NEUROENDOCRINE TUMOURS

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Contents

Foreword ................................................................. 4
Preface ........................................................................... 5
Editors ............................................................................. 6
Contributors ...................................................................... 8
Disclaimer ....................................................................... 10

General Aspects of Neuroendocrine Tumours

1. Epidemiology of Neuroendocrine Tumours ................. 12
2. Pathology of Neuroendocrine Tumours ..................... 36

Clinical Presentations of Neuroendocrine Tumours

3. Part I: Gastroenteropancreatic Tumours ..................... 56
   Part II: Neuroendocrine Tumours of the Lungs ............... 69
   Part III: Other Neuroendocrine Tumours ..................... 80

Diagnostics Aspects of Neuroendocrine Tumours

4. Biochemical Diagnosis of Neuroendocrine Tumours ....... 98
5. Imaging of Neuroendocrine Tumours ......................... 118

Management of Neuroendocrine Tumours

6. Surgical Management of Neuroendocrine Tumours ....... 154
7. External Beam Radiotherapy for Neuroendocrine Tumours . 183
8. Radiofrequency Ablation of Neuroendocrine Tumours ... 192
9. Arterially-directed Therapies for Neuroendocrine Tumours . 207
10. Medical Management of Gastroenteropancreatic Neuroendocrine Tumours ............................................. 229
11. Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumours ...................................................... 276
12. The Patient-centric Approach to Neuroendocrine Tumours .. 297

Index ........................................................................... 309
In recent decades, medical science has advanced by leaps and bounds and facilitated the understanding of complex disease conditions. It is no different for neuroendocrine tumours. We have gained greater knowledge of their complexity and the clinical challenges they pose due to the wide range of morphological, functional, and behavioural characteristics.

Accurate diagnosis and management of neuroendocrine cancer require a multimodal and multidisciplinary approach that takes into account clinical symptom evaluation, supported by hormone level determination, radiological and nuclear imaging, and histological confirmation as well as a combination of therapeutic options.

I would like to greatly commend the editors and contributors to this volume on neuroendocrine tumours, for their combined efforts to present current knowledge on the multidisciplinary approach to the management of neuroendocrine cancers. Much thought and research have been put in to ensure the currency of information. I am confident that it will be useful to clinicians who encounter neuroendocrine cancers in their practice and physicians who wish to be updated about this intriguing group of diseases.

Professor FONG Kok Yong
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Rapid advances in the understanding and clinical management of patients with neuroendocrine tumours have made a multidisciplinary approach to neuroendocrine diseases a necessity.

With the advent of molecular diagnostic tests and targeted therapies, an era of so-called “personalised medicine” has come to the fore.

The aim of this book is to present a concise volume reflecting the multidisciplinary nature of the management of neuroendocrine tumours. The book provides a systematic approach to the epidemiology, pathology, diagnostic workup, clinical management and outcomes. The contributors to this volume are active clinicians or advocates in the area of neuroendocrine tumours. We hope this book will help to bring some of the current knowledge of the field to a variety of audiences, from residents to specialists and all clinicians who encounter cases of neuroendocrine tumours in their routine clinical practice, particularly in the Asian-Pacific region.

It was wonderful to have such a dynamic group of contributors come together to write a book. The multi-disciplinary nature of our institutional practice made it possible for experts in different areas to meet and discuss medical management, particularly in complex and difficult cases. It was also a pleasure to work with the editorial team, especially Ms Lee Fengting, who gently nudged the book project along. Our deep appreciation to Professor Fong Kok Yong for his support and taking time to write the foreword. We hope this book will be a welcome addition to the literature on neuroendocrine tumours.

