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Are Neuroendocrine Neoplasms No Longer a Rare Cancer?

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Abstract

Background: Neuroendocrine neoplasms (NENs) are consistently referred to as a "relatively" rare heterogenous group of "tumours" with variability in their disease course and outcomes. However, there is a lack of consensus on (a) the group membership, that is, a lack of consistency in which "subtypes" of NEN are included in the group; (b) whether they should continue to be seen as a "heterogenous group," or as separate entities; and (c) whether the term and current definitions of "rare" accurately reflects the true patient population and healthcare requirement. ***Summary:*** This opinion article explores the concept of rare, as applied to NENs: the significance of a rare cancer label and what this means for awareness, healthcare provision and, tangentially, those diagnosed. It briefly explores rare cancer definitions, including incidence thresholds and interpretation of definition as demonstrated in the variability in what subtypes are included in databanks or registries, and it also asks whether the currently utilised rare cancer definitions reflect an accurate representation of the true disease burden and fully inform disease-appropriate healthcare planning and provision. ***Key Messages:*** The current definition of "rare cancer" based on incidence alone fails to reflect the true disease burden of NENs and is therefore inadequate, to fully inform healthcare policy, planning and provision for this patient population. This requires either a revision in definition or an alteration in how and what decision-makers utilise and include in their deliberations when assessing and planning service provision.

Introduction and Context

Neuroendocrine neoplasms (NENs) are consistently referred to as a "relatively" rare heterogenous group of "tumours" with variability in their disease course and outcomes [1–7]. For those with a NEN, and their loved ones, identified concerns related to the "rarity" of their diagnosis include recognition, gaining a timely, accurate diagnosis, access to specialised (experienced and expert) care and effective, accessible, and available treatment(s). They also report the largely unmet need of receiving the right support and information to fully meet physical, emotional and mental health needs. Essential to this is clarity and consistency in terminology and disease explanations [8].

The term NEN encompasses both well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) and may also include paragangliomas. However, available data suggest that despite some site-specific similarities and overlapping histologic features, they are not only genomically different, but they also have different degrees of

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proliferative aggressiveness, responses to medical therapy, risk factors, hereditary predispositions, and relationships to non-neuroendocrine neoplasia. There is also the unanswered question as to where MiNENs and treatment-emergent NENs sit within current classifications and incidence/prevalence reporting [6]:

> "Another scenario in which neuroendocrine differentiation can occur in neoplasms is in non-NECs following chemotherapy, molecularly targeted therapy, or radiotherapy. In some instances, a small cell carcinoma may arise following treatment of an adenocarcinoma (such as in the prostate or lung) and such poorly differentiated NECs can be considered within the present classification framework. In other scenarios, however, treated carcinomas may display apparent well-differentiated neuroendocrine elements, such as in the Paneth-like cell features of treated prostatic adenocarcinoma, or the well-differentiated neuroendocrine cell nests in rectal carcinomas following chemoradiotherapy" [6].

Herein, lies an issue – how NEN classifications are interpreted and applied (including clinical coding) – and the variability in the inclusion or exclusion of NEN subtypes into groups, datasets, and research, which may inhibit benchmarking and comparisons and may not accurately represent the entire NEN-diagnosed population. While continued efforts are needed to develop interventions for prevention, early detection, and treatment to reduce the patient's burden of a NEN diagnosis – there is also a need for a more unified, collaborative approach to accurately capture, reflect, and represent the current and future disease requirements of healthcare services. It is questionable whether current definitions of what rare cancers meet this need.

Rare Cancer Definitions

When thinking of rare, according to Kawai et al. [9]:

> "Conceptually, it is not incorrect to think of a rare cancer as any whose incidence is rarer compared to other common cancers. However, the boundaries of such rarity must be defined in order to allow appropriate measures to be taken."

