Unique Metastatic Patterns in Neuroendocrine Neoplasms of Different Primary Origin

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Keywords
Stage IV · Metastases · Gastroenteropancreatic neuroendocrine tumors · Lung · Survival · Brain · Carcinoid

Abstract
Introduction: Neuroendocrine neoplasms (NEN) can originate in different organs, for example, the gastroenteral tract (GE), pancreas (Pan), or lungs (L). Our aim was to examine metastatic patterns for patients with NEN of various primary origins with a special focus on brain metastases to indicate utility for screening. Methods: All NEN patients except for small cell lung cancer registered in the Netherlands Cancer Registry from 2008 to 2018 were selected. Metastatic patterns at initial diagnosis for NEN with different primary origins were compared. In a subcohort of patients from 2 referral hospitals (2014–2019), additional information on, for example, development of metastases after initial presentation was available. Results: In the nationwide cohort, 4,768/11,120 (43%) patients had metastatic disease at diagnosis (GE: 1,504/4,710 [32%]; Pan: 489/1,150 [43%]; and L: 1,230/2,978 [41%]). For GE- and Pan-NEN, the most prevalent metastatic site was the liver (25 and 39%), followed by distant lymph nodes (8 and 8%), whereas only few patients with brain metastases were identified (0% in both). In contrast, for L-NEN, prevalence of metastases in the liver (19%), brain (9%), lung (7%), and bone (14%) was more equal. In the reference network cohort, slightly more NEN patients had metastatic disease (260/539, 48%) and similar metastatic patterns were observed. Conclusion: Almost half of NEN patients were diagnosed with synchronous metastatic disease. L-NEN have a unique metastatic pattern compared to GE- and Pan-NEN. Remarkably, an important part of L-NEN metastases was in the brain, whereas brain metastases were almost absent in GE- and Pan-NEN, indicating utility of screening in L-NEN.

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Introduction

Neuroendocrine neoplasms (NEN) constitute a heterogeneous group of neoplasms with a histopathological neuroendocrine appearance as their typical hallmark. NEN can originate in different anatomical locations, for example, the gastroenteral tract, pancreas, and lungs [1–3]. NEN are subdivided in low/intermediate-grade neuroendocrine tumors (NET) and high-grade neuroendocrine carcinomas (NEC) [1–3]. In general, NEC have an aggressive behavior, whereas the course of NET might be more indolent with higher survival rates [1–3].

Metastases are found in up to 50% of all NEN patients with the liver as the most frequent metastatic site (up to 85% of all metastases) [4–11]. So far, metastatic patterns in NET from different primary organs have only been extensively described by Riihimaki et al. [11] in 7,334 patients. They found the liver as the most prominent site in gastroenteral and pancreatic NET (20 and 54% of all patients at diagnosis), with other metastases (e.g., lung and bone) at a maximum of 10%. In contrast, incidence of liver metastases at diagnosis in lung NET patients was only 10%, whereas lung (e.g., contralateral lesion), bone, and nervous system metastases also constituted an important part in this subgroup [11]. An important limitation of this study is the lack of data on tumor grade. Furthermore, NEC have been excluded from this analysis [11].

Only limited data considering the clinical relevance of brain metastases in NEN are available [12]. In the majority of patients, dissemination of the tumor is investigated by a $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) or somatostatin receptor targeting scan (e.g., $^{68}$Ga-DOTATATE-PET, $^{68}$Ga-DOTATOC-PET, or $^{111}$In-pentetreotide scintigraphy). FDG-PET is insensitive for the detection of brain metastases, because of high physiological brain glucose metabolism. Somatostatin receptor targeting scans might be able to show brain lesions; however, differentiation between meningioma and metastases can be difficult [13]. In the most common NEC, small cell lung carcinoma (SCLC), brain metastases are frequently present, and therefore, patients eligible for curative therapy are screened for asymptomatic brain metastases with magnetic resonance imaging (MRI) or computed tomography (CT) scans [14, 15]. For small cell NEC of other primary origins and for large cell NEC or low/intermediate-grade NET, guidelines do not advice on brain metastases screening. However, brain metastases have been described for NEN apart from SCLC and presence of (a)symptomatic brain metastases might influence prognosis and therapeutic choices [10–12, 15].

