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REVIEW ARTICLE

Epidemiology of non-gastroenteropancreatic (neuro)endocrine tumours

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Summary

The widespread availability and reliability of immunohistochemical techniques in the last three decades have allowed researchers to identify cells with common neuroendocrine markers in virtually every organ. As a whole, these neuroendocrine cells form the so-called diffuse neuroendocrine system. Tumours arising from the cells of the diffuse neuroendocrine system are defined as (neuro)endocrine tumours (NETs). NETs have been increasingly described in recent years. However, despite the increase in the number of published papers focused on NET, we still lack adequate epidemiological data, particularly for non-gastroenteropancreatic (GEP) NETs. Furthermore, the real incidence of neuroendocrine differentiation for most sites is not completely known and is probably underestimated. As a consequence, data on the clinical features of many NET subgroups are not well known or confusing. For all of these reasons, we have attempted to evaluate the epidemiology of non-GEP NETs, reviewing the limited data available in the literature.

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Introduction

Despite the substantial and progressive increase in published data since the first description at the end of the 19th century, we are still lacking adequate epidemiological information on (neuro)endocrine tumours (NETs), particularly for non-gastroenteropancreatic (GEP) NETs. This is probably a consequence of rarity, frequent lack of associated clinical signs, a multidisciplinary setting of occurrence, and the continuous evolution of diagnostic techniques and classification criteria. Contrary to other solid tumours, mortality cannot be used as an approximation of incidence and prevalence because they generally respond well to surgical treatment; furthermore, the well-differentiated NET is usually characterized by indolent behaviour. The histological definition of NET has been markedly improved in the last three decades by the wide availability of immunohistochemical techniques and by the formulation of valuable unified criteria, regardless the site of origin of the tumour.[1,2] Moreover, current opinion postulates that neuroendocrine cells may have different embryological origins and are widely dispersed around the body, not only limited to the gastrointestinal tract, but also within the lungs, larynx, thymus, thyroid, adrenal, gonads, skin and many other organs and tissues.[3] As a whole, these neuroendocrine cell aggregates dispersed in non-neuroendocrine tissues constitute the diffuse neuroendocrine system.

Apart from the GEP location, most of the published data on the epidemiology and clinical presentation of NETs are still scarce and generally limited to case reports or small series, where the real incidence of neuroendocrine differentiation for most sites is not completely known and probably underestimated. A further factor that limits the achievement of 'real' epidemiological data is the discrepancy between the estimated incidence of GEP NETs, around one case per million per year[4] and the higher prevalence of these tumours found in autopsy series.[5] In this study, we attempt to collect data available from the literature on the epidemiology of non-GEP NETs, arising from neuroendocrine cells dispersed in the lung, larynx, thymus, genital tract and skin. Organ-specific NETs such as those arising in the thyroid, pituitary and parathyroid are not included in this review due to their site-specific peculiarities.

Lung

The epidemiology of lung NETs varies greatly between well-differentiated and poorly differentiated forms. At the opposite sides of the spectrum of differentiation, the well-differentiated forms, typical and atypical lung carcinoids (TC and AC, respectively), are still considered rare tumours, while small-cell carcinoma (SCC), a poorly differentiated neuroendocrine carcinoma, represents one of the most common histological subtypes.

Epidemiological data vary considerably between the four different histological NET subgroups, identified by Travis *et al.* in the World Health Organization (WHO) classification for neuroendocrine

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Table 1. Male : female ratio of (neuro)endocrine tumours

Tumour site and histological subtype	Male : female ratio
Lung	
Typical carcinoid	1 : 1
Atypical carcinoid	1 : 1
Large cell neuroendocrine carcinoma	8 : 1
Small cell carcinoma	9·5 : 1
Larynx	
Typical	2 : 1
Atypical carcinoid	3 : 1
Paraganglioma	1 : 3
Small cell carcinoma	No data available
Thymus	
Typical carcinoid	9·5 : 1
Atypical carcinoid	9·5 : 1
Skin	
Poorly differentiated carcinoma	1 : 1

tumours of the lung.[1] The prevalence of tobacco abuse differs greatly between well-differentiated and poorly differentiated forms. In our series, among 152 surgically treated patients, the percentage of smokers varied between 46% for TC to 100% for SCC.[6] The same marked variation was found in male : female ratio, ranging from 1 : 1 for TC and AC to 8 : 1 for large-cell neuroendocrine carcinoma (LCNEC) and to 9·5 : 1 for SCC[6] (Table 1). Comparing these data, it appears obvious that this great difference between men and women cannot be entirely explained by the higher percentage of smokers among the male general population. However, the rising percentage of female smokers in the general population correlates to some extent with the decreasing male : female ratio, indicating some influence of this factor.

