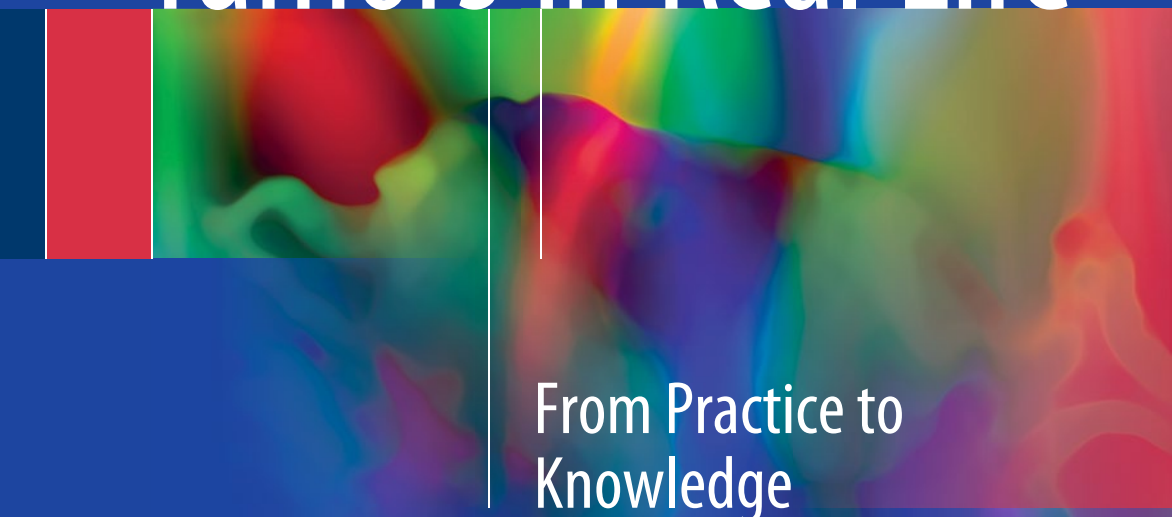
Neuroendocrine Tumors in Real Life



From Practice to Knowledge

Annamaria Colao
Antongiulio Faggiano
Wouter de Herder
Editors

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Preface

The large family of *neuroendocrine tumors* is diverse and nonhomogeneous since it includes tumors located in different organs with different functions and different degrees of differentiation. This confers a very variable diagnostic workup, treatment, and follow-up that should be appropriate to individual patients in order to ensure survival as long as possible with minimal adverse effects of the many therapeutic approaches available today. Therefore, in order to produce a comprehensive text on these heterogeneous neoplasms, a combination of basic knowledge on biology and genetics as well as an excellent familiarity with their clinical aspects is required.

This editorial initiative *Neuroendocrine Tumors in Real Life: From Practice to Knowledge* wants to overturn the classical presentation, which is only based on report and discussion of data from literature, and to take on deeply inside the real world of neuroendocrine tumors. With this impressive objective, we designed this book starting with four introductory chapters on epidemiology, pathology, biology, and staging, dedicated to clearly define and classify these tumors, and then proceeding with 20 other chapters, dedicated to prognostic factors, staging, diagnostic workup, and therapy: the common central idea is that every chapter starts from a real clinical case relative to the individual topic. Then some crucial points are answered in a dedicated section of open questions and tentative answers. In conclusion, updated evidence of literature is discussed. In this way, readers can find a large spectrum of clinical conditions which parallel with the heterogeneity of neuroendocrine tumors according to primary site, biology, and staging.

We trust that this innovative project, involving many worldwide experts of neuroendocrine tumors, can meet the learning objectives of specialists in different areas of medicine and research who are interested in being closer to the field of neuroendocrine tumors also providing some useful tools for the clinical management of patients affected with these tumors who are still diagnosed and treated in a too variable way in different parts of the world.

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General Remarks

Contents

Epidemiology of Neuroendocrine Tumours: By Site of Tumour and by Geographical Area

Federica Cavalcoli, Aoife Garrahy, Marco Castellaneta, and Gianluca Tamagno

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Overview

Neuroendocrine tumours are a heterogeneous group of neoplasms arising from cells of the diffuse neuroendocrine system virtually located in every organ, most frequently in the digestive tract and the respiratory system. Although rare, the worldwide incidence of neuroendocrine tumours is rising and ranges from 3.24/100,000 in Northern Europe to 5.25/100,000 in the USA. However, data on the epidemiology of neuroendocrine tumours are still incomplete due to the heterogeneity of tumours and the lack of large population-based databases in many countries. From the available data, it appears that the epidemiological characteristics and the biological behaviour of neuroendocrine tumours depend significantly on the anatomical site of origin and the biological features of the tumour cells. Interestingly, the distribution according to the primary tumour site differs across geographical areas and reflects possible ethnic/genetic factors. This chapter summarizes the demographic and epidemiologic features of the neuroendocrine tumours, including a brief overview of the rarest neuroendocrine tumours arising at uncommon sites. A better understanding of the epidemiological trends of neuroendocrine tumours may help and direct the next steps of patient care through a more precise patient-targeted approach.