Most medical oncologists and endocrinologists treat patients with NEN from various primary origins and different grades. This could result in suboptimal treatment plans for less prevalent NEN (e.g., low-grade pulmonary NET), since the use of clinical experience with more prevalent NEN (e.g., low-grade gastroenteral NET) might be unjustified because of different clinical, histopathological, or molecular characteristics. Therefore, insight in similarities and differences between various NEN will contribute to optimal treatment to every unique patient. In this study, we describe metastatic patterns in patients with NEN of various primary origins and tumor grade and investigate the effect of primary origin and metastatic sites on overall survival. Furthermore, we particularly focus on the incidence of brain metastases to indicate utility of cerebral screening in different types of NEN.

Methods

Cohort National Cancer Registry

Patient Selection

The first cohort of this study was selected from the Netherlands Cancer Registry (NCR). Specialized data managers collected patient data for this database with a nationwide coverage of >95% [16, 17]. A yearly linkage to the Centralized Civil Registry ensures up-to-date data on overall survival. In this cohort, all patients diagnosed with NEN (except SCLC) in the Netherlands between January 1, 2008, and December 31, 2018, were selected including similar morphology codes (International Classification of Diseases for Oncology) as described by Korse et al. [17]. Patients with another malignancy before or concurrent with the NEN diagnosis were excluded, since in these cases the registered metastases could also originate from the other primary malignancy (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513249). Anonymous data on patient characteristics (gender and age), primary tumor characteristics (primary origin and grade), metastatic status at diagnosis (including metastatic sites), and survival data were available. Patients were excluded if topography of metastatic sites was not available.

Subgroup Formation

For analysis of the primary tumor, 5 subgroups were created: (1) gastroenteral (GE), including esophagus, stomach, duodenum, jejunum, ileum, appendix, colon, and rectum; (2) pancreas (Pan); (3) lung (L); (4) other (O), including amongst others Merkel cell carcinoma (MCC), mesenteric tumors, thymus NEN, and NEN from the urogenital system; and (5) unknown (U). Three groups were created for tumor grade: (1) grade 1 (G1, including pulmonary typical carcinoid), (2) grade 2 (G2, including pulmonary atypical carcinoid), and (3) grade 3 (G3, including pulmonary large cell neuroendocrine carcinoma (LCNEC) and both grade 3 NET and NEC for GEP-NEN). Metastatic sites were categorized as follows: (1) liver metastases, (2) brain metastases, (3) lung metastases, (4) bone metastases, (5) distant lymph node metastases, (6) peritoneal metastases, and (7) other metastases (including metastases of pleura, skin, soft tissue, and adrenal glands).
Presentation of Data and Statistical Analysis
All statistical analyses were performed with IBM SPSS Statistics, version 25 for Windows (IBM Corp., Armonk, NY, USA). Metastatic patterns at diagnosis are presented for the different primary tumors, with a subdivision for tumor grade. Median overall survival (OS) was evaluated by Kaplan-Meier analysis for the total group of metastatic patients and for metastatic G1, G2, and G3 patients separately. Differences in OS, indicating prognostic factors, were tested for significance with the log-rank test and presented as hazard ratios (HR) with 95% confidence interval (95% CI). Investigated variables were gender (male and female), age (≤65 and >65), primary tumor (GE, Pan, L, O, and U), tumor grade (grades 1, 2, and 3), number of organs with metastases (1, 2-3, and ≥4), and liver, brain, lung, bone, and distant lymph node metastases (yes and no). Variables with a $p$ value of <0.10 in univariable analysis were selected for multivariable Cox regression analysis. Variables with a $p$ value of >0.10 were only included in multivariable analysis if they were regarded highly clinical relevant (i.e., metastatic sites). Interaction was tested between different metastatic sites included in the multivariable model. Interaction terms were included in the multivariable model if Omnibus Tests of Model Coefficients showed a difference between −2 log likelihoods of the models ($p < 0.05$). To prevent overfitting, we adopted an event per variable ratio of ≥10. The results of the full multivariable model are presented, and a $p$ value of <0.05 is regarded statistically significant.

