Mitigating the Paucity-of-Data Problem for Target Population Sizing: Exploring a Model-Based Approach for Advanced Gastroenteropancreatic Neuroendocrine Tumours

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Introduction

Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs) are relatively rare and complex neoplasms with a wide spectrum of clinical presentations. They are derived from neuroendocrine cells, with primary tumours located in the gastric mucosa, pancreas, small and large intestine [1,2]. With their distinct functional and biological behaviours, they consist of a heterogeneous group of tumours associated with a wide range of clinical symptoms that vary according to the tumour location, size and presence or not of metastasis [3]. The diagnosis of tumours at an early stage and the fortuitous discovery of lesions have substantially increased over the past decades owing to the greater availability of advanced endoscopic techniques and radiological imaging.

Although GEP-NETs can occur at all ages, the highest incidence estimates are found in individual's age 50 and over [1]. Survival of patients with GEP-NETs depends on the disease stage, tumour histology and location. Indeed, while patients with well- and moderately-differentiated GEP-NETs who present with distant metastases have a five-year survival probability of 35%, this survival drastically drops to 4% in patients with poorly-differentiated tumours also having distant metastases [4].

Furthermore, clinical presentation also depends on the site of the primary tumour and whether it is functioning or not i.e., whether the peptides and amines secreted by the tumour produce clinical symptoms. The majority of GEP-NETs are non-functioning and symptoms appear late during the disease progression, mostly related to tumour mass effects and/or distant metastases [1].

Epidemiologic data on GEP-NETs are scarce in the literature and obtaining reliable population-based estimates of incidence is hampered...
by the fact that national cancer registries document malignant tumours on the basis of clinical reports [3,5]. In addition, data have usually been collected over a time period during which the disease definition has evolved extensively. In 2000, the World Health Organization (WHO) classification divided NETs of the digestive system into three broad categories: (i) Well-differentiated endocrine tumours; (ii) Well-differentiated endocrine carcinoma; and (iii) Poorly differentiated endocrine carcinoma, which was further divided into large cell and small cell endocrine carcinoma [6].

Tumour categorization was then based on size, degree of tissular invasion and location. In 2010, the WHO updated its classification of NETs to account for tumour site of origin, clinical syndrome, and differentiation, which allowed for further improvements in prognostic stratification [7]. In this current classification, the well-differentiated NETs are divided into grade 1 and grade 2, according to their proliferative activity and biological features. The poorly differentiated neuroendocrine carcinomas (grade 3) are subdivided into large cell neuroendocrine carcinoma and small cell neuroendocrine carcinoma [8]. In this context, heterogeneous nomenclature and classification of NETs found in the literature is a major limitation for obtaining consistent epidemiologic data [9].

For innovative treatments, recommendations by payers or health technology agencies frequently involve sub-populations of patients that are more restricted than the approved indications. Because epidemiologic data published in the literature are not specific to GEP-NETs restricted sub-populations, generating relevant data to support pricing and reimbursement strategies, and providing robust estimates of their budget impact represent a major challenge for a successful market access. This study aimed at developing a model to estimate the number of patients with specific site and type of GEP-NETs over a five-year time period in the following countries: EU (France, Italy, Ireland, Poland, Portugal, Spain and United Kingdom), the United States (US), and Australia.

**Methods**

Two GEP-NET sub-populations, based on the secretory properties of the tumours, were considered reflecting respectively, the approved and the targeted restricted indication for reimbursement:

**Sub-population 1**: Patients with stable/slow progressing well-differentiated functioning and non-functioning GEP-NETs and unresectable, locally advanced and/or metastatic disease (i.e., approved indication).

**Sub-population 2**: Patients with stable/slow progressing well-differentiated, non-functioning GEP-NETs and unresectable locally advanced and/or metastatic disease. In order to be consistent with the European marketing authorization, both of these sub-populations exclude patients with tumours originating from the hindgut region (NETs of the colon and rectum). As shown in Figure 1, the second sub-population of interest is a subgroup of the first.

