RESEARCH

Management of neuroendocrine neoplasms: conformity with guidelines in and outside a center of excellence

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Abstract

Purpose: To improve neuroendocrine neoplasm (NEN) management, the European Neuroendocrine Tumor Society (ENETS) recognised 62 Centers of Excellence (CoE). This retrospective study compares conformity of patients' initial management within vs outside an ENETS CoE with clinical practice guidelines (CPGs).
Methods: Patients diagnosed with a NEN between August 2018 and July 2020 and presented in the Lyon-CoE Multidisciplinary Tumour Board (MDT) were included. Factors potentially associated with the conformity of initial management (work-up and first treatment) to CPG underwent univariate and multivariate analyses.
Results: Among the 615 included patients, 170 (27.6%) were initially managed in the CoE and 445 (72.4%) were only presented at the CoE-MDT. Patients in the CoE group more often had intestinal or pancreatic primaries, metastatic disease (61.8% vs 33%), hereditary syndrome, and a functioning tumour. Work-up conformity was 37.1% in the CoE (vs 29.9%, $P = 0.09$); this was 95.8% for the first treatment (vs 88.7%, $P = 0.01$). After multivariate analysis, CPG conformity was significantly higher for patients managed in the CoE, for younger patients, for those having a grade 1–2 tumour, and a genetic syndrome. Pancreatic and small intestinal (SI) NET surgeries performed in the CoE had a higher splenic preservation rate during left pancreatectomy, better detection of multiple tumours in SI surgeries, and higher number of resected lymph nodes.
Conclusions: Given the widespread observance of CPG, not all patients require management in the CoE. Referral should be considered for more complex cases such as metastatic diseases, G2 tumours, or carcinoid syndromes. Finally, we should encourage the centralization of NET surgery.

Key Words

- neuroendocrine neoplasm
- ENETS center of excellence
- diagnostic management
- conformity to clinical guidelines

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Introduction

Neuroendocrine neoplasm (NEN) is a rare disease, though its incidence is rising (1, 2). NENs are heterogeneous diseases regarding the number of primary origins, clinical presentation, staging, grading, and prognosis. Their initial characterizations and their management are varied and complex. Therefore, national (3) and international (4, 5, 6) guidelines were regularly updated to help physicians to optimize NEN management, both for neuroendocrine tumours (NET) and neuroendocrine carcinomas (NEC). To this end, the European Neuroendocrine Tumor Society (ENETS) has accredited 62 Centers of Excellence (CoE) around the world which aim to improve the diagnosis and therapy of patients with NEN in an international and interdisciplinary context. The Lyon-CoE, accredited in 2010, is one of the national coordinating centres of the French RENATEN network, aiming to enhance and homogenize the management of NEN patients across France. RENATEN now includes 23 centres in France; Lyon-CoE covers the Rhône-Alpes region (RA), which represents around 10% of the French population. Dedicated networks have proven their worth in other rare diseases, like sarcomas. Studies have documented the added value of these expert networks and helped us to determine when to direct patients to specialized centres (7, 8, 9, 10). These studies focused on sarcomas and only limited data demonstrating the efficacy of expert, multidisciplinary centres in NEN management are available (11, 12, 13). The populations initially managed within and outside the ENETS CoE have not yet been compared. Therefore, we designed a retrospective study, including all patients presented at least once in the MDT of Lyon-CoE for a new NEN diagnosis, which aims to assess the conformity to clinical practice guidelines (CPG).

Methods

Population

All patients diagnosed with a NEN between August 1, 2018, and July 31, 2020, and who presented at least once in the Lyon-CoE MDT were included. Patients were considered to have been initially managed in the CoE if they had been seen by one medical or surgical oncologist of the CoE within the 6 months following the NEN diagnosis. The date of diagnosis was histological in priority, but when no pathological proof was needed (for instance, imaging and history highly evocative of pancreatic NET in a multiple endocrine neoplasia type 1-MEN1 patient), it was the day of the first imaging showing the tumour. If patients had been referred after 6 months following NEN diagnosis or not referred at all during the study period, they were included in the 'just presented at the MDT of CoE' group.

From August 1, 2018, all patients with a NEN presented to the MDT-CoE were prospectively recorded in the NEN-Lyon-database, using a standardized form for the MDT presentation. This form includes data from the MDT (date), the referent physician (location and type of structure), patient information (sex, age, past medical history, performance status, genetic disorder), tumour characteristics (date of diagnosis either histological or morphological, location of the primary tumour, unifocal/multiple tumours, presence and type of secretory syndrome, maximal size of the primary tumour, stage, the location of metastatic disease, WHO classification, Ki67 index), date and type of biological test(s), date/type/results of standard imaging(s) and functional imaging(s)), and the date/type of treatment(s). Patients were then selected by automatic extraction from this computerized database.

In addition, we retrospectively collected missing data from pathological, imaging, and blood test reports, performed between 6 months before and 12 months after the diagnosis. We also collected data not available in this database, such as the place of residence, the patients' comorbidities in order to calculate the Charlson index, and the location and type of facility where the histological diagnosis was performed. Lastly, we collected data on all treatments performed within 12 months after diagnosis (type, location, and type of facility). Patients without NEN or with major pieces of missing information (unknown work-up and unknown treatment) were excluded.