Cohort Reference Network
For the second cohort of this study, all patients diagnosed and/or treated with a NEN (except for SCLC) between January 1, 2014, and December 31, 2019, in 2 NEN referral centers in the Netherlands (Maastricht University Medical Center and Maxima Medical Center) were selected. Most of the patients in this cohort were also included in the nationwide cohort, but this subcohort could provide us with more in-depth information, for example, imaging used for diagnostic workup and development of metastases in patients with local disease at diagnosis. Patients with unclear metastatic sta-
tus at diagnosis or who objected against use of their data for medical research were excluded (online suppl. Fig. 1). Data on patient and tumor characteristics, staging procedures, treatment, survival, and follow-up were retrieved from medical records. Subgroup formation was performed as described for the nationwide cohort. Metastatic disease was in general evaluated with CT-thorax/upper abdomen for all lung NEN and CT-thorax/abdomen for GEP-NEN, with a simultaneous or additional FDG-PET and/or somatostatin receptor targeting scan, if necessary [18–21]. For NEN of other primary origins, workup depends on the primary tumor. Metastatic patterns at initial presentation are presented for different primary tumor sites, with a subdivision for tumor grade. Furthermore, for patients without metastases at diagnosis, metastatic patterns during follow-up are presented for the different primary origins. The medical ethical review committee of Maastricht University Medical Center+ assessed this study as not being subject to the Medical Research Involving Human Subjects Act (WMO), and the study was approved by the board of directors of Maastricht University Medical Center+ (METC 2018-0911, January 24, 2019).

Results

Cohort National Cancer Registry
Study Population and Metastases
Between 2008 and 2018, 14,443 NEN patients were registered by the Netherlands Cancer Registry. A total of 3,318 patients were excluded because of a former or concurrent second malignancy, and 5 patients were excluded since no information on topography of metastases was available (online suppl. Fig. 1). Out of 11,120 included patients, 4,768 (43%) had metastatic disease at initial presentation. The number of patients in each subgroup and patient characteristics can be found in Figure 1 and Table 1. In GE- and Pan-NEN, most patients presented with grade 1 disease (69 and 46%), but L-NEN, O-NEN, and U-NEN presented most often with grade 3 disease (59, 82, and 65%) (Fig. 1; online suppl. Table 1).

Metastatic Patterns at Diagnosis
The liver was the most frequent site of metastatic disease in GE-NEN (1,158/4,710, 25%), whereas lung and bone metastases were rare (Fig. 2; online suppl. Table 1). The same pattern was seen in Pan-NEN with liver metastases in 447/1,150 (39%) of new cases. Brain metastases were observed in 7/4,710 (0.1%) GE-NEN and 4/1,150 (0.3%) Pan-NEN. The liver was also the most prevalent metastatic site in L-NEN (568/2,978, 19%), but brain, lung, and bone metastases were also present in a substantial number of patients (9, 7, and 14%, respectively). In O-NEN, liver, bone, and lymph node metastases were

Table 1. Patient characteristics of all patients with neuroendocrine neoplasms and for subgroups of different primary origins

| All, n (%) | GE, n (%) | Pancreas, n (%) | Lung, n (%) | Other, n (%) | Unknown, n (%) |
|-----------|-----------|-----------------|------------|-------------|---------------|
| N 11,120  | 4,710     | 1,150           | 2,978      | 1,075       | 1,207         |
| Gender    |           |                 |            |             |               |
| Male 5,588 (50) | 2,356 (50) | 594 (52)        | 1,442 (48) | 580 (54)    | 616 (51)      |
| Female 5,532 (50) | 2,354 (50) | 556 (48)        | 1,536 (52) | 495 (46)    | 591 (49)      |
| Age ≤65 6,354 (57) | 2,984 (63) | 732 (64)        | 1,640 (55) | 515 (48)    | 483 (40)      |
| >65 4,766 (43) | 1,726 (37) | 418 (36)        | 1,338 (45) | 560 (52)    | 724 (60)      |