In order to determine the progression of the target population size annually over a five-year period, a multi-step approach was used that involved determining the population size at baseline, followed by the development of a target population growth model in order to cover the follow-up period.

**Determination of baseline population sizes**

Key epidemiologic data required to calculate the size of each sub-population of interest at baseline included the following:

- Prevalence rates of patients with well-differentiated Grade 1, Grade 2 GEP-NETs (functioning and non-functioning);
- Prevalence of patients with unresectable locally advanced or metastatic disease;
- Prevalence of patients with stable or slow progressing disease.

In the absence of published data specific to these sub-populations, a three-step approach was used:

- Crude prevalence and incidence rates for the broad GEP-NET population were identified in the literature;
- Estimates specific to each sub-population of interest were obtained using proportions of GEP-NETs by site and type (i.e., functioning/non-functioning tumours) reported from clinical studies;
- Further refinement of these estimates using proportions derived from clinical expert opinions since published estimates in some clinical studies remained too broad.
A depiction of the three-step approach may be found in Figure 2.

Whenever possible, epidemiologic data from the same source population were used in order to reduce biases related to variations in the disease definition over time and settings. Otherwise, when data from several publications had to be combined, an attempt was made to use estimates derived from comparable populations and disease definitions.

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of patients with well differentiated Grade 1, Grade 2 GEP-NETs (functioning &amp; non-functioning)</td>
<td>Country total population × 13.22/100,000</td>
</tr>
<tr>
<td>Prevalence of patients with unresectable locally advanced or metastatic disease</td>
<td>Result of 1 × 50%</td>
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<tr>
<td>Prevalence of patients with stable or slow progressing disease</td>
<td>Result of 2 × 50%</td>
</tr>
<tr>
<td>Prevalence of patients with GEP-NETs, excluding hindgut origin</td>
<td>Result of 3 × 77.6% or Result of 3 × 70%</td>
</tr>
</tbody>
</table>

*Sub-population 1: Stable/slow progressing well-differentiated, functioning and non-functioning GEP-NETs and unresectable locally advanced/metastatic disease

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<tr>
<td>Prevalence of non-functioning tumors</td>
<td>Result of 3 × 70%</td>
</tr>
<tr>
<td>Prevalence of patients with GEP-NETs, excluding hindgut origin</td>
<td>Result of 4 × 77.6% or Result of 4 × 70%</td>
</tr>
</tbody>
</table>

*Sub-population 2: Stable/slow progressing well-differentiated, non-functioning GEP-NETs and unresectable locally advanced/metastatic disease; pNET: Pancreatic neuroendocrine tumour; ESMO: European Society for Medical Oncology

Table 1: Estimation of target population size–sub-population 1*.

Table 2: Estimation of target population size–sub-population 2*.

Size of target population at baseline was obtained using prevalence estimates, as shown in Tables 1 and 2. First, published prevalence rate of well differentiated Grade 1 and Grade 2 GEP-NETs was applied to the population size of each country of interest in order to obtain a total number of patients with disease. Estimates were further refined by applying the proportion of GEP-NETs with tumour resectability, disease progression and tumour functionality as obtained from clinical studies and experts opinions.

Development of the target population growth model

A target population growth model that mapped the population dynamics throughout the five-year period was then developed (Figure 2). This model required the following epidemiologic data for each sub-population of interest: baseline target population size, annual incidence rate of GEP-NETs, and annual mortality rates for the prevalent and incident cases.