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David NG Chee Eng received postgraduate medical training in both Internal Medicine and Nuclear Medicine. He became a Member of the Royal College of Physicians (UK) in 1996, a Fellow of the Academy of Medicine in Nuclear Medicine in 1999 and a Fellow of the Royal College of Physicians (Edin) in 2012. He was awarded and completed an overseas Fellowship in Nuclear Medicine in Clinical PET Centre, Guy’s, St Thomas’ and Kings’ Hospital, University of London and in the Hospital of the University of Pennsylvania, Philadelphia, USA. He also has degrees in Mathematics and Biomedical Engineering. He is currently a Senior Consultant at the Department of Nuclear Medicine and PET, Singapore General Hospital, Clinical Teacher with the National University of Singapore Yong Loo Lin School of Medicine and an Assistant Professor (Adjunct) at the Duke-NUS Graduate Medical School. Dr Ng is currently the President of the Nuclear Medicine Society (Singapore) and Chair of the Chapter of Nuclear Medicine in the College of Radiologists, Singapore. His field of sub-expertise is in the treatment of thyroid cancers, radioimmunotherapy, SIRT and other radionuclide therapy, as well as PET/CT imaging, molecular diagnostic techniques and physiological mathematical modelling. He has published over 50 papers in international journals such as the *Journal of Nuclear Medicine*, *International Journal of Radiation Oncology • Biology • Physics* and *Clinical Nuclear Medicine*, and 6 book chapters, and has given numerous lectures and talks.

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This publication contains information reflecting the prevailing recommendations and practices at Singapore General Hospital (SGH) and National Cancer Centre, Singapore at the time of print. It is intended for the use of qualified healthcare professionals, and is applicable in the context of Singapore only.

This publication is not intended to describe what constitutes reasonable or appropriate care for any given medical condition or circumstance. Healthcare professionals must exercise their own independent judgement and/or consult a suitably qualified expert for a professional opinion on what may constitute a suitable course of action. Before prescribing a treatment, healthcare professionals are advised to check and obtain the most up-to-date information about that treatment.

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GENERAL ASPECTS OF NEUROENDOCRINE TUMOURS

1. Epidemiology of Neuroendocrine Tumours
   *by Donald Poon Yew Hee*

2. Genetics, Molecular and Pathological Aspects of Neuroendocrine Tumours
   *by Jacqueline Hwang Siok Gek*
Key Points

- Studies show that the global incidence of neuroendocrine tumours (NETs) is rising; however, the rising trend may be partly attributed to improvements in medical diagnostic methods.

- Databases used for the analyses of NET epidemiology trends include:
  - Surveillance, Epidemiology, and End Results database (SEER)
  - Swedish Family-Cancer Database
  - Niigata Cancer Registry
  - GEP NET
  - EuroNETS

- When analysing databases, one needs to be aware of the potential biases in the databases, e.g. prior to 1986, only tumours designated as “malignant” were included in SEER.

- The prevalence of NETs is considerably higher than common gastrointestinal malignancies even though its incidence rates are significantly lower. This is due to NETs’ relatively indolent course of disease.

- The recent standardisation of classification of NET pathology and nomenclature has enabled more coherent analyses of NET epidemiology.
BACKGROUND

Langhans\(^1\) (Figure 1) first described a carcinoid tumour in the ileum in 1867 and Lubarsch\(^2\) (Figure 2) documented in detail the anatomical features of an ileal carcinoid tumour, contrasting it with tuberculosis infection of the gut. Ransom\(^3\) described the classical symptoms associated with the carcinoid syndrome in 1890, and Oberndorfer\(^4\) coined the term “karzinoid” in 1907 to distinguish carcinoid tumours from adenocarcinoma of the gut. Interestingly, he initially believed that they were benign, owing to their very indolent growth; but in 1929, he amended his report to suggest that they may metastasise like any other malignant tumour. It was not until 1914 that Gosset and Masson identified them to be endocrine-related tumours\(^5\). These tumours arise from neuroendocrine cells and their site-specific occurrence frequency corresponds to the site-density of neuroendocrine cells.