1.1 Introduction

Neuroendocrine tumours (NET) consist of a spectrum of rare and highly heterogeneous neoplasms with distinct functional and biological behaviour in relation to location, tumour size, and histological differentiation. NET arise from the neuroendocrine cells of the diffuse neuroendocrine system located in almost every organ [1]. The most common primary sites for NET are the gastroenteropancreatic system (about 70%) and the lungs (more than 25%), reflecting the high density of neuroendocrine cells in these organ systems [1, 2].

NET are usually divided into functioning and non-functioning forms [3]. Non-functioning NET frequently secrete pancreatic polypeptide, chromogranin A, neuron-specific enolase, neurotensin, and other peptides, but they do not usually produce specific hormonal syndromes. Functioning NET produce specific hormones that can be responsible for different clinical syndromes. Thus, functioning NET are further classified based on their specific functional behaviour and synthetic products (e.g. carcinoid syndrome, insulinomas, gastrinomas). Functioning NET are usually detected earlier due to the presence of typical hormonal syndromes, while non-functioning forms are more often detected in advanced stage of disease due to mass effect (jaundice, pain, intestinal obstruction, or palpable masses) [4–6].

NET are usually sporadic and often occur during adulthood or in the elderly. However, these tumours may also be multiple and can occur as part of several genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL) syndrome, neurofibromatosis type 1, and tuberous sclerosis, usually presenting in younger patients [7, 8]. Their frequency in the setting of these syndromes varies from very low (<1%) for carcinoid to high (80–100%) for pancreatic endocrine tumours

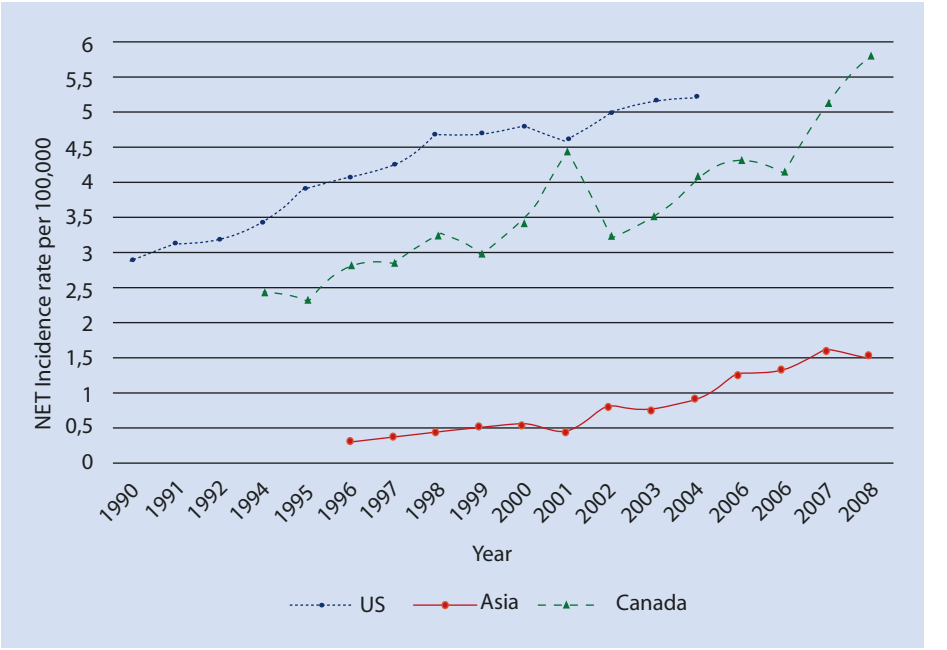

Fig. 1.1 NET incidence per geographical areas (References: for the USA, Yao et al. (2008) [2]; for Asia, Tsai et al. (2013) [14]; for Canada, Hallet et al. (2015) [13]

(insulinoma 5–20%, gastrinoma 25–30%, non-functioning tumour >50%) [9]. Patients with inherited syndromes typically present at a younger age, in most cases between 30 and 50 years of age [10]. A few cases of familial clustering, characterized by younger onset, have also been reported [11, 12].