To estimate the population size during a given year of follow-up, the number of cases occurring during that year (i.e., incident cases) was added to the number of patients present at the start of the year (i.e., prevalent cases). Number of deceased patients during the year was subsequently deducted from this number. To account for differences in survival rates between prevalent and incident cases, distinct mortality rates were applied to patients of the baseline target population and to incident cases that occurred during the follow-up period. In addition, for incident cases, the number of years since disease diagnosis was also considered in order to estimate the number of deceased patients during a given year because, during the first five years following diagnosis, survival rate is not uniform. Subsequently, using these epidemiologic data as well as disease incidence rates in both sub-populations, the five-year population growth model was constructed.

Results

Country-specific epidemiologic data

Two relevant large population-based studies on GEP-NETs were identified in the literature. The first was conducted by van der Zwan et
al. [10], in which estimates of incidence, prevalence and survival of NETs were assessed through 76 population-based cancer registries in Europe. The second was a study by Yao et al. [4] which focused on the epidemiology and prognostic factors of NETs using 35,825 cases identified in the Surveillance, Epidemiology, and End Results (SEER) Program registries in the US. However, none of these studies provides epidemiologic data at the level of granularity required to calculate the target population size of the sub-populations of interest. In particular, there were no data on tumour resectability or disease progression. Consequently, additional epidemiologic data were sought from other smaller studies in order to adequately estimate the required prevalence rates [3,11,12]. Reports on the epidemiology of GEP-NETs outside the US and EU were particularly scarce [9]. For Australia, data were available from population-based registries [5,13]. However, these figures may underestimate the target population size of the sub-populations of interest since only poorly differentiated, invasive and malignant tumours tended to be included in those registries [5]. For this reason, European and US prevalence and incidence rates were used to derive the Australian target population sizes.

Target population sizing

As shown in Tables 1 and 2, published prevalence of well-differentiated Grade 1 and Grade 2 GEP-NETs is 13.22/100,000 [10]. This figure was applied to the population size of each country of interest and further stratification was undertaken to take into account tumour resectability, disease progression and tumour function. Specifically, Lepage et al. [11] and Walter et al. [12] estimated that approximately 50% of GEP-NETs are unresectable. Although these estimates were obtained from European registries, this figure was applied to all countries, including the US and Australia, due to the lack of published specific data in these countries. The prevalence of patients with GEP-NETs with stable or slow progressing disease was not found in the literature. To fill this gap, consultation with two experts in oncology revealed that, based on their clinical experience, about 50% of unresectable GEP-NETs may be characterized by slow and steady disease progression. For patients with non-functioning stable/slow progressing well-differentiated GEP-NETs and unresectable, locally advanced/metastatic disease (sub-population 2), the prevalence of non-functioning NETs was retrieved from the European Society for Medical Oncology clinical practice guidelines on GEP-NETs [1], which estimated that 70% of tumours are non-functioning. It is to be noted that the prevalence of non-functioning NETs was also available in the study by van der Zwan et al. [10].

However, the authors mentioned that prognostic information regarding the neoplasms of the digestive tract was missing in the majority of pathological reports. As a result, major concerns can be raised regarding the completeness of prognostic parameter evaluation, which includes depth of invasion and tumor size. Because of this information bias, one can assume that the prevalence of more specific sub-populations, such as those corresponding to patients with functioning tumors, may have been under-estimated in the van der Zwan et al. study, as evidenced by a lower number of cases than estimates found in other studies. Finally, for the present study, the disease definition of the sub-populations of interest excluded patients with tumours originating from the hindgut region (NETs of the colon and rectum), which represent between 22.4% and 30% of the total GEP-NETs according to Niederle et al. [3] and Lepage et al. [11], respectively.

Five-year population growth

The mortality rate for prevalent cases in the sub-populations of interest, which was required to estimate the population growth over five years, could not be found in the literature. Rather, it was derived from the survival rates that were provided in the Yao et al. [4], in which it was estimated that the 10-year survival of patients with well-differentiated NETs with distant metastasis is 17%. From this study, it can be observed that the survival rate is not distributed uniformly and linearly over the 10-year period. However, based on the difference in mortality rate between year n and n+1, it can be noticed that, over time, this rate reaches a plateau at year 7, corresponding to a mortality rate of approximately 3% (Table 3).