Figure 1. Theodor Langhans (1839–1915), from the University of Bern (shown in the background) first described a carcinoid tumour in the ileum in 1867. Langhans also made significant contributions to the pathology of nephritis, drawing attention to the giant cell, which became known as the Langhans cell (lower left inset). (Reproduced with permission from Modlin IM, Shapiro MD, Kidd M. Siegfried Oberndorfer: origins and perspectives of carcinoid tumors. Hum Pathol. 2004 Dec;35(12):1440–51.)
The observation explains the predominance (approximately 60%) of all neuroendocrine tumours (NETs) arising in the intestine (the largest endocrine organ in the body), and about 25% of all NETs arising in the bronchial epithelium (has an abundance of Kultschitzky cells).

It is now apparent that these tumours are certainly not benign; they have a propensity to metastasise, and display biological behaviours and clinical outcomes distinct from the more common epithelium-derived adenocarcinomas. The well-described eclectic clinical manifestations of the carcinoid syndrome are engendered by the various biochemical factors produced by these tumours in about 90% of patients\textsuperscript{6}.

The general cognisance of the manifold bioactive peptide-producing functions, as well as the malignant nature of these tumours, have progressively led to informed revisions of the nomenclature and pathobiological classifications of these tumours. The term “carcinoid” as a ubiquitous nominal “catch-all” is being gradually forsaken as it
does not allow precise identification of the specific neuroendocrine cell type which has developed features of neoplastic proliferation. The move towards a more refined approach for analysing these tumours will change the way epidemiological data on these tumours is organised in tandem with revisions in histopathology classification and clinical tumour nomenclature coding. This ongoing endeavour will better clarify prognostic and predictive factors with improvement in treatment strategies for this group of tumours in the future.

**INCIDENCE AND PREVALENCE**

In the largest series of NET epidemiological analyses, the age-adjusted incidence of total NET cases ranged from 1–5 in 100,000 per year\cite{7,8,9}. NETs are relatively rare, forming about 0.5% of all malignancies diagnosed. However, due to its indolent course with the majority of NET patients surviving longer at every stage of the disease than the majority of non-NET cancer patients, the prevalence of NETs is expected to be high in the population relative to its incidence. The estimated 29-year limited duration prevalence of NETs in the US has been estimated to be about 35 in 100,000, adjusted for standard population, age, sex and race\cite{9}. When compared to other gastrointestinal tumours, the 29-year limited duration prevalence of 103,312 NET cases in 2004 in the United States makes NETs significantly more common than oesophageal cancers (28,664), gastric cancers (65,836), pancreatic cancers (32,353) and hepatobiliary cancers (21,427)\cite{9}. Hence, the relative rarity of NETs belies its true prevalence.

Analysis of data on the epidemiology of NETs is challenging because of many factors. The prime reason is the lack of NET registries that systematically compile information on NETs, allowing for cogent analysis of NET epidemiology. NET epidemiology data culled from generic cancer registries are further confounded by different registry inclusion criteria for NET diagnosis, site, classification, tumour grade and histology. Although a better understanding of the natural biology of NETs has engendered a more uniform approach towards the
diagnosis and classification of NETs, these changes have only taken place over the last 10 years. An understanding of the limitations posed by different sources of epidemiological data, variance in population characteristics, ante-mortem versus post-mortem studies, and data collection methodology is needed for prudent interpretation of trends in the epidemiology of NETs.

**Trends of NET Incidence**

The global incidence of NETs has risen over the years. SEER data records a rise in overall incidence of NETs from 1.09 in 100,000 per year [95% confidence interval (CI) 0.92–1.28] in 1973 to 5.25 in 100,000 per year (95% CI 5.09–5.42) in the US in 2004 (Figure 3)\(^9\). The same is seen when time-trend analyses were done for incidence of NETs by primary sites and stage at diagnosis with strong statistical significance (P <0.001).

