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ORIGINAL ARTICLE

Healthcare cost by primary tumour, functioning status and treatment among patients with metastatic neuroendocrine tumours: The LyREMeNET study

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Abstract

The annual prevalence of metastatic neuroendocrine tumours (mNETs) is rising, leading to significant healthcare costs. The present study aimed to describe healthcare resource use (HRU) and the corresponding costs among patients with mNETs, according to primary tumour location, functioning status and type of treatments. The LyREMeNET study included consecutive mNET patients with a diagnosis performed between January 2010 and December 2017, who were seen at least once in the ENETS center of excellence in Lyon. The median HRU and costs per patient were estimated, up to 3 years before and after the diagnosis. The Cancer database of the center was linked to the French national health data system. HRU and related costs were described per person per month (PPPM). Among 316 patients presenting with a mNET, 48.4% had a small-intestinal mNET, 32.3% had a pancreatic mNET and 39.2% had carcinoid syndrome. The mean overall cost increased from €615 to €2875 PPPM between the years preceding and following the diagnosis, and remained above €2500 in the two subsequent years. The two main cost drivers of total healthcare expenditure were drugs (€1161) and hospital stay (€662). Median costs of mNETs arising from pancreas and small intestine were €2325 and €2540 PPPM, respectively. Costs were higher in patients with a functional mNET (€2807 PPPM for carcinoid syndrome) and during peptide receptor radionuclide therapy (PRRT) (€8835 PPPM). The highest overall cost was found during the first year following the diagnosis. Cost of care was higher for small intestine mNETs, for functional mNETs and during peptide receptor radionuclide therapy.

KEYWORDS
cost, healthcare resource, metastatic, neuroendocrine tumors

1 | INTRODUCTION

Neuroendocrine tumors (NETs) are rare and include a heterogeneous group of neoplasms derived from the gastrointestinal tract, the pancreas and the lung. The annual incidence of all NETs has been estimated to 6.98 per 100,000 person-years in 2012 and is steadily rising.[1] Approximately 40–50% of patients with NET present with distant metastases (m) at the time of diagnosis.[2] Current treatment options extend from locoregional (surgery, trans-arterial [chemo]-embolization, radiofrequency ablation) to

systemic therapies (somatostatin analogues [SSAs], cytotoxic chemotherapy, targeted therapies, and peptide receptor radionuclide therapy [PRRT]). The appropriate therapeutic decision making is challenging and depends on tumour grade, primary site, functional status, disease burden, growth rate, uptake on somatostatin receptor imaging and, finally, the patient's general condition.[2] Despite distant metastases, the 5-year survival rate varies from 28% to 69% depending on the NET primary site,[1] explaining an increasing prevalence of NETs and therefore a significant cost for NET care.

However, few previous studies have investigated healthcare resource use (HRU) and the associated costs among mNET patients.[3] Most data on costs for NET care come from the US Surveillance, Epidemiology and End Results (SEER)-Medicare databases,[4] but the US healthcare system is not always exhaustive and differs from European ones. Lesen et al.[5] recently reported cost-of-illness of gastroenteropancreatic (GEP) mNETs in Sweden, showing that drug prescription was the largest contributor to direct medical costs. In France, only one study, presented at the ENETS 2021 meeting (Perrier M, Mouawad C, Gueguen D, Bouille C, Laborey M, Lapeyre-Mestre M and Walter T, unpublished data), estimated the direct and indirect healthcare costs of NET patients with carcinoid syndrome, and showed that costs were highest during the first year in incident patients and the year preceding death. Cost-analysis was focused on carcinoid syndrome and used the French national health data system (*système national des données de santé*, SNDS), but it was not matched to a clinical database, leading to inclusion bias and a lack of characterization of tumours and treatments received. In addition, as a result of the usual delays between first symptoms and NET diagnosis (mean of 4 years in a recent international survey including French patients[6]), we hypothesized that the HRU/cost progressively increases within the 3 years prior the diagnosis.

Therefore, we aimed to assess the HRU and economic costs associated with the management of mNETs, according to primary tumour location, functioning status and along the four main systemic treatments.