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival Probability</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>0.7</td>
<td>0.70–0.57=0.13 (Mortality rate between Y1 and Y2)</td>
</tr>
<tr>
<td>Y2</td>
<td>0.57</td>
<td>0.57–0.48=0.09 (Mortality rate between Y2 and Y3)</td>
</tr>
<tr>
<td>Y3</td>
<td>0.48</td>
<td>0.48–0.40=0.08 (Mortality rate between Y3 and Y4)</td>
</tr>
<tr>
<td>Y4</td>
<td>0.4</td>
<td>0.40–0.35=0.05 (Mortality rate between Y4 and Y5)</td>
</tr>
<tr>
<td>Y5</td>
<td>0.35</td>
<td>0.35–0.29=0.06 (Mortality rate between Y5 and Y6)</td>
</tr>
<tr>
<td>Y6</td>
<td>0.29</td>
<td>0.29–0.25=0.04 (Mortality rate between Y7 and Y8)</td>
</tr>
<tr>
<td>Y7</td>
<td>0.25</td>
<td>0.25–0.22=0.03 (Mortality rate between Y7 and Y8)</td>
</tr>
<tr>
<td>Y8</td>
<td>0.22</td>
<td>0.22–0.19=0.03 (Mortality rate between Y8 and Y9)</td>
</tr>
<tr>
<td>Y9</td>
<td>0.19</td>
<td>0.19–0.17=0.02 (Mortality rate between Y9 and Y10)</td>
</tr>
<tr>
<td>Y10</td>
<td>0.17</td>
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</tr>
</tbody>
</table>

Table 3: Derived mortality rates over a 10-year horizon for patients with well-differentiated gastroenteropancreatic tumours with distant metastasis.

Five-year population growth

The mortality rate for prevalent cases in the sub-populations of interest, which was required to estimate the population growth over five years, could not be found in the literature. Rather, it was derived from the survival rates that were provided in the Yao et al. [4], in which it was estimated that the 10-year survival of patients with well-differentiated NETs with distant metastasis is 17%. From this study, it can be observed that the survival rate is not distributed uniformly and linearly over the 10-year period. However, based on the difference in mortality rate between year n and n+1, it can be noticed that, over time, this rate reaches a plateau at year 7, corresponding to a mortality rate of approximately 3% (Table 3).

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival probability for well- and moderately differentiated distant NET 1,2</th>
<th>Mortality rate per year (1-year probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Y2</td>
<td>0.57</td>
<td>0.43</td>
</tr>
<tr>
<td>Y3</td>
<td>0.48</td>
<td>0.52</td>
</tr>
<tr>
<td>Y4</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Y5</td>
<td>0.35</td>
<td>0.65</td>
</tr>
</tbody>
</table>

1NET: Neuroendocrine Tumour; 2As reported in Yao et al. [4]

Table 4: Derivation of 1-year survival probabilities for well and moderately-differentiated distant neuroendocrine tumours used in the five-year population growth model.
We can thus assume that the annual mortality rate of baseline prevalent cases of metastatic well-differentiated NETs is on average 3%. Distinct annual survival probabilities of incident cases over the five-year period were subsequently derived by applying the 3% mortality rate associated with the baseline cases to incident cases that occurred during the follow-up period (Table 4).

For patients with stable/slow progressing functioning and non-functioning well-differentiated GEP-NETs and unresectable, locally advanced/metastatic disease (sub-population 1), the predicted number of patients is expected to increase from 7,473 to 9,393 in the five-year span in selected European countries (France, Italy, Ireland, Poland, Portugal, Spain, United Kingdom); from 8,051 to 10,119 in the US, and from 593 to 746 in Australia. For patients with stable/slow progressing well-differentiated, non-functioning GEP-NETs and unresectable locally advanced/metastatic disease (sub-population 2), the predicted total number of patients in the selected European countries is expected to increase from 5,231 to 6,575 in the five-year span; from 5,636 to 7,083 in the US and from 415 to 522 in Australia (Figures 3-5).