Although NET are rare, based on the current medical literature, their worldwide incidence seems to have increased; current incidence rates range from 3.24/100,000 in North Europe [1] to 5.25/100,000 in USA [2]. In particular, in the SEER database, the annual age-adjusted incidence increased from 1.09/100,000 in 1973 to 5.25/100,000 in 2004 [2]. A similar significant increase over time has been reported from other authors in different geographical areas [13, 14] (Fig. 1.1). However, data on the epidemiology of NET appear incomplete due to the extreme heterogeneity of classification in different countries, different methods of patient identification, and the lack of large population-based databases in most countries. Moreover, NET distribution according to the primary site is different in the various geographical areas and reflects possible ethnic or genetic differences [1, 2, 13–16] (Fig. 1.2). These appear to be relevant considering that NET incidence, characteristics, and biological behaviour are highly heterogeneous depending on the specific site of origin.

Finally, several risk factors have been recognized in NET development. Family history of cancer appears to be the most relevant risk factor for NET at all investigated sites, followed by high BMI and diabetes mellitus. Cigarette smoking and alcohol consumption are also associated with increased risk of NET, especially for selected anatomical sites [17, 18]. In particular, cigarette smoking has been identified as a risk factor for small intestine,

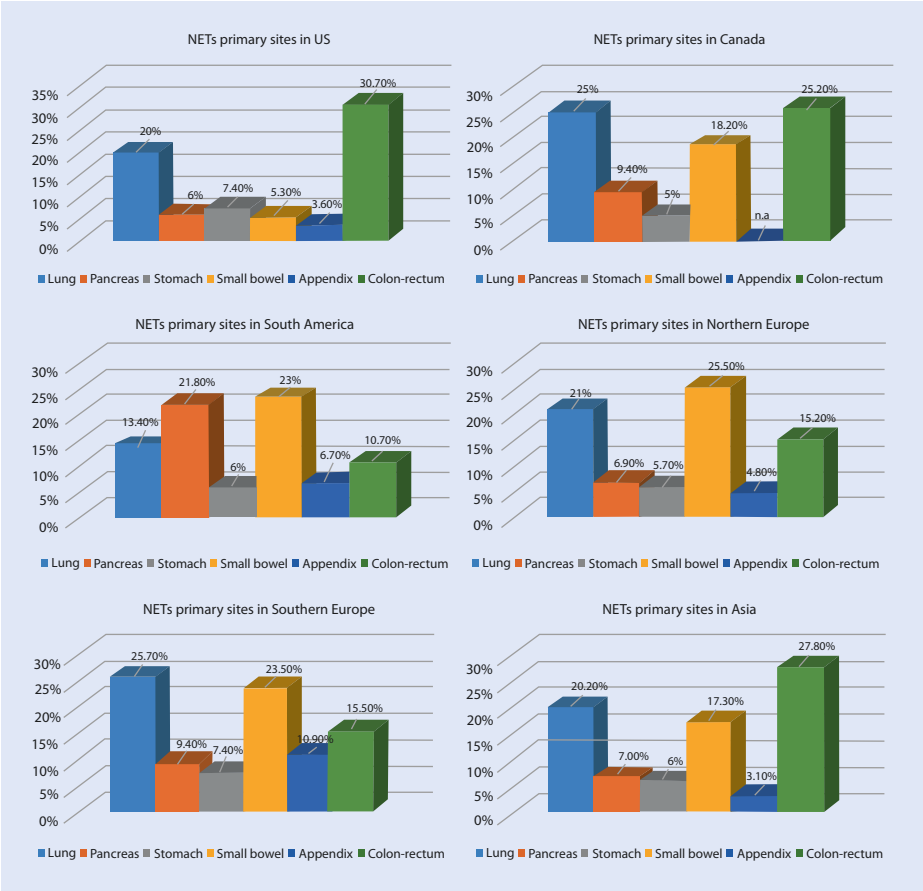

Fig. 1.2 Primary NET sites per geographical areas (References: for the USA, Yao et al. (2008) [2]; for Asia, Tsai et al. (2013) [14]; for Canada, Hallet et al. (2015) [13]; for South America, O'Connor et al. (2013) [17]; for Northern Europe, Hauso et al. (2008) [1], for Southern Europe, Caldarella et al. (2011) [18]

pancreas, and some types of bronchial NET, while alcohol intake represents a risk factor for rectum and pancreas NET. In general terms, the risk factors for gastrointestinal NET development appear to somehow overlap those predisposing to non-neuroendocrine cancers at the various sites of the respiratory and the gastroenteropancreatic tract [18]. A better knowledge of NET epidemiological data appears to be essential, and it may help clinicians in the diagnostic and therapeutic management of these patients.

