differences in incidence and survival, it is necessary that in the future pathologists should use the same diagnostic criteria and classification.

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