Cohort reference network

| N | 539 | 219 | 96 | 103 | 80 | 41 |
|---|-----|-----|----|-----|----|----|
| Gender |     |     |    |     |    |    |
| Male 276 (51) | 108 (49) | 49 (51) | 48 (47) | 45 (56) | 26 (63) |
| Female 263 (49) | 111 (51) | 47 (49) | 55 (53) | 35 (44) | 15 (37) |
| Age ≤65 277 (51) | 124 (57) | 52 (54) | 55 (53) | 30 (38) | 16 (39) |
| >65 262 (49) | 95 (43) | 44 (46) | 48 (47) | 50 (63) | 25 (61) |
| WHO PS 0–1 408 (76) | 173 (79) | 76 (79) | 77 (75) | 54 (68) | 28 (68) |
| ≥2 22 (4) | 4 (2) | 1 (1) | 5 (5) | 4 (5) | 8 (20) |
| Unknown 109 (20) | 42 (19) | 19 (20) | 21 (20) | 22 (28) | 5 (12) |

GE, gastroenteral; WHO PS, World Health Organization Performance Score.
Fig. 2. Metastatic patterns in neuroendocrine neoplasms of different primary origins in the cohort national cancer registry. Percentage of patients with liver, brain, lung, bone, distant lymph node, peritoneal cavity, and other metastases at diagnosis is presented, in relation to the total group of patients (both metastatic and nonmetastatic). Percentages can add up above the total percentage of metastatic patients, since the majority of patients have metastases in multiple organs. a Gastroenteral neuroendocrine neoplasms (N = 4,710), b Pancreatic neuroendocrine neoplasms (N = 1,150), c Pulmonary neuroendocrine neoplasms (N = 2,978).
most frequent (15, 13, and 13%, respectively). The majority of U-NEN presented with liver metastases (66%), followed by lymph node metastases (39%) (Fig. 2; online suppl. Table 1).

Overall Survival

In nonmetastatic patients, median OS was not reached for all grades together, G1 and G2. The median OS in nonmetastatic G3 was 22.8 months (95% CI: 20.7–24.9 months). Metastatic patients of all grades had a median OS of 8.3 months (95% CI: 7.7–8.8 months). Poor prognostic factors in univariable analysis of metastatic patients were male sex, age >65 years, Pan-NEN, L-NEN, O-NEN, or U-NEN as primary tumor (compared with GE-NEN), higher tumor grade, higher number of organs with metastases, and metastases in the brain, lung, bone, and lymph nodes. In multivariable analysis, age >65 years, L-NEN, O-NEN, or U-NEN as primary tumor, higher tumor grade, higher number of organs with metastases, and liver, brain, lung, and bone metastases were poor prognostic factors, whereas presence of lymph node metastases was a good prognostic factor (online suppl. Table 2).

Metastatic G1 patients had a median OS of 67.4 months (95% CI: 61.3–73.4 months). In multivariable analysis, male sex, age >65 years, Pan-NEN, L-NEN, or U-NEN as primary tumor (compared with GE-NEN), and liver and brain metastases were poor prognostic factors, whereas pulmonary metastases was a good prognostic factor (online suppl. Table 3). Metastatic G2 patients had a median OS of 38.3 months (95% CI: 32.8–43.7 months). Multivariable analysis revealed age >65 years, Pan-NEN, L-NEN, or U-NEN as primary tumor (compared with GE-NEN), and brain, lung, and lymph nodes metastases as poor prognostic factors (online suppl. Table 4). Metastatic G3 patients had a median OS of 3.9 months (95% CI: 3.6–4.2 months), and in multivariable analysis, age >65 years, L-NEN and U-NEN (compared with GE-NEN), ≥2 organs with metastases, and liver metastases were poor prognostic factors. In contrast, Pan-NEN and presence of lymph node metastases were good prognostic factors (online suppl. Table 5).