1.2 Gastroenteropancreatic Neuroendocrine Tumours

Gastroenteropancreatic neuroendocrine tumours (GEP-NET) originate from the diffuse neuroendocrine cell system of the gastrointestinal tract and pancreas and represent 1–4% of all gastrointestinal neoplasms [2, 19, 20].

1

The incidence of GEP-NET has been progressively increasing over the last 30 years [2, 21]. Data from different series have documented this epidemiologic change for GEP-NET in the USA, South America, Europe, Asia, and Oceania [15, 20–22]. Interestingly, this trend contrasts with those of other gastrointestinal malignancies. A recent study reported an average annual increase of 4.4 per year in the US population from 1973 to 2009 [20]. In the same study, a greater increase for primary NET arising in the stomach and rectum is reported, while the incidence of primary appendiceal NET has decreased [20]. Similar results have been observed in a German study reporting a significant overall increase in GEP-NET incidence between 1976 and 2006 from 0.31/100,000 inhabitants to 2.27/100,000 per year for men and from 0.57/100,000 to 2.38/100,000 per year for women [23]. Possible explanations for this trend include increased use of screening and diagnostic endoscopy, increased availability of cross-sectional imaging, and improved clinician's awareness of NET. Moreover, a possible role for environmental factors such as proton pump inhibitors has been proposed [21, 23, 24].

1.2.1 Stomach

Gastric NET are increasingly recognized due to increased use of upper gastrointestinal endoscopy and biopsy. The yearly age-adjusted incidence is of around 0.2/100,000 per year [25, 26]. Gastric NET account for 5–14% of all NET; however their relative frequency varies widely according to geographical area. Recently an Austrian prospective study found gastric NET to be the most common of all GEP-NET [26]. In a Korean study, the stomach was the second most common site for GEP-NET after the rectum [27].

According to the European Neuroendocrine Tumor Society (ENET) guidelines, gastric NET are divided into three types [28]. Type-1 gastric NET occur in patients affected by chronic atrophic gastritis with hypergastrinaemia caused by the reduction of gastric acid secretion. Lesions are usually polypoid, mostly limited to the mucosa or submucosa, and located in atrophic oxyntic mucosa in the fundus [29]. Such neoplasms are mostly multiple (65% of cases) with a median diameter of 5 mm. They are usually benign and well-differentiated, with Ki-67 <1% (NET G1) [29]. Type-2 gastric NET develop in response to hypergastrinaemia resulting from the neoplastic secretion from gastrinomas [Zollinger-Ellison syndrome (ZES)], mostly in patients with MEN1 [30]. Type-3 gastric NET are sporadic, unrelated to hypergastrinaemia, and not associated to enterochromaffin-like cell hyperplasia and arise from a normal mucosa [31]. These tumours are usually solitary and poorly differentiated, with an elevated Ki-67 (NEC G3). Deep wall invasion, lymphatic invasion, or metastases can be present at the time of their diagnosis [32].

The main epidemiological characteristics of gastric NET are further detailed in Table 1.1. In recent years however, few cases of gastric NET not completely meeting the current classification criteria have been reported. A possible association with proton pump inhibitor therapy has also been suggested [33–35]. Mean age at presentation of gastric NET is 60–64 years in the USA and Europe [2, 12, 36] and slightly higher (67 years) in Taiwan [37]. In the USA, the incidence of gastric NET is higher in the Afro-Americans [2, 25].

Table 1.1 Main epidemiological characteristics of gastric NET according to the ENET classification [28]

Gastric neuroendocrine tumours	Type 1	Type 2	Type 3
Proportion among gastric NET	70–80%	5–6%	14–25%
Tumour characteristics	Often small (<1–2 cm), multiple in 65% of cases, polypoid in 78% of cases	Often small (<1–2 cm) and multiple, polypoid	Unique often large (>2 cm) Polypoid and ulcerated
Associated conditions	Chronic atrophic gastritis	Gastrinoma/MEN1	None
Metastases (%)	2–5	10–30	50–10
Tumour-related deaths (%)	0	<10	25–30

Most patients present with local disease and prognosis are usually good [25, 38]. In a recent prospective study, gastric NET have a benign behaviour in 68% of cases, uncertain in 12%, and a malignant behaviour in 20% of cases [26]. Overall, the incidence of malignant NET in the stomach was low, calculated as 0.08/100,000 per year.

Reported risk factors for gastric NET include a positive family history of cancer (especially other neuroendocrine neoplasms) and, according to a case-control study from the USA, history of diabetes mellitus [39].