A population-based study of the demographics of patients with lung NET grouped by histological subtype, performed using a cancer registry-based analysis of patients in Denmark from 1978 to 1999, showed that the recorded incidence of NETs other than SCC increased twofold among men (from 0·24 to 0·53 per 100·000 inhabitants per year) and by threefold in women (from 0·14 to 0·41 per 100·000 inhabitants per year) during the study period, while the incidence of SCC decreased among men and levelled off among women.[7]

Due to the existence of substantial differences in all of the epidemiological aspects, it is more convenient to consider each different grade of differentiation separately.

Well-differentiated NETs (carcinoids)

The annual incidence of lung carcinoids ranges from 0·7 to 4·8 per million. TC is more common than AC with a ratio ranging from 8 : 1 to 12 : 1. The prevalence of TC is estimated to be 0·6% to 2% of all lung cancers, and 7% to 25% of the total carcinoids of all sites. In the largest reported series by Modlin *et al.* a sharp increase in incidence of lung carcinoids has been noted in recent years, but it is still unclear whether this is related to advances in diagnostic techniques in asymptomatic forms or a real increase.[3]

No gender prevalence has been reported. In a series of 100 lung carcinoids, the male : female ratio was exactly 1 : 1. However, in a large series of 2931 patients, a female prevalence was seen in patients under the age of 50 years.[8] The mean age at diagnosis was 54·1 ± 15·2 years (ranging from 18 to 73 years of age).[6] AC tends to occur generally in older patients. Several hypotheses have been formulated to explain this finding. The increasing incidence of smoking-related molecular abnormalities found in lung NETs, ranging from TC to AC, LCNEC and SCC seems to support the theory of a 'continuum' in the spectrum of neuroendocrine differentiation.

In lung carcinoids, there is an underestimated percentage of multiple forms. Synchronous multicentric forms have been found after performing serial sections in our series in 5% of cases. Single or multiple tumorlets were found in our series in 10% of cases. Lymph-node involvement (N1, N2) at diagnosis was present in our series in 13·8% of cases (unpublished data). These findings must be carefully considered in the choice of surgical treatment.[6]

Poorly differentiated neuroendocrine carcinomas

Together with necrosis, the number of mitoses in 10 high-power fields is the main criterion for separating LCNEC and SCC from AC. Due to the irregular distribution of mitoses in the tissue, the use of additional reproducible criteria, which is partially described in the WHO classification of lung tumours, précising that mitoses must be counted in the areas with the highest mitotic activity, are needed. For this reason, Ki67 and other reliable biological markers are advocated to reduce the percentage of misdiagnoses.

SCC accounts for 20% of lung cancers and represents the third type of primary lung malignancy after squamous cell carcinoma and adenocarcinoma. Contrary to TC, a slight reduction in the frequency of SCC among lung cancer subtypes became apparent when comparing data registered prior to 1985, with those registered between 1983 and 1987. In all of the reported series, a strict correlation between SCC and cigarette smoking was found. In our series, 98·9% of SCC patients were smokers and only 1·1% non-smokers.[6] The mean age of patients at the time of diagnosis was around 60 years, ranging from 30 to 80 years. The male : female ratio was 9·5 : 1.