**Cohort Reference Network**

**Development of Metastatic Patterns**

A total of 539 patients were included in the cohort of the reference network, of which 260 (48%) had metastatic disease at initial presentation (Fig. 1; Table 1; online suppl. Fig. 1). Metastatic patterns were comparable to the patterns in the nationwide cohort (online suppl. Table 6). Patterns of developing metastases were quite similar to patterns seen at diagnosis, but distant lymph node metastases were slightly more frequent than liver metastases (12 and 9% of all nonmetastatic patients at diagnosis) (online suppl. Table 7).

**Brain Metastases**

Brain metastases were found at initial presentation in 16/103 (16%) L-NEN patients and in 1/41 (2%) patient with U-NEN, but not in patients with GE-NEN, Pan-NEN, or O-NEN. Although the absolute number of brain metastases was most frequent in G3 L-NEN (i.e., LCNEC, 12/54 [22%]), relative incidence of brain metastases in this cohort was roughly the same for G2 (i.e., atypical car-

![Fig. 3. Cumulative incidence of brain metastases in large cell neuroendocrine carcinoma of the lung in patients with metastatic disease at diagnosis and nonmetastatic disease at diagnosis (cohort reference network).](image)
Table 2. Overview of the current literature on incidences of liver, brain, lung, bone, lymph node, peritoneal, and other metastases at diagnosis in gastroenteral, pancreatic, and lung neuroendocrine neoplasms

| Primary tumor type | Metastases | Gastroenteral | Pancreas | Lung |
|--------------------|------------|---------------|----------|------|
|                    | N          | liver, n (%)  | brain, n (%) | lung, n (%) | bone, n (%) | lymph node, n (%) | peritoneal, n (%) | other, n (%) |
| GE-NET             | 5,581      | 1,125 (20)    | 37 (1)    | 95 (2)   | 149 (3)   | –               | –               | 564 (10) |
| GE-NEN             | 14,685     | 1,459 (10)    | 27 (0)    | 144 (1)  | 115 (1)   | –               | –               | –       |
| GE-NET             | 270        | 114 (42)      | 0 (0)     | 1 (0)    | 1 (0)     | 101 (37)        | 36 (13)         | –       |
| SI-NEN             | 277        | 52 (19)       | 1 (0)     | 1 (0)    | 3 (1)     | –               | –               | 13 (5)  |
| GE-NEN             | 3,413      | –             | –         | –         | –         | 213 (6)         | –               | –       |
| Pan-NET            | 275        | 148 (54)      | 3 (1)     | 12 (4)   | 28 (10)   | –               | –               | 44 (16) |
| Pan-NEN            | 3,909      | 1,133 (29)    | 5 (0)     | 28 (1)   | 21 (6)    | –               | –               | –       |
| Pan-NET            | 116        | 74 (64)       | 1 (1)     | 4 (3)    | 2 (2)     | 44 (38)         | 5 (4)           | –       |
| Pan-NET            | 114        | 49 (33)       | –         | –        | –         | –               | –               | –       |
| Pan-NEN            | 701        | –             | –         | –         | –         | 21 (3)          | –               | –       |
| L-NET              | 1,113      | 116 (10)      | 54 (5)    | 43 (4)   | 74 (7)    | –               | –               | 86 (8)  |
| LCNEC              | 1,681      | 323 (19)      | 322 (19)  | 188 (11) | 294 (17)  | –               | –               | –       |
| LCNEC              | 383        | 47%          | 23%       | 14%      | 32%       | 16%            | –               | –       |

GE, gastroenteral; NET, neuroendocrine tumor; NEN, neuroendocrine neoplasm; SI, small intestine; Pan, pancreas; L, lung; LCNEC, large cell neuroendocrine carcinoma (pulmonary). 1 Total nervous system included. 2 Including metastases of the pleura/mediastinum, “other” intra-abdominal (=non-liver) metastases, and “other” metastases in general. 3 Remarkably high number of grade I tumors (7,387/10,107 with known grade [73%]) and low number of grade III/IV tumors (1,108/10,107 [11%]), reason unknown. 4 Might also include nondistant lymph nodes. 5 Partly overlapping with our nationwide cohort. 6 Liver, gall, and pancreatic neuroendocrine tumors included. 7 198 patients (5%) had multiple metastases. Those are not included in numbers of liver, brain, bone, and lung metastases. 8 Exact numbers not available.