1.2.2 Duodenum

Duodenal NET comprise up to 3% of all duodenal tumours and almost 3% of all NET tumours in the SEER (Surveillance, Epidemiology, and End Results) Registry [40, 41]. In 2015, Fitzgerald et al. [42] found a significant increase over the last three decades in the incidence of duodenal NET, from 0.027/100,000 in 1983 to 1.1/100,000 in 2010, representing an impressive fourfold increase.

Duodenal NET include functional (mainly gastrinomas and somatostatinomas) and non-functional NET, duodenal gangliocytic paragangliomas, and high-grade poorly differentiated NEC [40]. They may be sporadic or associated with familial syndrome, such as neurofibromatosis and multiple endocrine neoplasia type 1. Multiple tumours should raise the suspicion of an inherited syndrome [26]. Duodenal NET arise more frequently (90%) in the first and second part of the duodenum, while approximately 20% occur in the periampullary region [43]. They are characteristically small (mean, 1.2–1.5 cm) and >75% have a diameter of <2 cm [43, 44]. The majority of patients present with localized disease at the time of diagnosis, while regional lymph node metastases have been reported to occur in 10–60% of cases [2, 3, 42]. Liver metastases generally occur in <10% of all patients with duodenal NET [2, 43].

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Overall duodenal NET have a favourable prognosis with a 5-year disease-specific survival ranging from 80% to 100% [42, 45, 46]. Whether duodenal NET should be treated by surgical resection or by endoscopic resection has not been fully established [43]. However postsurgical morbidity can be relevant especially in patients with other medical conditions that may increase the risk of surgical resection [43].

1.2.3 Small Bowel

Small bowel NET represent the most frequent primary site of all GEP-NET in some publications [2, 23, 47] and the second or third subgroups of GEP-NET in other series [26, 48]. Interestingly, in eastern Asia small bowel NET are much less common than in Western countries [37, 49].

The reported incidence of small bowel NET ranges between 0.32–0.33/100,000 in England and Japan [47, 49] and 0.67/100,000 in the USA [2] and up to 1.12/100,000 in North Europe [50]. Small bowel NET account for up to 30–50% of all small bowel neoplasms [26, 51], and similar to other neuroendocrine neoplasms, their incidence is on the rise, as demonstrated by recent epidemiological studies [52]. In an autopsy series, the incidence of small bowel NET is significantly higher than the clinical incidence, being 1.22:100, suggesting that the majority of small bowel NET may remain at an early stage for years [53].

The incidence rate of small bowel NET increases with age starting at age 40, reaching a peak at the eighth decade of life [24]. The mean age at diagnosis is between 59 and 65 years [53]. A slight male preponderance has been suggested in some studies [51, 54]; however these data has not been confirmed by other series [2, 47, 55]. As suggested by the SEER database findings, small bowel NET may have a different ethnic distribution being more frequent in Afro-Americans and less common in Asian patients [2].

The majority of small bowel NET are characterized by a low proliferation rate, G1 or G2, while G3 tumours are exceptionally rare. Despite the often low to intermediate proliferation rate, these tumours may present with loco-regional (36%) and/or distant metastases (48%) at the time of the diagnosis and, moreover, may be discovered at a relatively advanced disease stage possibly due to their indolent course [52]. The main prognostic factors for small bowel NET are TNM stage and histological grading, based on Ki-67 index [52]. Recently, it has been reported that the 5-year survival rate for jejunoileal NET is 100% for stages I and II, 97.1% for stage III, and 84.8% for stage IV [56]. In the same study, the grading-dependent 5-year survival rate for small bowel NET was 93.8% for G1, 83.0% for G2, and 50.0% for G3 [56].

1.2.4 Appendix

The incidence and the relative frequency of appendiceal NET are difficult to assess because of different classifications of these neoplasms, with the arbitrary inclusion or exclusion of some appendiceal tumour types in the NET register in the various countries. For example, in some registers the incidental, benignly behaving, sub-centimetre appendiceal NET are excluded [2, 22]. Furthermore, in some countries the NET of the

appendix are included as part of all colon NET. Again, the goblet cell tumours of the appendix are inconsistently included or excluded in the various NET registers.

Overall, NET of the appendix are a relatively frequent subgroup of NET with an incidence of 0.15–0.6/100,000 per year [2]. However, they represent the least common NET subgroup in the SEER database (3.44%) in years 1973–2007, in Norway (4.8% of all NET) in years 1993–2004, and in Asia [1, 2, 22, 27, 37]. On the other hand, appendiceal NET are among the most frequent NET in other European series and comprise up to 38% of all GEP-NET in UK and in Spain [47, 57]. Part of this high geographical variability is probably due to recording differences.