2 | MATERIALS AND METHODS

2.1 | Study population

The Lyon Real-life Evidence in Metastatic NeuroEndocrine Tumors study (LyREMeNET, NCT03863106) included consecutive mNET patients seen at least once in the ENETS center of excellence in Lyon. Patients with mNETs were retrospectively selected from the neuroendocrine neoplasm (NEN) database. In January 2018, there were 857 patients in this database with a diagnosis of mNET, either synchronous or metachronous. The survival data of LyREMeNET have been reported previously.[7] Patients diagnosed with a mNET between 1 January 2010 and 31 December 2017 were included.

2.2 | Data sources

The Cancer database on NEN of the Lyon civil hospices (so called in French "*Hospices Civils de Lyon*", HCL) was linked to the French national health data system (SNDS) database that includes the national health insurance information system, *système national d'information interrégimes de l'Assurance Maladie* (SNIIRAM) and the *programme de médicalisation des systèmes d'information* (PMSI) for hospitalizations.

Clinical data at the time of the mNET diagnosis and during the follow-up were found in the NEN database of the HCL: patient cancer characteristics (tumour site, functioning status, genetic syndrome, localization of metastasis, World Health Organization [WHO] classification, etc.) and their care pathway (type and dates of medical and surgical therapies undergone, etc.).

Reimbursement and medical data related to in- and outpatient admissions (such as the diagnoses leading to an inpatient admission, procedures performed) were targeted in the SNDS database. Data related to consultations, procedures and pharmacological treatments provided in the ambulatory sector were also extracted thanks to this process. Illness benefits and general healthcare use such as transportations and full coverage for specific populations were available in the SNDS database.

SNDS data were linked to the Cancer database on NEN of the HCL using a probabilistic method. The following variables were used: month and year of birth, sex, place of residence, all dates of consultations and hospitalizations in the HCL with associated procedural codes, and, in addition for hospitalizations, the diagnoses (using the International Classification of Diseases, ICD-10) and the Diagnosis-Related-Group (DRG), the healthcare facility identify number (FINESS) and, if applicable, date of death.

2.3 | Economic statistics

We assessed the HRU with associated costs over all mNETs, and among subgroups by tumour site (NETs from the pancreas, the small intestine, the lung and from unknown/other primary location), functioning status (not functional, carcinoid syndrome, other functional syndrome), treatment types (SSA, cytotoxic chemotherapy, targeted therapies and PRRT) and tumour grade. We described the mean HRU with corresponding costs per patient, up to 3 years before and after the pathological diagnosis of mNETs. For the tumour site, grade and the functioning status, median HRU with corresponding costs were given from the diagnosis of mNETs up to 3 years. For the four treatment subgroups, the respective study period was between the first and last administration of each treatment; if the treatment was stop during more than 3 months, this was considered as another treatment line. Specifically, for PRRT (usually four injections, given every 8 weeks), the duration of PRRT treatment comprised from the first to the last injection followed by another 8 weeks, and this must have been performed within 1 year. The four treatments subgroups were assessed during the entire study period (January 2007 to December 2020, 3 years after the last included patient).

The following resources and costs of NET were described as direct medical drivers, direct non-medical drivers (transportations to and

from specialist outpatient care visits and inpatient admissions) and indirect drivers (compensation payment with daily illness benefits paid by the French health insurance fund among patients < 65 years of age and disability pension). Direct medical drivers included outpatient consultations, biology exams (biological samples taken on an outpatient basis), imaging (ultrasound, somatostatin-receptor scintigraphy, magnetic resonance imaging, endoscopy, etc.), paramedical care (nursing care, physiotherapist, etc.), drugs including reimbursements of those related to mNETs (SSA such as octreotide and lanreotide, α-interferon, everolimus, sunitinib, chemotherapies, PRRT, etc.) and hospital stay.

Data handling and analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). HRU and costs were respectively reported as median or mean of units and euros (€) per patient per month (PPPM).

3 | RESULTS

3.1 | Patients

In total, 857 patients with mNET were registered in the Cancer database on NEN of the HCL, and 408 had a mNET diagnosed between 1 January 2010 and 31 December 2017. Among them, 92 patients were not accurately matched in SNDS; thus, 316 patients were included in the present study.