According to the Surveillance of Rare Cancers in Europe project, now RARECARENet, the definition of rare is based on incidence, that is, the number of newly diagnosed cases per year, with a cut off of less than 6 per 100,000 persons per year [10]. Applying this definition to UK and Europe data, rare cancers represent approximately 24% of cancer cases, indicating a significant public health burden. In Australia, the Cancer Council groups cancers into rare, less common, and common categories: rare has an incidence rate of less than 6 cases in 100,000 Australians per annum; less common cancers are those that have an incidence of between 6 and 12 (inclusive) per 100,000 Australians per annum: collectively rare and less common cancers account for one-third of diagnoses and half of all cancer deaths in the country [11]. In Japan, rare cancers are defined as malignant tumours with an incidence rate of less than 6 cases per 100,000 individuals, accounting for approximately 15% of the Japanese cancer population [9]. However, in the USA, as defined by the National Cancer Institute, rare cancer is that which occurs in fewer than 15 out of 100,000 people each year, despite the difference this still has rare cancer accounting for "approximately one quarter of all cancers diagnosed each year in the USA" [12].

In terms of NENs, RARECARENet has classified 198 rare cancers into 12 "families," each with an incidence of less than 6 per 100,000: one of these "families" is NETs. In Japan, 190 types of cancer are classified as rare; these include NETs. In the USA, 181 rare cancers were identified, including both NETs and NECs, but across different groupings.

Globally, the incidence of NENs is rising, but so is overall survival, particularly in the more common NET classification. This has significant implications for long-term outcomes, how these are managed and funding of care [13].

Global Incidence of NENs

The global distribution of NENs varies, whole country data are both inconsistent and sparse, with many studies varying in terms of the inclusion/exclusion of the many subtypes of NENs within their data analysis (see Table 1). This lack of consensus challenges the accuracy and comparability of data, may complicate awareness initiatives and disease recognition, and may delay, or even prevent, an informed answer to the question whether NENs are no longer a rare cancer.

If subtypes, particularly morphologically coded types, such as small and large cell NECs, are excluded, then real incidence and prevalence rates will always be underestimated – compounding existing barriers for those diagnosed. It will also impact on healthcare training and education programmes, as well as infrastructure, resource planning and healthcare service planning and delivery [20].

There are many other cancers with a similar and indeed lower incidence to NENs, but with a higher profile: the key difference is that they tend to be a cancer of a single site (even if they have various subtypes), rather than a heterogenous group of individually rare to

Table 1. Presents a snapshot of incidence data from various countries and their exclusions

Country	Date	Incidence (per 100,000)	% increase over study time	Exclusions
England [13][a]	1995–2018	8.61	371%	Large cell neuroendocrine and small cell carcinomas of the lung, Merkel cell carcinoma, and MiNEN
Australia (Queensland) [14]	1986–2015	NET 6.3	315%	NEC including Merkel cell carcinoma
Norway [3]	1993–2021	NET 9.97 NEC 9.95	268%[a]	Uncertain
Canada (Ontario) [15]	1994–2009	NET 5.86	236%	Small cell and large cell lung carcinoma, pheochromocytoma, paraganglioma, extra-adrenal paraganglioma, medullary thyroid carcinoma, and Merkel cell carcinoma
Italy [16]	1976–2012	5.46	546%	Small cell and large cell NEC of the lung, phaeochromocytoma, paraganglioma
Beijing [17]	1998–2018	NEN 3.53	329%	Not stated
USA [18]	1973–2012	NET 6.98	640%	NECs
China [19]	2008–2013	NEN 1.14	n/a	Histology codes 8002, 8040–8045, 8013, 8700, 8680, 8693, and 8510 were excluded

[a]In Norway, while overall incidence was not statistically significant, Merkel cell carcinoma increased by 287% and GI NECs increased by 200%.

ultra-rare cancers. This, maybe, has fuelled debate as to whether NENs should continue to be seen as a collective group (with an increasing incidence exceeding the definition of rare) or as individual and separate site-specific entities (rare to ultra-rare incidence). It remains to be seen whether the increasing move towards personalised medicine, as informed by molecular, genetic, and genomic knowledge advances, rather than simply the location of a cancer, adds to this discussion [21]. While incidence may help at the front end of care – enabling an assessment of diagnostic capability and capacity [20] – the significance of prevalence cannot be overlooked. NENs as a group are often incurable, especially when metastatic, regardless of grade [5], but may still have a favourable prognosis depending on site, stage, grade, behaviour (functionality), and treatment response. In England, despite being a rare group of cancers by overall incidence, NENs are the 10th most prevalent malignancy, even with less than 20% diagnosed at potentially curable Stage 1 disease [13].