Primary objective: conformity according to clinical practice guidelines

The main outcome was the quality of care, assessed by the minimal work-up performed between 6 months before to 12 months after the NEN diagnosis, and the first and second treatment received within the 12 months after diagnosis. The conformity to CPG for the work-up and the initial treatments was defined according to ENETS guidelines (French guidelines are similar) (3, 6). Minimal work-up included laboratory test (chromogranin A), endoscopy along with endoscopic ultrasound (EUS), imaging (CT scan, MRI, and cerebral imaging), functional imaging (somatostatin receptor imaging-SRI, FDG-PET, and FDOPA-PET) and expert pathological reviews. We paid specific attention to the work-up performed for carcinoid syndrome: 5HIAA was defined as necessary for all suspected

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cases of carcinoid syndrome, as well as for metastatic NET from the small-intestine/right colon or the lung. For these patients, or in case of elevated 5HIAA, a cardiac echography to look for carcinoid heart disease (CHD) was considered recommended by CPG. Other examples of conformity used in the present study are described in Supplementary Table 1 (see section on supplementary materials given at the end of this article). For each patient, every element was considered and sorted into one of the following categories: performed and recommended (P-R), not performed and not recommended (NP-NR), not performed but recommended (NP-R), performed but not recommended (P-NR). When exams were performed for other reasons than NEN's work-up, they were not considered. Conformity to an exam was defined as the ratio of patients whose exams conformed to guidelines (P-R and NP-NR) to the whole population considered for the exam. In addition, the non-conformity to treatment according to CPG was assessed and described in Supplementary Table 2.

Finally, we defined the global conformity of both the whole work-up and the first performed treatment. We considered every element for each patient. If at least one of the exams was non-conforming (NP-R or P-NR), the patient was sorted into the non-conforming group. That implies that patients who were sorted into the conforming group had all their exams and treatments performed according to CPG.

Secondary objectives

In addition, we aimed to assess different times of management from the date of diagnosis to the first MDT-CoE and to the first treatment. We especially focused on functioning NET (time between diagnosis and first prescription of somatostatin analogue for carcinoid syndrome) and metastatic NEC (time between diagnosis and the first prescription of chemotherapy), which both represent emergency situations. Finally, we compared pancreatic and small intestinal (SI) NET surgeries (type, complications, lymph node resection, margin resection, splenectomy performed during left pancreatectomy, cholecystectomy performed during the SI-NET surgical procedure, length of SI resection, and number of SI-NETs identified) in the CoE vs those performed in other structures.

Statistical analysis

Categorical data are expressed as 'number (percentage)'. Continuous variables are presented as median and interquartile range. Comparisons between groups were done using the chi^2 test and/or Fisher's exact test for qualitative data and using the Mann–Whitney test to compare the continuous variables. The following factors potentially associated with conformity to initial management were evaluated by univariate and multivariate analyses: management in the CoE, period of diagnosis, age, gender, place of residence, comorbidities, performance status, symptoms at diagnosis, genetic syndrome, primary site, functioning status, differentiation and grading, and the metastatic status. A P-value <0.05 was considered statistically significant. No formal hypothesis testing was used, but a sample size over 400 patients was considered clinically sufficient to represent a real-life population of patients. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS).

Results

Patient characteristics

After automatic extraction from the clinical software, 877 patients discussed at least once in the MDT of the Lyon ENETS CoE were identified; 180 had been diagnosed before the study period, 57 finally presented a tumour other than NEN, and 25 patients were excluded because of major missing data. Therefore, 615 patients were included in the present study, 170 (27.6%) initially managed in the CoE, and 445 (72.4%) just presented at the MDT of CoE or seen in the CoE after 6 months following their diagnosis (shown in Fig. 1).

Among them, 311 and 304 were diagnosed during the first or second year of the study period. Patients had a median age of 63 y/o, 264 (42.5%) were female, and 166 (27.0%) lived in the same area as the CoE (Rhône 69). They were no significant differences between the two groups in age, gender, and comorbidities. By contrast, patients living in the same department as the CoE (33.5% vs 24.5%), patients having a better performance status 0–1 (90.6% vs 83.8%), a genetic disorder (5.9% vs 2%, mainly a MEN1 in 13 patients), a non-fortuitous finding (67.6% vs 54.8%), and a primary tumour localized in the duodenopancreas (40.6% vs 36%), or the SI (33.5% vs 17.8%) were more frequent in the CoE group. Furthermore, tumours localized in the appendix, the rectum, or the stomach were more frequent in patients just presented at the MDT-CoE. NENs were more often functioning (16.5% vs 2.9%), larger in primary tumour size (median of 22 mm vs 15 mm), more often multiple (21% vs 8%), and of grade 2 (44.1% vs 24.9%) in patients initially managed in the CoE. There were, on the