Most appendiceal NET are asymptomatic and incidentally diagnosed on postoperative histopathological examination of resected appendectomy specimens with a rate of approximately 3–5/1000 appendix resections [58]. The prevalence of appendiceal NET has been reported to be related to the total number of appendectomies performed [59]. In last decades, an increase in appendiceal NET incidence has been observed probably because of a better knowledge by surgeons and pathologists. The median age of diagnosis is of 40–50 years with a higher prevalence in female patients. Appendiceal NET incidence rates in females are about twice those of males in Europe and in the USA [2, 60]. These gender differences could be related to the higher rates of appendectomies and gynaecological procedures in females [24]. The incidence of appendiceal NET in children is far lower than in the adult population, although appendiceal NET are the most common tumour of the gastrointestinal tract in children. The prognosis of appendiceal NET seems to be excellent in children [58, 61]. Some reports suggest the existence of ethnic differences, but data are still inconclusive [1, 2, 24]. However, malignant tumours seem to occur more frequently in the Caucasians as compared to other populations [58]. In general, the prognosis of appendiceal NET strongly depends on the TNM staging and grading. The prognosis is considered to be excellent for the low-stage tumours with 5-year survival rates of up to 100% [62]. Prognosis is less favourable for higher-stage tumours with 5-year survival rates ranging between 70% and 85% [63, 64].

A recent meta-analysis shows that the risk of occurrence of an appendiceal NET is higher among patients with history of other NET or tumours of the urinary tract, breast, or endocrine glands [18]. Interestingly, also a positive familial history for NET, tumours of nervous system, or endocrine gland neoplasms appears to be associated with the risk of occurrence of appendiceal NET [18].

1.2.5 Colon

The incidence of colon and rectum NET is difficult to assess, as registers variably reported data of colorectal, colon, and rectum NET either together or separately. Furthermore, appendiceal NET have been included with colorectal NET in some studies. For these reasons, comparisons among geographical areas are especially challenging.

Colon NET account for 4–7% of all NET in European and US series [2, 52]; a higher proportion (8%) has been reported in Asian series [65]. The incidence of colon NET in different countries is increasing. In the US SEER database, colon NET incidence has risen from approximately 0.02 to approximately 0.4/100,000 from 1973 to 2007 [22, 49]; simi-

larly a fourfold increase has been reported in the UK [47]. On the other hand, a less marked increase in incidence rates has been observed in Norway [1]. Interestingly, in 2010 a report from Austria has demonstrated a particularly low incidence of colon NET of 0.06 [26].

In the USA, a slightly higher incidence of colon NET has been observed in the Afro-American ethnic group, while the lowest incidence was reported in the population of Asiatic ethnic origin [2]. As regards the gender, a slightly higher incidence was reported in males in the USA [1, 2], while a female predominance was observed in Europe [1, 12, 16].

Colon NET are often aggressive, poorly differentiated, and high in grade (G3), and they are often metastatic at the time of diagnosis (approximately 30–40%), possibly because of the later presentation due to the absence of early symptoms. The main sites of metastatic involvement are the liver, the lymph nodes, the mesentery, and the peritoneum. Overall survival at 5-year is roughly 43–50% [2].

A few studies have focused on the risk factors possibly involved in the development of the NET of the colon. It appears that the risk is significantly higher among patients with a parental history of NET (RR 2.78) [66].

1.2.6 Rectum

Rectal NET often present as an incidental finding at sigmoidoscopy or colonoscopy with an incidence of about 1:2500 examinations. From the latest SEER report, rectal NET have an incidence of 0.86/100,000 [2]. The incidence of rectal NET has been found to be on the rise probably due to expanding indications for lower gastrointestinal endoscopy and implementation of screening colonoscopy. For these reasons, rectal NET represent the most common gastrointestinal neuroendocrine neoplasm in Asian studies and in the SEER database in years 2000–2007 [2, 14, 22, 67].

Median age at diagnosis is of 56.2 years, lower than that reported for other gastrointestinal NET [68]. Rectal NET show a peculiar ethnic distribution. In the USA, the highest incidence was observed in Asians (OR 10), Afro-Americans (OR 1.96), and Hispanics (OR 2.6) [2, 69]. As regards to the gender distribution, a higher incidence in female patients has been reported in the USA (OR 1.20). On the contrary, Asian reports suggest a male prevalence (OR 1.92) [69, 70].