Results from this model yielded, for example, an expected increase in the predicted number of patients of sub-population 2 from 4,179 to 6,139 for the selected European countries. It should be emphasized that, because the second sub-population of interest is a subgroup of the first, lower estimates were obtained.

Discussion

Evidence on the real-world value of new treatments largely relies on assessing burden of illness and estimating the size of the target population at the country or region level. We developed a method that is based on a combination of epidemiologic data published in the literature, mathematical modelling, and clinical expert judgment to estimate the number of patients with advanced GEP-NETs over a five-year horizon overall, and for various sub-populations.

In the estimates presented, some assumptions were made due to the scarcity of data published in the literature. Indeed, the target population sizing model aimed to integrate, whenever possible, country-specific information. However, due to the paucity of published epidemiologic data on patients with GEP-NETs, it was not always feasible. Consequently, for all countries, the incidence rate of gastrointestinal, pancreatic, well-differentiated NETs consisted of EU estimates. Survival rates were derived from US data published by Yao et al. [4]. In addition, we could not identify survival probabilities for unresectable tumours only. As patients with unresectable or metastatic tumours are most likely to have a lower survival rate, the population estimates may have been slightly over-estimated. In addition, the model did not take into consideration the annual population growth in each region/country of interest, which may slightly under-estimate the number of incident cases over the years. However, given the slow population growth and the low prevalence of GEP-NETs in all countries of interest for this study, this under-estimation is expected to be negligible.

It is to be noted that the same calculation strategy was used for both sub-populations. For patients with non-functioning stable/slow...
progressing well-differentiated GEP-NETs and unresectable, locally advanced/metastatic disease (sub-population 2), a prevalence of 70% corresponding to non-functioning tumours was applied to the calculations. We assumed that the survival rate of the prevalent cases was similar between functioning and non-functioning tumours, because in the Yao et al. study [4], there is no distinction between the survival rates of these two types of tumours. However, since patients with functioning tumours usually have a higher mortality rate than patients with non-functioning tumours, using the same mortality rate for both tumours may have underestimated the target population size of sub-population 2. However, since the annual mortality rate for all the tumours (functioning and non-functioning) is relatively low (3%), this under-estimation may be negligible.

Finally, the majority of studies that were retained for the calculations were conducted prior to the latest WHO classification of NETs, which highlights the challenges in elucidating specific epidemiologic data on the sub-populations of interest. In this context, additional observational studies are required to assess the burden of illness of GEP-NETs, particularly for the smaller sub-populations, for which the social and economic burdens persist despite the therapeutic and diagnostic advances observed in recent years. Since large-scale population-based studies on GEP-NETs are difficult to implement due to the rarity of this disease, adopting a model-based approach to estimate the target population size can be an alternative.

**Conclusion**

In the absence of published epidemiologic data on specific GEP-NET sub-populations, the population growth modelling strategy that was developed in this study can be used to estimate trends in size of sub-populations that correspond to varying labelling hypotheses, such as the two sub-populations presented in this study. In addition to highlighting trends in the burden of disease in specific sub-populations, estimates obtained in this study lead to a better understanding of the population health impact of this disease. As new epidemiological data on these specific sub-populations are generated, the model will be updated and adjusted accordingly.

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**Conflict of Interest Disclosures**

Aurore Bergamasco (AB), Anne-Marie Castilloux (AMC) and Yola Moride (YM) are affiliated with YOLARX Consultants, which received a grant from IPSEN Pharma to conduct this study. Gabrielle Nayroles (GN), Jerome Dinet (JD), Anthony Berthon (AnB), Sylvie Gabriel (SG) are employees of IPSEN Pharma.

**References**