Among the 316 patients, the median age was 63.6 years and 48.1% ($n = 152$) were women. The small intestine (jejunum and ileum) was the most frequent primary site ($n = 153$; 48.4%), followed by pancreas-duodenum ($n = 102$; 32.3%), then lung and thymus ($n = 35$; 11.1%); other locations were found in 26 (8.2%) patients. The mNETs were non-functioning in 52.5% ($n = 166$) of patients, a carcinoid syndrome was present in 39.2% ($n = 124$), and another hormonal release by duodeno-pancreatic mNET was reported in 8.2% ($n = 26$). Metastases were more often synchronous (73.4%; $n = 232$), mainly localized in the liver (83.5%, $n = 264$). Most mNETs were G1 or G2 ($n = 106$; 33.5% for G1 mNETs and $n = 175$; 55.4% for G2 mNETs). During the study period, 108 (34.2%) patients died. SSAs (75.9%, $n = 240$) and surgery of the primary NET (51.8%, $n = 163$) were the most frequent treatments among patients, followed by cytotoxic chemotherapy, targeted therapies, surgery of metastases, liver embolization or PRRT. Surgery of the primary NET was performed in 111 (72.5%) and 36 (35.3%) patients with small-intestine and pancreatic NET, respectively. Most patients with small-intestine NET received SSAs ($n = 143$; 93.5%), whereas most patients with pancreatic NET were treated with cytotoxic chemotherapy ($n = 73$; 71.6%) (Table 1).

3.2 | Cost according to pre- and post-periods of diagnosis in metastatic NET patients

Figure 1 describing the mean overall costs of care on an annual basis showed increasing costs during the 3 years preceding the diagnosis (€294 PPPM, €380 PPPM and €615 PPPM for years −3, −2 and −1 respectively). The highest mean overall cost was found during the first year following the diagnosis (€2875 PPPM), then it gradually slightly decreased annually but remaining above €2500 PPPM. The two main cost drivers of total healthcare expenditure during the first year were hospital stay (€1280 PPPM) and drugs (€974 PPPM), followed by compensation payments, transportations, imaging, paramedical care, outpatient consultations, laboratory tests and, finally, disability pension. This distribution of healthcare costs was globally observed in the 2 subsequent years, although the costs related to hospital stay decreased and drugs then exceeded those of hospitalizations.

3.3 | HRU and the associated costs according to primary tumour locations

Median total cost for mNETs care was €2448 PPPM and median total HRU was 12.2 units PPPM. These costs were €2325 for mNETs arising from the pancreas and €2540 PPPM when arising from the small intestine. The two main cost drivers of total healthcare expenditure were drugs (€1161 PPPM) and hospital stay (€662 PPPM). Among patients with pancreatic mNETs, the cost of hospital stay was higher than those of the drugs; this was the opposite in small intestine mNETs. Indeed, SSAs were more often used in small-intestine mNETs (Table 1) and given for a long-time period (Table 2), usually as monthly injections performed by nurses at home (higher HRU for paramedical care for small-intestine compared to pancreatic mNETs). By contrast, cost for transportations (often prescribed for hospital stay, especially for i.v. chemotherapy that is used more for pancreatic mNETs) was the highest in pancreatic and unknown/other primary mNETs (Table 3).

Among 153 patients with small-intestine mNETs, the 72.5% who underwent surgery for their primary tumour were associated with higher costs for imaging, hospital stay and drugs compared to patients without surgery. By contrast, the 36 of 102 (35.3%) patients who underwent pancreatic surgery were associated with lower costs for hospital stay and transportations (see Supporting information, Table S1).

3.4 | HRU and the associated costs according to functioning status

Median total cost of functional mNETs (€2807 PPPM for carcinoid syndrome and €2659 PPPM for other secretory syndromes) was higher than that of non-functional NETs (€2135 PPPM). Among patients with carcinoid syndrome, the main cost driver was drugs (€1588 PPPM), whereas median costs for hospitalizations or transportations were less (€689 and €55 PPPM, respectively). Patients with another secretory syndrome experienced higher costs of care for hospitalizations and transportations (€954 and €133 PPPM, respectively) (Table 4).

3.5 | HRU and the associated costs according to WHO classification

Higher HRU and costs were observed in patients with G3 NETs (€3739 PPPM vs. €2450 PPPM in G1–G2 patients). The main cost

TABLE 1 Patient characteristics and treatments received by patients during the study period