Rectal NEN are small, non-functioning, polypoid lesions located between 4 and 20 cm above the dentate line on the anterior or lateral rectal wall [71]. NET arising from the rectum are generally low to intermediate grade (G1 or G2), and distant metastases are rarely present at the time of diagnosis. Small rectal NET (<2 cm) rarely metastasize, and endoscopic or trans-anal excision is curative; however larger tumours may present a higher malignant potential, and metastases to the bone, lymph nodes, and liver have been reported [49]. Overall, the prognosis of rectal NET appears to be very good. In the USA, 5-year survival of patients with a rectal NET is up to 90% [22, 38, 68]. Similarly, a high 5-year survival rate has been reported in a patient series from Taiwan (86%) [37], while slightly lower survival rates have been observed in Norway (74%) and in Spain (64%) [1, 60].

The role of risk factors in the development of rectal NET has not been fully elucidated. There are conflicting data on the impact of cigarette smoking, alcohol consumption, obesity, and previous history or family history of NET [18]. As a matter of curiosity,

a Korean study found low high-density lipoprotein-cholesterol levels to be an independent risk factor for rectal NET [70].

1.2.7 Pancreas

Pancreatic NET are a heterogeneous group of neoplasm with a reported incidence of almost 5/1000,000 year. They are relatively uncommon, accounting for only 1–2% of all pancreatic tumours [49, 72]. However, the incidence of pancreatic NET is on the rise in recent decades, both due to increased awareness of these neoplasms and the diffusion of highly sensitive and specific imaging techniques, such as computed tomography, functional imaging, and endoscopic ultrasound [24]. The American SEER database shows that the incidence of pancreatic NET had increased approximately fivefold in the past 30 years [2], and similar results have been reported in a number of other countries [23, 49].

Pancreatic NET are usually divided into functioning and non-functioning. In some recent series, 60–90% of pancreatic NET are non-functioning. These tumours are generally diagnosed at more advanced stages because of the absence of a clinical syndrome, and also their biological behaviour and slow growth can contribute to a delay in the onset of symptoms and, subsequently, in the diagnosis [73]. However, there is also an exponential increase in the incidental diagnosis of non-functioning pancreatic NET, probably due to the widespread use of high-quality imaging techniques [74, 75]. Functioning pancreatic NET are further subdivided according to clinical syndrome and their incidence. The more frequent are gastrinomas (0.5–21.5/1000,000 per year) and insulinomas (1–32/1000,000 per year), followed by VIPomas (0.05–0.2/1000,000 per year) and glucagonomas (0.01–0.1/1000,000 per year). Other functioning pancreatic NET, such as GRFomas, ACTHomas, and somatostatinomas, are indeed very rare, and their incidences have not been elucidated [73].

Insulinomas are the most common functioning NET of the pancreas and are characterized by hypoglycaemia due to inappropriate insulin secretion [76–78]. Less than 10% are malignant. There is an age-specific incidence peak in the fifth decade of life, and the incidence is slightly higher in women than in men. Approximately 10% are multiple, and approximately 5% are associated with MEN1 syndrome.

Gastrinomas account for up to 30% of all functioning pancreatic NET [76, 79]. According to the WHO 2010 classification, gastrinomas are usually G1–G2 NET, often with a diameter of about 1 cm, and may show local invasion and/or proximal lymph node metastases [80]. Liver metastases are reported in 22–35% of cases of pancreatic gastrinomas [81].

Rare functioning pancreatic NET represent less than 10% of all pancreatic NET, and the majority present with metastatic disease (40–90%) in the liver. Not enough data is currently available to give accurate estimates on survival. The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution [81].

Most pancreatic NET occur as sporadic tumours, although a variable proportion of the different functioning pancreatic NET may occur in the setting of an inherited syndrome. MEN1 is the most important inherited condition responsible for 20–30% of gastrinomas. Non-functioning pancreatic NET have been reported to be more frequent in the setting of VHL disease, in which up to 17% of the patients can develop a pancreatic NET, in von Recklinghausen syndrome (neurofibromatosis 1), and in tuberous sclerosis [10].

According to the National Cancer Institute's SEER data in the USA, incidence of pancreatic NET is higher in males (male to female = 2:1), with an increasing incidence with age [82]. The peak incidence rate of pancreatic NET occurs in the sixth to eighth decade, and the median age of presentation is 60 years [2, 24, 48].

The overall survival in patients with a pancreatic NET is highly variable in different countries. Data from the SEER register show the lowest 5-year survival rate (27–38%) in comparison to the other GEP-NET. Such rate is even lower in patients with an already advanced stage of the tumour at the time of diagnosis [2, 22, 74]. Higher 5-year survival rates have been reported in Norway (43%), Italy (62%), and Spain (71–78%) [1, 16, 60].