cinoid, 2/12 [17%]). Imaging of the brain with MRI-cere-

Discussion

A large nationwide retrospective cohort study has

been performed in which metastatic patterns of NEN of

various primary origins were investigated, and additional

information on temporal evolution of metastatic spread

and diagnostic workup was available for a subcohort of

patients from 2 referral centers. Almost half of the 11,120

NEN patients presented with metastases at diagnosis. In

GE- and Pan-NEN, the liver was the most prevalent met-

astatic site at diagnosis, whereas in L-NEN, incidence of

liver, brain, bone, and lung metastases at time of diagno-

sis was more equal. Remarkably, brain metastases were

almost exclusively found in L-NEN.

Besides our data, the presence of metastases at diagnosis

in up to 50% of NEN patients was also found in other series

[4–10]. These studies are in contrast with the study of Rii-

himaki et al. [11], reporting only 23% of patients presenting
with metastases at diagnosis. However, in the latter study, only NET were included whereas large cell and small cell NEC were excluded, and moreover, distant lymph node metastases and ill-defined or unspecific metastatic sites were not reported [11]. An overview of studies reporting on incidence of metastases in GE-, P-, and L-NEN is provided in Table 2 [7, 9–11, 22–26]. In general, the metastatic patterns we found were comparable to the previous literature. However, to the best of our knowledge, we are the first to include grade 1–3 GE-, P-, and L-NEN in one study, herewith providing data for a reliable comparison between the different primary origins. Differences in reported metastatic patterns between studies might be explained by inclusion of solely NET patients (i.e., excluding NEC patients) in some of the studies and diverse definitions used for "distant" lymph node metastases or "other" metastases.

Even without routine active screening, brain metastases were found in 14% of all pulmonary LCNEC patients and in 24% of patients with stage IV disease in the nationwide cohort. This is in line with previous studies reporting on incidence of brain metastases [9, 23]. Furthermore, in the cohort of the reference network, 1 out of 4 patients with stage IV pulmonary LCNEC without brain metastases at diagnosis developed brain metastases during follow-up, resulting in a cumulative incidence of 51% in stage IV LCNEC. In our study, only 5% (1/19) of non-stage IV LCNEC patients developed brain metastases during follow-up, whereas Zhao et al. [27] found that 35% (18/52) of LCNEC patients treated with curative intent developed brain metastases during follow-up, most of them within 2 years after diagnosis. The low percentage of development of brain metastases we found in nonmetastatic LCNEC at diagnosis might be due to the short follow-up time. Therefore, considering the substantial numbers of brain metastases found in pulmonary LCNEC, screening for brain metastases may be considered in these patients to improve treatment management. For patients initially diagnosed with stage I-III LCNEC, presence of asymptomatic brain metastases will result in palliative treatment instead of more aggressive treatment with curative intention. For LCNEC patients already diagnosed with metastases, presence of additional brain metastases might influence treatment management. No large sets of data are available on effectivity of systemic therapy for brain metastases in LCNEC. However, based on experience from NSCLC and the fact that some LCNEC can present with targetable mutations, it might be reasonable to perform mutational analysis in LCNEC patients and especially those with brain metastases and treat selected patients with new-generation TKIs instead of chemother-apy [28–32]. The prevalence of brain metastases in 3% of atypical carcinoids might be an underestimation since screening was not performed in this cohort. Therefore, the actual number of patients could even be higher, which might also justify screening in this NEN subgroup.

So far, only limited evidence about the prognosis of NEN of different primary origins and with specific patterns of metastatic spread has been reported. Improved survival has been observed in patients with liver metastases, compared to patients with brain, bone, or lung metastases in GE-NEN [26]. However, in our cohort presence of liver metastases was a poor prognostic factor. Unfavorable survival has been reported for NEN patients with bone metastases, as is confirmed by our data [5, 33, 34]. We found a lower survival in metastatic L-NEN, O-NEN, and U-NEN compared to GE primary origin, as was described for unknown primary origin by Riihimaki et al. [11]. On the other hand, based on our results, Pan-NEN was only a poor prognostic factor in G1 and G2, whereas it seems to be a good prognostic factor in G3 NEN. Taken together, both primary tumor origin and metastatic patterns appear to be inconsistent as prognostic indicators, and therefore, prognosis can better be predicted by robust factors as age, tumor grade, and number of organs with metastatic lesions.