Global Prevalence of NENs and the Relevance of Prevalence

Despite the potentially life-limiting nature of an NEN diagnosis, the prolonged survival/relatively high prevalence reported in the NET cohort has somehow downplayed its seriousness, severity, and healthcare-reliance implications, within some medical circles: this may be due to the often-reported indolent nature of low-grade disease. Assumptions of low rate of growth can divert attention from both the psychosocial impact [22] of a malignant diagnosis, the impact of disseminated disease (where present) and the physiological effects of a functioning tumour (where excess hormone secretion is a characteristic that affects symptom experience and can have potentially life limiting sequelae, e.g., carcinoid syndrome and carcinoid heart disease) [23]. It also removes focus from those with a higher grade NET and the 5–35% (dependent on age group) diagnosed with a NEC [13].

According to the National Disease Registration Service (NDRS), at the end of 2021, in England alone, there were more than 32,000 people living with a "neuroendocrine cancer" diagnosis: data regarding stage at diagnosis are only available for the preceding 5 years (76.5% of 17,421 diagnosed beyond potentially curable Stage 1): 52% of all diagnosed, fell within the category of working age range of 18–70 [24].

In Norway, between 1993 and 2021, the prevalence rose by 665% – with around 35% of NETs and less than 10% of NECs diagnosed with Stage 1 disease. The authors of this study note that "limited-duration prevalence

estimates will tend to underestimate the prevalence" [3] but are incomplete.

Recent, and emerging, prevalence data, if included alongside incidence reporting, could be vital to better understanding the disease burden of the NEN population: raising awareness and creating a more complete picture of the impact they have on both the individual and healthcare services. This information also has implications for longer term healthcare provision [20] but faces similar challenges, in collation and reporting, as that identified in incidence: that is, should it be gathered and published as a group or as individual cancers.

Conclusion

The designation of "rare cancer" is based on the number of new diagnoses per year and can inform improvements at the front end of the cancer journey trajectory; however, prevalence should not be overlooked.

- Within the NEN community, it is a key influencer in terms of addressing unmet needs: while incidence is diagnosed, the life-changing news received on a single day, the prevalence is a cancer that stays with many for their lifespan, not something they live beyond.
- Within healthcare, accurate disease burden information is essential for informing policy and long-term health investment, planning, and prioritisation: including health research initiatives and innovation.

Many healthcare systems are simply not set up to manage potential chronicity in cancer care, that high prevalence of cancers, such as NENs, more specifically NETs, require. NENs are complex – *heterogeneity with respect to site of origin*, *grading and staging criteria*, as well as behaviour and consequences, compounded by considerable *revisions to histopathological classification schemes, present their own challenges* [7].

The challenges those diagnosed face are well-documented and a rare disease designation can be shown to hinder understanding, awareness, advances in care, and investment in research, to the detriment of patient experience and outcomes [8, 22, 25, 26]. If we apply the aforementioned definitions of rare, NENs as a group can no longer be considered rare (in England and many other countries) as incidence rates continue to rise above 6 per 100,000: however, the individual cancers that fall under this umbrella term are.

A more integrated approach to data capture and utilisation, and greater consensus and consistency in data group inclusion, will be key to improving outcomes for patients with NENs. The current definition of "rare cancer," based on incidence alone, fails to reflect the true disease burden of NENs, and is therefore inadequate to fully inform healthcare policy, planning, and provision for this patient population. This requires either a revision in definition or an alteration in how and what decision-makers utilise and include in their deliberations when assessing and planning service provision.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

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