	Population (2010–2017) (*n* = 316)	Small intestine NETs (*n* = 153)	Pancreatic NETs (*n* = 102)
Median age in years (range)	63.6 (67.5)	63.7 (64.0)	62.3 (64.4)
Female, *n* (%)	152 (48.1)	77 (50.3)	47 (46.1)
Primary site, *n* (%)			
Small intestine (jejunum and ileum)	153 (48.4)	153 (100.0)	–
Pancreas and duodenum	102 (32.3)	–	102 (100.0)
Lung and thymus	35 (11.1)	–	–
Other	26 (8.2)	–	–
Functioning status, *n* (%)			
Non-functioning	166 (52.5)	43 (28.1)	102 (100.0)
Carcinoid syndrome	124 (39.2)	110 (71.9)	0 (0.0)
Other hormone release (duodeno-pancreatic)	26 (8.2)	0 (0.0)	0 (0.0)
Multiple endocrine neoplasia type 1, *n* (%)	5 (1.6)	0 (0.0)	3 (2.9)
Type of metastasis, *n* (%)			
Synchronous metastasis/locally advanced	232 (73.4)	132 (86.3)	61 (59.8)
Metachronous metastasis	79 (25.0)	20 (13.1)	39 (38.2)
Localization of metastases, *n* (%)			
Liver	264 (83.5)	128 (83.7)	91 (89.2)
Distant lymph nodes	111 (35.1)	51 (33.3)	38 (37.3)
Peritoneum	68 (21.5)	57 (37.3)	8 (7.8)
Bone	51 (16.1)	11 (7.2)	17 (16.7)
Lung	23 (7.3)	3 (2.0)	3 (2.9)
Brain	4 (1.3)	1 (0.7)	0 (0.0)
Other	30 (9.5)	16 (10.5)	8 (7.8)
WHO classification, *n* (%)			
NET G1 or typical carcinoid	106 (33.5)	74 (48.4)	17 (16.7)
NET G2 or atypical carcinoid	175 (55.4)	63 (41.2)	73 (71.6)
NET G3	19 (6.0)	2 (1.3)	11 (10.8)
Undefined NET or carcinoid	16 (5.1)	14 (9.2)	1 (1.0)
Death, *n* (%)	108 (34.2)	50 (32.7)	34 (33.3)
Systemic treatments during follow-up, *n* (%)			
Somatostatin analogue	237 (75.0)	143 (93.5)	57 (55.9)
Cytotoxic chemotherapy	118 (37.3)	15 (9.8)	73 (71.6)
Targeted therapies	77 (24.4)	26 (17.0)	34 (33.3)
Peptide receptor radionuclide therapy	25 (7.9)	11 (7.2)	11 (10.8)
Locoregional treatments during follow-up, *n* (%)			
Surgery of the primary	163 (51.8)	111 (72.5)	36 (35.3)
Surgery of metastases	67 (21.2)	35 (22.9)	16 (15.7)
Liver embolization	48 (15.2)	28 (18.3)	9 (8.8)
Radiologic ablation	12 (3.8)	5 (3.3)	4 (3.9)
Cardiac valve replacement for CHD	5 (1.6)	5 (3.3)	0 (0.0)
External radiotherapy	12 (3.8)	3 (2.0)	3 (2.9)

Abbreviations: CHD, carcinoid heart disease; G, grade; NET, neuroendocrine tumour; WHO, World Health Organization.

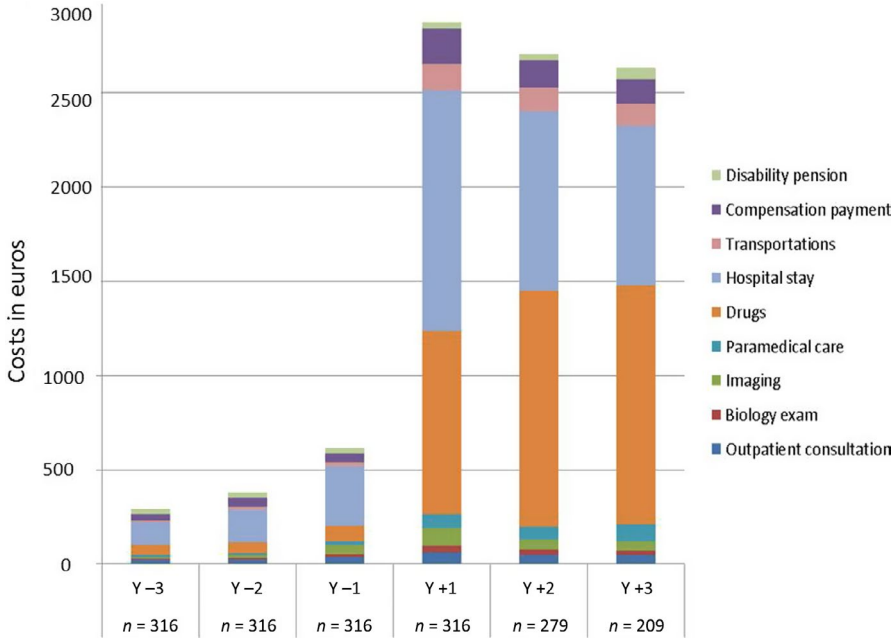

FIGURE 1 Mean costs in euros per person per month (PPPM) according to pre- and post-periods of diagnosis in patients with metastatic neuroendocrine tumours