LCNEC is a rare NET subtype. However, recent reports have underlined that a significant percentage of LCNEC have been misdiagnosed and may be revealed by retrospectively analysing lung tumour surgical samples, according to the criteria of the last WHO Travis Classification.[2] A recent study allowed researchers to reclassify 75 out of 560 (13%) poorly differentiated primary lung cancers as LCNEC[9] on the basis of their immunoreactivity for neuroendocrine markers; moreover, 13% of patients with poorly differentiated carcinoma of an unknown primary site were found to exhibit neuroendocrine features, which were consistent with the diagnosis of LCNEC.[10] Frequent misclassification of LCNEC has also been confirmed by a histological and immunohistochemical revision of tumour samples from 97 patients with an initial diagnosis of poorly differentiated neuroendocrine carcinoma; 42% of them were consistent with the diagnosis of LCNEC, while reclassification as a well-differentiated NET, SCC or mixed endocrine–exocrine tumours was made in the remaining 58% (personal unpublished data). A misdiagnosis is also possible between LCNEC and adenocarcinomas or other non-neuroendocrine tumours, as 2·9% of 766 lung tumours surgically treated in a single centre were identified to be consistent with the diagnosis of LCNEC, according to Travis criteria.[11] As a

whole, the subgroup of LCNEC represents 3·3% of the non-small-cell NETs, including both pulmonary and extra-pulmonary forms, as highlighted in a retrospective analysis on 1255 patients followed at the 'Institut Gustave Roussy' from 1990 to 2001 (unpublished data).

When compared to SCC, there was a slightly lower male prevalence in LCNEC (9·5 : 1 for SCC *vs.* 8 : 1 for LCNEC in our series) (Table 1).[6] However, the gender difference is substantially abrogated when extra-pulmonary LCNEC are also included (male : female ratio 1·4 : 1) (unpublished data). Mean age at diagnosis was around 63–65 years with a large variability, ranging from 26 to 84 years of age.[6] Similar to the SCC small cell type, a large majority LCNEC cases had a history of tobacco abuse. Another potential risk factor was the exposure to chemical or physical transforming agents. Among 41 patients with LCNEC, 15% had been previously treated with chemo- or radiotherapy for another tumour 1–28 years before LCNEC occurrence (unpublished data). However, this finding needs to be further validated since no relationship between poorly differentiated LCNEC and chemo- or radiotherapy has previously been reported.

Carcinoid tumorlets

According to the WHO classification criteria, neuroendocrine proliferations can be divided in a spectrum of lesions that ranges from neuroendocrine cell hyperplasia to tumorlets and/or carcinoid tumours.[2]

Due to the fact that the maximum diameter of these lesions must, by definition, be less than 0·5 cm and that they are generally not associated with any clinical symptomatology, carcinoid tumorlets are often an incidental pathological finding. Therefore, the real incidence and prevalence remains hard to establish. Neuroendocrine cell hyperplasia, with or without associated tumorlets, is a relatively common finding in both TC and AC, but not in SCC and LCC. Tumorlets are significantly more frequent than carcinoid tumours and may be multifocal and bilateral.[10,11] They are very often associated with inflammatory processes like bronchiectasis and interstitial fibrosis, and the correct histological diagnosis requires an accurate serial dissection of the pulmonary parenchyma. In 1958, Cunningham *et al.* found the presence of tumorlets in 20% of cases by performing serial sections of lung parenchyma in bronchiectatic lungs.[12] Some large autopsy series showed the prevalence of tumorlets in the general population ranging from 0·1% to 0·22%. Also in these series, tumorlets were observed more frequently in patients with chronic lung diseases, mainly bronchiectasis, interstitial fibrosis, and other chronic inflammatory lung diseases.

The real significance of these lesions is still not completely understood and it is debated whether they represent an 'early' stage of carcinoid.[13] Nevertheless, the report of tumorlets associated with clinical syndromes contradicts the lack of clinical meaning postulated by various authors. Studies using molecular and subcellular techniques have been performed, but further studies are required to completely clarify these aspects.

Larynx

Neuroendocrine neoplasms affect laryngeal mucosa much less frequently then squamous cell carcinoma of the larynx. NETs represents 0·6% of all laryngeal neoplasms.