In Scandinavian countries, the trend is similar. The total incidence of NETs has increased from 2.35 in 100,000 per year in the period 1993–1997 compared with 4.06 in 100,000 per year in the period 2000–2004 in Norway\(^10\). There is a variation in the trend in Sweden, with a plateau in total incidence seen occurring in the mid-1980s. The incidence of 2.2 in 100,000 per year has remained stable in the period 1983–1998\(^11\). With improvements in medical diagnostic methods frequently cited as one of the reasons for the rise in NET incidence, this plateau in the 1980s was ascribed to a saturation of medical investments in Sweden.

The individual trends seen in the different subtypes of NETs and in the different regions cumulatively contributed to this global overall rise in total incidence. This rise largely reflects unique geographical epidemiological trends influenced by the general population’s innate predisposition to development of NETs as well as advances in medical diagnostic methods (See Box 1).
Figure 3. Annual age-adjusted incidence of NETs by year (1973–2004). The incidence is presented as the number of tumours per 100,000 (with 95% CIs), age-adjusted for 2000 US standard population. Cases are selected from the SEER database (1973–2004) using International Classification of Diseases for Oncology histology codes 8150–8157, 8240–8246, and 8249. (Reproduced with permission from Yao JC, Hassan M, Phan A. 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.)
Box 1. Influence of modern diagnostic methods

Immunohistochemistry (IHC), first developed by Coons\textsuperscript{13} in 1940 as an investigative immunofluorescence technique to detect antigens in frozen tissue sections, has over the recent decades transformed into an indispensable diagnostic tool. Adaptation of its application to paraffin-embedded and formalin-fixed tissue specimens as a widespread practice started in the 1990s\textsuperscript{14}. The specific diagnosis of NETs nowadays is seldom made without IHC being positive for synaptophysin and chromogranin A, which are specific markers of neuroendocrine differentiation in tumours\textsuperscript{15,16}. Improved histopathology diagnostic techniques are major factors accounting for the rise in incidence of NETs.

The arrival of improved endoscopic instruments for bronchoscopy and enteroscopy — minimally invasive surgeries with the aid of laparoscopic devices — have coincided with the rise in NET incidence. This begets the question as to the extent these new techniques contributed to the increased diagnoses of NETs. While the association is apparent and may contribute to the rise in NET incidence, closer examination of epidemiological data seems to indicate that the causative effect is certainly not likely in many instances.

Use of serum chromogranin A\textsuperscript{17} and improved tumour imaging in somatostatin receptor scintigraphy using radio-labelled octreotide scans\textsuperscript{18} such as Octreoscan\textsuperscript{®} and PET scan with Gallium-68 labelled DOTATOC, DOTANOC or DOTATATE linkers have not been widely applied enough in the diagnostic screening of NETs to have a significant impact on incidence by conferring the over-diagnosis effect.

Sources of data

The medical literature is replete with reports describing on average, 100–300 NET patients in larger series, from primarily western hospital-based white populations, with NET epidemiological trends that may not be an accurate portrayal of NETs epidemiology globally.

Apart from these studies, Godwin\textsuperscript{7}, Modlin and Sandor\textsuperscript{19}, Modlin \textit{et al}\textsuperscript{8} and Yao \textit{et al}\textsuperscript{9} made the more substantial contributions with their analyses of 2,837 cases in 1975, 8,305 cases in 1996, 13,715 cases in 2002, and 35,825 cases in 2007 respectively, using data describing NET patients residing in the US and which used general population-based data. Godwin evaluated information compiled in the End Results Group (ERG) and the Third National Cancer Survey (TNCS) programmes of the
US National Cancer Institute (NCI) between 1950 and 1971. Modlin and Sandor then analysed the combined data from the above ERG/TNCS databases and NET data from the USA NCI Surveillance Research Program with the updated report that included the period 1973–1991. In 1973, the Surveillance, Epidemiology, and End Results (SEER) database, compiled by the USA NCI Surveillance Research Program, succeeded the two NCI programs, ERG and TNCS. In 2002, Modlin et al. updated their analysis using SEER registry data circa 1973–1999. Yao et al. analysed a SEER data set that registered 4,926,760 neoplasms in 4,466,501 patients from 1973–2004 (Table 1).