TABLE 2 Healthcare resource use in units and costs in euros, per person per month, according to type of treatment received during the study period

Variables	SSA (*n* = 244)	Cytotoxic chemotherapy (*n* = 124)	Targeted therapies (*n* = 85)	PRRT (*n* = 46)
Median time in months of treatment period (range)	24.1 (90.5)	4.6 (18)	5.9 (39.9)	7.1 (13.3)
Median direct medical HRU (cost €)				
Outpatient consultation	1.2 (35)	1.1 (29)	1.9 (54)	1.3 (30)
Biology exam	1.1 (14)	2.8 (50)	2.5 (57)	2.7 (55)
Imaging	0.3 (30)	0.3 (27)	0.4 (35)	0.1 (8)
Paramedical care	2.2 (23)	2.8 (39)	1.5 (26)	2.3 (21)
Drugs	4.6 (1642)	6.7 (464)	5.7 (2960)	3.8 (256)
Hospital stay	0.2 (263)	1.4 (884)	0.4 (296)	0.5 (7443)
Median direct non-medical HRU (cost €)				
Transportations	0.5 (56)	2.4 (163)	0.9 (96)	1.5 (195)
Median indirect HRU (cost €)				
Compensation payment	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Disability pension	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Median total HRU (cost €)	11.7 (2316)	20.3 (2549)	15.4 (4380)	13.1 (8835)

Abbreviations: HRU, healthcare resource use; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.

driver was hospital stay in G3 NET patients (€1876 PPPM) (see Supporting information, Table S2).

3.6 | HRU and the associated costs according to treatment type received during the study period

Median time of treatment was longer in patients treated with SSAs (24.1 months) than in patients receiving PRRT, targeted therapies or cytotoxic chemotherapies (7.1 months, 5.9 months and 4.6 months, respectively). Overall, median total healthcare costs were highest especially in patients treated with PRRT (€8835 PPPM), followed by targeted therapies (€4380 PPPM), and then by cytotoxic chemotherapies (€2549 PPPM) and SSAs (€2316 PPPM). Among patients treated with PRRT or cytotoxic chemotherapies, the main cost driver was hospital stay (€7443 and €884 PPPM). By contrast, the main costs in patients receiving targeted therapies or SSAs were a result of drugs (€2960 and €1642 PPPM, respectively) because other items of expenditure were less expensive (e.g., hospitalizations, transportations or indirect costs). Transportations were higher among patients

TABLE 3 Healthcare resource use in units and costs in euros, per person per month, according to primary tumour location

Variables	Pancreas ($n = 102$)	Small intestine ($n = 153$)	Lung ($n = 35$)	Unknown/other ($n = 26$)	Total ($n = 316$)
Median direct medical HRU (cost €)					
Outpatient consultation	1.5 (49)	1.3 (40)	1.5 (46)	1.6 (52)	1.4 (45)
Biology exam	1.8 (34)	1.2 (17)	1.6 (23)	1.9 (32)	1.6 (24)
Imaging	0.5 (77)	0.4 (52)	0.6 (94)	0.5 (83)	0.5 (63)
Paramedical care	1.6 (23)	2.2 (24)	1.8 (31)	1.8 (32)	2.0 (24)
Drugs	4.7 (554)	4.4 (1481)	4.5 (859)	5 (775)	4.5 (1161)
Hospital stay	0.4 (761)	0.3 (661)	0.4 (503)	0.4 (619)	0.3 (662)
Median direct non-medical HRU (cost €)					
Transportations	0.8 (85)	0.5 (51)	0.8 (67)	0.9 (80)	0.6 (62)
Median indirect HRU (cost €)					
Compensation payment	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (2)	0.0 (0)
Disability pension	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Median total HRU (cost €)	12.5 (2325)	11.8 (2540)	12.7 (2275)	14.5 (2393)	12.2 (2448)

Abbreviations: HRU, healthcare resource use; PPPM, per person per month.