The histological classification of NET is similar between the lung and the larynx; NETs of the larynx consist of TC and AC, SCC and laryngeal paraganglioma. These four histological subtypes account, respectively, for 3% (TC), 54% (AC), 34% (SCC) and 9% (paraganglioma) of cases.[14,15] While laryngeal TC is a very rare entity, AC can be considered as the most frequent non-squamous carcinoma of the larynx. The distinction between the four subtypes is of crucial importance because the therapeutic approach and prognosis are different. At diagnosis, TC and paraganglioma are generally limited to a loco-regional extension and associated with a good prognosis.[16] AC is a much more aggressive tumour and only 50% of patients are alive 5 years after the intervention. SCC always needs chemo- and radiotherapy and the percentage of survivors at 5 years is only 5%. However, the percentage of local or distant metastasis is also relevant in well-differentiated forms.[17]

To date, more than 500 cases of NET of the larynx have been reported in the literature. The peak incidence in various series is around a mean age of 58 years (range, 45–80 years) for TC, 61 years (range, 36–83 years) for AC, 50–70 years (range, 23–91 years) for SNEC and 44 years (range, 14–83 years) for paraganglioma. In every series, a male prevalence has been described, especially in the AC group, while the paraganglioma is the only laryngeal neuroendocrine neoplasm with a female preponderance that reaches a ratio of 3 : 1 (Table 1). A large majority of the patients had a history of tobacco abuse, especially in the AC and SCC subgroups, which reflects a similar finding in the lung counterpart of these tumours. The majority of these tumours arise in the supraglottis.[15,17] Paraneoplastic syndromes have been reported only occasionally in association with NET of the larynx, often with the syndrome of inappropriate antidiuretic hormone production.[18]

Thymus

According to Rosai WHO classification criteria, thymic tumours can be classified as neuroendocrine only when the neuroendocrine elements constitute the predominant or exclusive component of the neoplasm.[19] In fact, many typical carcinomas (type C thymomas) contain a certain number of neuroendocrine cells.[20,21] The prevalence of thymic carcinoid is approximately 0·3% of total carcinoids of all sites. The term carcinoid is still used to define well-differentiated NET of the thymus, although this tumour entity is now better defined as well-differentiated neuroendocrine carcinoma. The well-differentiated subgroup can be divided into classic, spindle cell, pigmented, with amyloid and atypical forms. The ratio between typical and atypical forms is characterized by a higher proportion of atypical forms. The poorly differentiated subgroup comprises SCC and the LCC in homology with the lung NETs.[19]

Since 1972, when Rosai and Higa reported the first description of eight thymic carcinoids as a separate entity from thymomas, more then 300 cases have been reported in the world literature.[22,23] In the same year, the same authors reported that thymic carcinoids may occur in association with multiple endocrine neoplasia type 1 (MEN-1), a genetic disorder that predisposes to the development of multiple endocrine and non-endocrine proliferations.[24,25] Thus far, more than 30 cases of this association have been reported. However, the prevalence of a thymic neuroendocrine tumour is probably

underestimated. In the same manner, their association with MEN-1 is very frequently unrecognized. Among 185 mediastinal masses and among 65 tumours arising from the thymus, we found neuroendocrine differentiation and association with MEN-1 in a significant percentage of cases.[26,27] Associations with other syndromes, including MEN-2, have only been reported in anecdotal cases.

More than 90% of cases are men (Table 1). Virtually all of the reported patients were heavy smokers. At time of the diagnosis, most of the patients with thymic NET were asymptomatic, although a metastatic stage occurred in 20–30%.

A large number of cases of a NET arising in the thymus are associated with paraneoplastic syndromes. Among these, Cushing's syndrome is the most frequent given that an increased secretion of ACTH has been reported in one-third of sporadic thymic NETs; interestingly, it is extremely rare in MEN-1-related thymic carcinoid. Among all causes of ectopic ACTH secretion, about 10% is associated with thymic NETs. Carcinoid syndrome has never been reported in thymic NETs.