As regards risk factors, alcohol intake has been associated with an increased risk of developing pancreatic NET with a OR of 2.44 for heavy alcohol drinkers [18]. Also a slight increased risk for tobacco smokers and obese patients has been observed in a recent meta-analysis [18]. Patients with pancreatic NET were more likely to report a personal history of diabetes and family history of other pancreatic NET or cancer (in particular sarcomas, oesophagus, gallbladder, stomach, and ovarian cancer) [18, 39, 74, 83]. Finally, in a large case-control study from Italy, a previous history of chronic pancreatitis was associated with an increased pancreatic NET risk [83].

1.3 Thoracic Neuroendocrine Tumours

1.3.1 Lung

Lung NET account for approximately 20–30% of all NET and 1–2% of all lung malignancies in adults [2, 68]. Overall, pulmonary NET are rare tumours with an incidence of 0.2–2.0/100,000 in both the USA and Europe. However, an impressive increase in prevalence of about 6% per year has been reported in the last 30 years [84]. The increase in prevalence appears to be mainly due to a better knowledge of pulmonary NET and the implementation of radiological and immunohistochemical techniques for the diagnosis [68].

Lung NET include typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC), the latter two being very rare.

Lung NET mostly occur in the fourth to sixth decades of life, with a median age at diagnosis of 64 years [2]. An earlier age at diagnosis (45 years) has been reported for TC. TC represents the most common primary lung neoplasm in children and late adolescents [85], and, in this setting, TC prevails over AC. As regards to the gender distribution, pulmonary NET present a slightly higher incidence in women over men [84]. There is a trend toward a higher prevalence in patients of Caucasian origin over those of African and other origins [1, 2, 84, 86].

Pulmonary NET are usually sporadic. They may also occur in the setting of MEN1 (up to 5% of patients had bronchial NET, usually TC with a smaller number of AC) [87, 88]. Moreover, rare familial cases have been reported [89, 90].

Published reports provide contrasting evidence regarding environmental risk factors associated with thoracic NET. A US case-control study identified a family history for cancer as the main prognostic factor for pulmonary NET, and the estimated OR for pulmonary NET was 2.40 for every positive family history of cancer with a higher risk

carried by first-degree relatives. A Swedish study reported a slightly increased risk of developing PC (OR 2.60) in patients with a family history of NET [18]. Data on cigarette smoking are controversial; however it may be possible that smoking is associated with an overall increase in susceptibility to develop bronchial NET (OR 1.50). In contrast to that hypothesis, a few series have demonstrated that the majority of patients who develop bronchial NET have never been or are just light cigarette smokers [39, 91]. AC patients are more often current or former smokers than patients with TC [36, 91]. In contrast, it is well established that SCLC and LCNEC are associated with heavy smoking habit [92].

1.3.2 Thymus

Thymic NET are rare and account for approximately 2–5% of all thymic malignancies [93]. Data from the most recent SEER database showed an incidence for thymic NET of 0.02/100,000 population per year [94]. The median age at diagnosis is about 54 years with a male prevalence [94]. Up to 25% of thymic NET arise in patients affected by MEN1; on the other hand, 3–8% of patients with MEN1 develop a thymic NET [95]. Rarely, thymic NET may be found in MEN-2A patients [93]. Nearly all cases associated with MEN1 are men and smokers [94]. The clinical behaviour of these tumours closely correlates with the histologic degree of differentiation. The disease-free survival is 50% at 5 years and 9% at 10 years for well-differentiated tumours, 20% at 5 years and 0% at 10 years for moderately differentiated tumours, and 0% at 5 years for poorly differentiated tumours [96]. One-third of patients are asymptomatic, and the lesions may be discovered incidentally by imaging performed for other reasons or during MEN1 surveillance. Not infrequently, distant metastases are already detected at the time of diagnosis [97].

1.4 Other Sites

As already stated, NET arise from the neuroendocrine cells of the diffuse neuroendocrine system which is located in almost every organs, and, for this reason, a neuroendocrine neoplasm can virtually occur in any organs of the human body. Rare neuroendocrine tumours include a heterogeneous group of neoplasms with varying epidemiology and clinical behaviour, which are difficult to assess due to their extreme rarity and heterogeneous characteristics. In many cases, due to the low frequency of the rarest NET, reliable data on incidence and survival may be absent or limited. An additional issue affecting the epidemiological analysis of most of these rare tumours is represented by the lack of a homogeneous classification system and the use of multiple or non-specific denominations.

The group of non-neuroendocrine cancers carrying some degree of neuroendocrine differentiation and those which are primarily mixed neuroendocrine and non-neuroendocrine tumours fall out of this epidemiological picture since they are essentially not NET. Thus, they have not been considered here. The most important rare and ultra-rare sites for NET are listed in Table 1.2, and the gross epidemiological figures from the literature are shortly described below following the order of frequency.