TABLE 4 Healthcare resource use in units and costs in euros, per person per month, according to functioning status

Variables	No functional ($n = 166$)	Carcinoid ($n = 124$)	Other ($n = 26$)	Total ($n = 316$)
Median direct medical HRU (cost €)				
Outpatient consultation	1.6 (49)	1.3 (41)	1.1 (43)	1.4 (45)
Biology exam	1.6 (28)	1.3 (20)	2.0 (42)	1.6 (24)
Imaging	0.5 (77)	0.4 (54)	0.4 (48)	0.5 (63)
Paramedical care	1.7 (23)	2.3 (27)	1.7 (28)	2.0 (24)
Drugs	4.5 (660)	4.6 (1588)	4.6 (969)	4.5 (1161)
Hospital stay	0.4 (536)	0.3 (689)	0.7 (954)	0.3 (662)
Median direct non-medical HRU (cost €)				
Transportations	0.6 (56)	0.6 (55)	1 (133)	0.6 (62)
Median indirect HRU (cost €)				
Compensation payment	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Disability pension	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Median total HRU (cost €)	12.0 (2135)	12.1 (2807)	12.7 (2659)	12.2 (2448)

Abbreviations: HRU, healthcare resource use; PPPM, per person per month.

receiving PRRT and cytotoxic chemotherapy for their mNET (€195 and €163 PPPM, respectively) (Table 2).

4 | DISCUSSION

There is a lack of data in the current literature about HRU and the associated costs for NET care because most of data come from the US healthcare system, which differs greatly from European ones.[3] The LyREMeNET study was the first to describe the general characteristics of patients with mNETs, as well as the average HRU and the corresponding costs for mNET management in France. The median total healthcare cost was €2448 PPPM for mNET care. The first year after diagnosis was the most expensive period, and the two main cost drivers were drugs and hospital stay. Finally, higher costs were observed in patients with a primary tumor arising from the small intestine, in patients with functional mNETs and in patients treated by PRRT or targeted therapies.

The economic burden of the first year following the diagnosis of NET has already been described in elderly NET patients.[4] The initial phase indeed induces costs for the diagnostic phase (imaging, laboratory tests, in- and outpatient consultations, production loss), the initial surgical management and also drug use (especially in patients with a secretory syndrome requiring SSAs or locoregional therapies).[8] A recent French study has also showed higher overall costs during the first year in incident patients presenting with a carcinoid

syndrome and during the year preceding death (Perrier M, Mouawad C, Gueguen D, Bouille C, Laborey M, Lapeyre-Mestre M and Walter T, unpublished data). Similar results were observed in our year-by-year cost analysis, showing progressively increasing mean overall costs before the diagnosis up to a maximum during the first year, and then a progressive decrease during mNET management, but remaining relatively high. Tight control of the disease course would appear to induce less healthcare expenditure by limiting the requirement of hospitalizations or additional investigations, in keeping with similar drug costs. In addition, the present results confirmed the hypothesis that the cost progressively start to rise within 3 years before the diagnosis. During this time, patients with a suspected NET underwent a complete battery of explorations (biology exams, imaging, endoscopy and biopsy). Some of these are performed during a day-care hospital stay. The increase in cost must also take into account that the separation between year −1 and year +1 was defined according to the histological diagnosis of mNET, although some patients may be already hospitalized for their management before obtaining the histopathological diagnosis by surgery or biopsy.

The two main cost drivers when managing patients with mNETs were drugs and hospital stay throughout the post-diagnostic period (75% of overall costs). This result is consistent with findings of Lesen et al,[5] showing that the largest proportion of total costs (77%) was because of direct medical costs, especially those as a result of drugs (54% of direct medical costs) in a population of metastatic GEP-NET patients. Interest may be also focused on indirect medical costs (compensation payments and disability pension), which are estimated to be around 7% of total healthcare costs.