Similar efforts in analysing NET epidemiology data in Europe and Asia have been made. In 2001, Hemminki and Li analysed 5,184 NET cases from the Swedish Family-Cancer Database (including the years 1958–1999). In 2003, the Niigata Cancer Registry in Japan yielded 11,842 cases of NETs for analysis by Soga while Li et al. described the occurrences of NETs in 228 Chinese patients diagnosed within a single institution, the Veterans General Hospital in Taipei, Taiwan,

Table 1. Databases used for epidemiological studies of NETs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of cases</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godwin7</td>
<td>1975</td>
<td>2837</td>
<td>ERG, TNCS</td>
</tr>
<tr>
<td>Modlin and Sandor10</td>
<td>1996</td>
<td>8305</td>
<td>ERG, TNCS and USA NCI Surveillance Research Program</td>
</tr>
<tr>
<td>Modlin et al8</td>
<td>2002</td>
<td>13715</td>
<td>SEER</td>
</tr>
<tr>
<td>Yao et al9</td>
<td>2007</td>
<td>5825</td>
<td>SEER</td>
</tr>
<tr>
<td>Hemminki and Li12</td>
<td>2001</td>
<td>5184</td>
<td>Swedish Family Cancer Database</td>
</tr>
<tr>
<td>Soga20</td>
<td>2003</td>
<td>11842</td>
<td>Niigata Cancer Registry</td>
</tr>
<tr>
<td>Li et al21</td>
<td>2007</td>
<td>228</td>
<td>Data from Veterans General Hospital</td>
</tr>
</tbody>
</table>
over a 35-year period in 2007\textsuperscript{20}. The Novartis-sponsored Asia-Pacific Gastroenteropancreatic Neuroendocrine Tumor (GEP NET) registry and the European Neuroendocrine Tumor Society (ENETS)-driven European Neuroendocrine Tumor Registry (EuroNETS) have just been established in 2009 and are not ready for analysis yet.

**DATABASE FACTORS THAT MAY CAUSE POTENTIAL BIASES IN ANALYSES**

The SEER registry\textsuperscript{10} underwent two major expansions in 1992 and 2000 to cover 13.8\% and 26.2\% of the total US population from an initial base of 9.5\% since its inception. The expansions not only bolstered the database in numerical terms but also improved coverage of the minority ethnicities of Asian, American Indian, Hispanic, and African-American origin, which was hitherto sparse. These changes allowed for comparative epidemiology analysis based on ethnicity to be done in recent decades. The other noteworthy aspect of the SEER data is the inclusion of only tumours that are designated “malignant” prior to 1986. Hence, prior to 1986, certain NETs that were designated “benign” (such as some cases of appendiceal carcinoids) may not have been reported to the SEER registry.

The International Classification of Diseases for Oncology histology codes (ICD-O) have changed over time\textsuperscript{22}. Since its inception in 1948, the ICD series was compiled and published by the World Health Organization (WHO), which was formed after World War II. The classifications have evolved from a purely topographical system to one that incorporates morphological features (Figure 4). As NETs have been increasingly recognised to have specific morphological features and a unique immunohistochemical profile, the number of cases captured in registries using ICD-O coding for the categories relevant to NETs will increase in tandem.
### Figure 4

The WHO compiles and publishes the ICD-O histology codes, which classifies NETs based on their topological and morphological features. ICD = International Statistical Classification of Diseases, Injuries, and Causes of Death, ACS = American Cancer Society, CAP = College of American Pathologists, SNOP = Systematized Nomenclature of Pathology, MOTNAC = Manual of Tumor Nomenclature and Coding, SNOMED = Systematized Nomenclature of Medicine, ICD-O = International Classification of Diseases for Oncology.