Genital tract

NETs can also originate from the genital tract; they are generally more frequent in females. The most common of these are, in fact, uterine SCC and ovarian carcinoids. Primary ovarian carcinoids have a relatively benign prognosis in contrast with ovarian metastases from GEP carcinoids, which show a more aggressive behaviour. Primary ovarian carcinoids may develop in association with other non-NET histological subtypes, mainly teratomas. Carcinoid syndrome is described in about 30% of cases.[28]

Poorly differentiated neuroendocrine carcinomas in the ovary include both SCC and LCC; they are associated with an aggressive presentation at the time of diagnosis and have a poor prognosis. SCC and LCC may also arise from the uterus, both endometrium and cervix, potentially involved as primary site.[29,30] In contrast, uterine carcinoids have been reported in only few cases. NETs have been rarely reported to arise from the vulva and vagina and, in these cases, they are consistent with the SCC subtype.

In men, the most common and perhaps underestimated site of NET development is the prostate. Among the well-differentiated forms, the carcinoid subtype has been described to originate from the testis, while carcinoids originating in other sites are very rare. Carcinoids of the testis have been described to secrete serotonin, occasionally associated with carcinoid syndrome.[31] On the other hand, SCC has been sporadically described in the scrotum, penis and urethra.

Apart from in the prostate, NETs have been reported only anecdotally and it is therefore impossible to establish their real prevalence and incidence. However, what must be underlined is that true prostate NETs are very rare tumours, whereas most of the prostate tumours with neuroendocrine appearance are consistent with non-NET adenocarcinomas with positive immunostaining for neuroendocrine markers.[32]

Skin

Skin harbours a subset of neuroendocrine cells with secretory capacities, the so-called Merkel cells. Merkel cell neoplastic proliferations represent therefore primary cutaneous NETs. They are rare tumours (approximately 2000 cases reported in literature) and their rarity is still more accentuated in comparison to the high frequency of skin tumours as a whole, which accounts for about 10% of all human malignancies.

From a histological point of view, Merkel cell tumours are poorly differentiated neuroendocrine carcinomas, while a carcinoid-like subgroup is not encountered among skin NETs.[33,34] However, these tumours include a spectrum of neoplasias with different diagnostic and prognostic features.[35] At the time of diagnosis, these tumours are generally characterized by a primary lesion, growing in the dermis and subcutaneous tissues, with or without lymph node metastases. The head and neck represent the most common site of Merkel cell tumour onset (> 50%), followed by extremities (40%) and trunk (5–10%).[36,37]

As far as clinical presentation is concerned, Merkel cell tumours generally occur in older white adults with a mean age of 67·9 years, although age of onset has been reported to vary from 15 to more than 95 years. No gender difference has been described[38] (Table 1). In contrast with most of NETs from other primary sites, the Merkel cell tumour has well-defined risk factors that are in common with other skin neoplasias. Sun exposure, in fact, is found in the majority of these patients and immunosuppression represents another relevant risk factor.[39,40]

Merkel cell tumours have been shown to express several neuropeptide and neuroendocrine markers; however, apart from their utility for diagnosis and follow-up, an endocrine-related functional syndrome has never been reported in skin NETs.

Conclusion

This overview on the epidemiology of non-GEP NETs gathers data on incidence and clinical presentations of different NET subtypes arising from the diffuse neuroendocrine system, which could be a tool for specialists interested in this fascinating and incompletely understood topic. As pointed out for the GEP NETs, which have represented the paradigm for the study of this bizarre pathology, the natural history of non-GEP NETs presents a distinct character regardless of the site of origin. In fact, the neurosecretory pattern and the existence of a complicated biological network, which regulates proliferation and secretory activity and which is susceptible to modulation by specific hormone receptors, characterizes all NET subtypes to a variable extent. On the other hand, although unifying biological and histological criteria have been pointed out in recent years, the current review highlights the great difference between one subtype and another, according to their specific site of onset. The classical indolent clinical course and the association with a functional endocrine syndrome are classically considered distinctive features of NETs. However, this is not true for all NET subgroups and rapidly progressing, clinically aggressive NETs may be the exclusive or predominant forms in some organs like skin or lung, whereas a given NET-related functional syndrome often indicates a specific site of primary tumour and excludes some others. Accurate knowledge about the natural history of these tumours may help clinicians recognize early or exclude a NET diagnosis; moreover, it can allow them to perform correct tumour staging and establish the best therapy and follow-up strategy.

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