Costs of care also varied by functional status among patients with mNETs. Patients presenting with a functional mNET (carcinoid syndrome or other secretory syndromes) had higher costs compared to patients without. Of note, even if the HRU did not differ with respect to the number of drugs, it differed with respect to type, and the cost was thus driven by expansive drugs in this population, such as SSAs. This finding is consistent with the recent study conducted by Shen et al.[9] using the SEER database, in which carcinoid syndrome was associated with higher costs of care during the first year after diagnosis compared to in patients without carcinoid syndrome. Furthermore, secretory syndromes of pancreatic origin (e.g., gastrinomas, insulinomas, or more rarely glucagonomas, VIPomas [i.e., tumour overproducing vasoactive intestinal peptide], somatostatinomas, etc.) were associated with similar median overall costs than for carcinoid syndrome. However, the distribution was different: patients with carcinoid syndrome receive SSAs on an outpatient basis (inducing less hospital stay and transportations), whereas functional pancreatic mNETs generally require more often systemic chemotherapy and therefore regular hospitalizations. Only one study has described the cost of carcinoid syndrome management in France using the SNDS (Perrier M, Mouawad C, Gueguen D, Bouille C, Laborey M, Lapeyre-Mestre M and Walter T, unpublished data). However, no specific ICD-10 code is available to describe NET and the SNDS was not linked with a national specific NET database, inducing a selection bias for the population and a lack of NET characterization.

In the present study, we also examined the cost of care for mNET patients by tumour site. The management of mNET patients of small intestine origin was the most expensive (€2540 PPPM), followed by those of unknown/other (€2393 PPPM) and pancreatic (€2325 PPPM) origin. This was not the case in a previous Sweden study showing higher costs in patients with pancreatic mNET compared to patients with small intestinal mNET.[5] Overall costs were mainly driven by drugs in patients with small intestinal mNETs (€1481 PPPM, 58%), especially because of a more prevalent and lifelong use of SSAs. In pancreatic mNETs, the overall costs were mainly related to hospitalizations (€761 PPPM, 33%) and drugs (€554 PPPM, 24%) in patients usually receiving cytotoxic chemotherapies (sometimes i.v. chemotherapies in a day care hospitalization unit) or targeted therapies. The cost of surgery, which is usually performed soon after diagnosis, was not precisely evaluated with this methodology. However, it does not appear to be a key driver of cost at metastatic stage: the cost for hospital stay was slightly higher in patients who underwent surgery for their small-intestinal NET, although it was clearly the opposite for patients who underwent surgery of their pancreatic NET, compared to patients without surgery of their primary tumour. In addition, the management of patients with G3 mNETs was more costly. This could be explained both by a rapidly deteriorated health status (requiring more hospital stays and transportation) and also because they are mainly treated by chemotherapy[2] often given at a day-care hospital unit.

To date, no studies have performed detailed analyses of HRU and costs by type of treatment received in patients with mNETs. Previous studies have only compared HRU and costs between octreotide and lanreotide among NET patients, showing that long-acting octreotide was associated with lower costs in USA (with a difference of approximately $3700 per month),[10] and especially in patients with metastatic GEP-NETs.[11] Our findings showed the highest costs and HRU in patients treated by PRRT (€8835 PPPM), mainly driven by hospital stay (€7443 PPPM, 84%). By contrast, costs associated with targeted therapies (€4380 PPPM) and SSAs (€2316 PPPM) were mainly related to drug prescription (68% and 71%, respectively); many patients receiving targeted therapy or SSAs were in fact outpatients with lower costs related to hospitalizations or transportations. In France, the current cost of a long-acting SSA injection is around €1300 per injection for the maximal dose of octreotide or lanreotide, usually given every 4 weeks, with an average treatment duration of 24 months; we therefore suspect that some patients required increased doses of SSA for its anti-secretory and/or anti-tumoral effects. This cost estimated PPPM has to be interpreted according to the duration of treatment and according to the median progression-free survival of 14.3 months (octreotide-PROMID) and 38.5 months (lanreotide-CLARINET) obtained in the respective phase III studies with SSA.[12-14] By contrast, the total cost of targeted therapies (sunitinib and everolimus) was almost twice as higher than that for SSAs by month of treatment in the present study, although they were given during a shorter time (average treatment duration of 5.9 months and between 4.6 and 9.3 months in the phase III studies allowing the

approval of sunitinib and everolimus);[15,16] these drugs allowed a median progression-free survival of 11.4 months (sunitinib, pancreatic mNET) and 11.0 months (everolimus, for both RADIANT-3 and −4) usually given for more aggressive disease after SSA and/or after chemotherapy.[15,16] PRRT usually includes four intravenous infusions of ^{177}Lu-Dotatate at a dose of 7.4 GBq given every 8 weeks during a short hospital stay (thus, its reimbursement is included in the "hospital stay"); the current cost is around €16,000 per injection in France, with an average treatment duration of 6 months. The present study that was performed in real-life using SNDS data confirms this estimation (more than €8000 PPPM). However, the high cost of PRRT during the treatment period has to be interpreted according to its efficacy; at this time, this is the most efficient treatment for small intestine NETs in second-line after SSA (the median PFS was 33 months in NETTER-1 study).[17] In summary, the description of overall healthcare costs by type of treatment, according to the disease control under each line of treatment, is therefore of major interest to guide public health decision making in France.