Despite the fact that we could get inside in the temporal evolution of patterns of metastatic spread in NEN from different primary origins for patients in our reference network, the median follow-up time was limited (15 months). Therefore, only an indication of development of metastases during the first years after diagnosis could be provided, whereas especially for low- and intermediate-grade tumors, metastases might develop years after initial presentation. Another limitation of this study is the retrospective design. For the comprehensive large nationwide cohort, only limited variables are available and, for example, development of metastases during follow-up and WHO performance score are not registered in this database. In the cohort of our reference network, we could obtain most of the data from medical records for the last 5 years. However, the number of patients in the 2 centers was limited and some data were missing due to follow-up outside the referral centers. The slight differences between the 2 cohorts might be explained by the fact that patients of 2 NEN referral centers were included in the latter one, whereas a nonselected population was used for the nationwide cohort. Maybe patients with nonmetastatic G1 or G2 NEN are not consequently referred to one of our centers. The same might apply to patients with G3 NEC and a very poor prognosis.
In conclusion, our data show that nearly half of the patients with NEN present with metastatic disease at initial diagnosis. In GE- and Pan-NEN, liver metastases are most common, whereas in L-NEN, incidence of liver metastases is less frequent and incidence of brain, lung, and bone metastases is more equal. Interestingly, brain metastases are almost exclusively observed in L-NEN, and more than half of pulmonary LCNEC patients with metastases at diagnosis have brain metastases at initial presentation or develop brain metastases during follow-up. Therefore, screening for brain metastases might be considered in metastatic LCNEC and other L-NEN which may impact treatment management. Since brain metastases were very rare in GE-, P-, and O-NEN, screening does not seem useful in these subtypes.

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Statement of Ethics

The medical ethical review committee of Maastricht University Medical Center+ assessed this study as not being subject to the Medical Research Involving Human Subjects Act (WMO), and the study was approved by the board of directors of Maastricht University Medical Center+ (METC 2018-0911, January 24, 2019). This study was performed in accordance with the World Medical Association Declaration of Helsinki and the Dutch "Federa, Human Tissue and Medical Research: Code of conduct for responsible use (2011)" regulations not requiring patients’ informed consent.

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Conflict of Interest Statement

Drs. Hermans reports grants from Bristol Myers Squibb and nonfinancial support from AbbVie, outside the submitted work; Dr. de Vos-Geelen reports personal fees from AstraZeneca, personal fees from MSD, and grants and personal fees from Servier, outside the submitted work; Dr. Derks reports personal fees from BMS, Pfizer, Boehringer Ingelheim, Novartis, and Ipsen, outside the submitted work; Dr. Speel reports grants from Bristol Myers Squibb, AstraZeneca, Pfizer, Novartis, and MSD, personal fees from AbbVie and Roche, and nonfinancial support from AbbVie, outside the submitted work; Dr. Dingemans reports grants from Bristol Myers Squibb, personal fees from Roche, BMS, Eli Lily, Takeda, and Boehringer Ingelheim, and nonfinancial support from AbbVie, outside the submitted work. The other authors did not report conflicts of interest.

Author Contributions

Drs. Hermans: conceptualization, methodology, investigation, formal analysis, visualization, and writing – original draft. Drs. De Vos-Geelen: conceptualization, methodology, resources, formal analysis, and writing – review and editing. Dr. Derks: conceptualization, methodology, and writing – review and editing. Drs. Lat- ten: conceptualization, resources, and writing – review and editing. Drs. Lien: conceptualization and writing – review and editing. Dr. J.M. van der Zwan: methodology, resources, and writing – review and editing. Prof. Speel: conceptualization, methodology, and writing – review and editing. Dr. Dercks: conceptualization, methodology, resources, and writing – review and editing. Prof. Dingemans: conceptualization, methodology, resources, formal analysis, supervision, and writing – review and editing.