The main limitation of the LyREMeNET study was the small size of the retrospective cohort with a limited number of patients with mNETs. The SNDS was linked to the regional Cancer database on NEN of the HCL, allowing precise characterization of mNETs and comprehensive data collection. Further studies are warranted using national specific NET databases to ensure completeness of data about mNETs and healthcare costs in a specific country. Moreover, our analyses did not include costs related to treatments furnished by some clinical trials testing new drugs, although this concerned very few patients (probably less than 5% according to our personal data). Lastly, we may hypothesis a bias of patient selection with more severe mNET (thus more costly) because the LyREMeNET study included mNET patients who were seen at least once in the tertiary center (ENETS center of excellence).

The French healthcare system offers major advantages for investigating HRU and costs for NET care because all HRU and insurance-reimbursed costs are centralized into the SNDS. The SNDS covers almost the whole French population (66 million inhabitants) and provides extensive data on out-hospital reimbursements (for drugs, laboratory tests, medical acts, transportations and indirect costs), inpatient care (through linkage with the national hospital discharge database, PMSI) or even sociodemographic characteristics of patients and causes of death.[18,19] However, no specific ICD-10 code is available to describe NET, as is commonly observed for rare diseases. This makes it impossible to achieve a valid selection of patients with mNETs directly from the SNDS. This also explains the methodology of the present study that employed a dedicated database of NET with detailed clinical information, allowing the valuable opportunity to track patients with NET in a population-based database as a result of an appropriate linkage method.

In conclusion, the present study has increased our knowledge about patients with mNETs in a real-life setting, which is expected to be of value for current and future patients, as well as healthcare professionals, and also for healthcare planning. The management of patients with mNETs was associated with higher healthcare costs during the first year following the diagnosis, in patients with a primary tumor arising from the small intestine and in patients with a functional mNET. The monthly cost of treatment is the highest for PRRT, although this has to be interpreted according to the disease control achieved.

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CONFLICT OF INTERESTS

CLB: Ipsen, Novartis; AD: none; TW: Novartis, Ipsen, Keocyt, Sirtex. The remaining authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Marine Perrier: Visualization; Writing – original draft; Writing – review & editing. **Stephanie Polazzi:** Data curation; Formal analysis; Investigation; Resources; Writing – original draft; Writing – review & editing. **Annie Lemelin:** Data curation; Investigation; Resources. **Violaine Fernandez:** Data curation; Formal analysis; Investigation; Resources. **Stephanie Labonne:** Data curation; Investigation; Resources. **Delphine Maucort-Boulch:** Data curation; Investigation; Resources; Software. **Catherine Lombard-Bohas:** Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. **Antoine Duclos:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. **Thomas Walter:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

ETHICAL STATEMENT

This study was performed according to the World Medical Association Declaration of Helsinki. The HCL-Database was approved by CNIL (Commission nationale de l'informatique et des libertés) on 6 November 2015 (n°15–111). Informed consent of "non-opposition" was included in medical chart for all patients seen after January 2017. Additionally, patients were informed about the secondary use of their SNDS data with the possibility to refuse sharing their own data for study purpose. If patients were still followed-up in the HCL oncology department, a specific information letter was given to them during outpatient visit; otherwise, it was sent to them by mailing at their last known address. Access to data from the national registers and data extracted from the medical charts was restricted to participants in the project group. The results were presented in an aggregate manner so that no individual may be identified. Extraction and analysis of SNDS data was approved by the

CNIL (Commission Nationale de l'informatique et des Libertés n° DR-2018–179 on 31 July 2018) after a preliminary assessment by the CEREES (Comité d'Expertise pour les Recherches les Etudes et les Evaluations dans le domaine de la Santé n° TPS-43298 on 18 May 2018). The LyREMeNET study was registered on the clinicaltrials.gov website (NCT03863106).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jne.13092.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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