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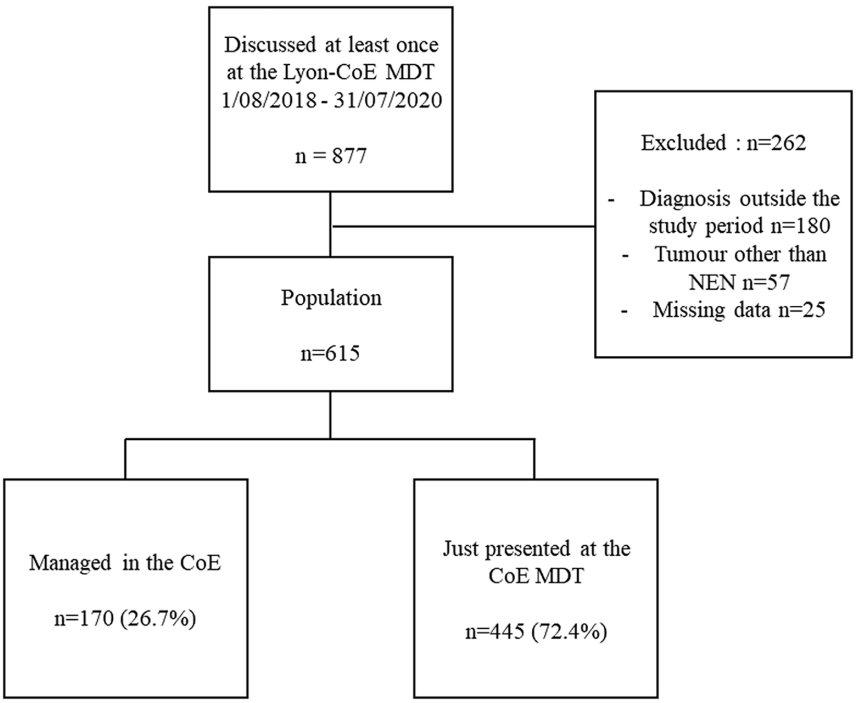

Figure 1
Flow chart of the study population.

other hand, fewer grade 1 tumours in this group. Similar proportions of grade 3 tumours were observed in both groups. Finally, patients with metastatic disease were more frequent in the CoE group (61.8% vs 33%) but stage I were less frequent (13.5% vs 33.7%) (Table 1).

Initial work-up

Regarding the conformity with CPG to work-up, more than a third of the recommended chromogranin A and 5HIAA dosages were NP-R. Conformities for chromogranin A (81.2% vs 60.5%) and for 5HIAA (90% vs 82.2%) were higher when managed in the CoE vs not. Conformity to cardiac echography was also higher in the CoE (96.4% vs 87.4%); among the 27 patients with carcinoid syndrome, this was 19/20 (95%) in the CoE vs 3/7 (42.8%) when just presented at the MDT-CoE. Among the 355 P-R first SRI undergone by patients, 276 (78%) were a ^{68}Ga-DOTA-PET whereas 79 (22%) were a scintigraphy (Octreoscan®). All the Octreoscans® were prescribed outside of the CoE. The global conformity of functional imaging was similar between both groups (71.8 and 78.2%); this was also less than 80% for MRI. There was a trend towards higher global conformity of work-up in the CoE group (37.1% vs 29.9%, $P = 0.09$) (Table 2).

Regarding the expert pathological review by TENpath network, 54 were NP-R: 45 NEN-G3, 5 with unusual primary location, 2 NET with incomplete immunostaining profile, and 2 NEN with imprecise initial characterization.

Treatments performed within the 12 months following the diagnosis

The median time between diagnosis and the first CoE-MDT was significantly shorter for patients initially managed in the CoE (34 days vs 61 days). By contrast, the median time between diagnosis and first treatment was five times longer for patients of the CoE group (36 days vs 7 days); however, we must note that 47/52 appendiceal and 42/43 rectal tumours were in the non-CoE group, which were usually treated the same day as diagnosed. There were no significant differences in the time from the diagnosis to the SSA start in patients with carcinoid syndrome, and from the diagnosis to the chemotherapy start in NEC (Table 3).

A total of 46 (27.7%) in the CoE group and 36 (8.1%) patients in the non-CoE group were included in a clinical trial within the 12 months following their NEN diagnosis ($P < 0.001$). The first treatment was performed in 72.6% of cases in the CoE group. The type of treatment is presented in Table 3; liver embolization, targeted therapies, and peptide receptor radionuclide therapy (PRRT) were more frequent in the CoE group even if they were rare as first-line, while endoscopic or surgical resections were more frequent in the non-CoE group (Table 3).

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Table 1 Patients and tumours baseline characteristics.

	Total population	Managed in the CoE	Just presented at the MDT of CoE	*P* value
	n = 615	170 (27.6%)	445 (72.4%)	
Period of diagnosis, *n* (%)				0.85
First year	311 (50.6)	87 (51.2)	224 (50.3)	
Second year	304 (49.4)	83 (48.8)	221 (49.7)	
Median age in years (IQR)	63 (52–72)	63 (51–70)	63 (52–73)	0.21
Female, *n* (%)	264 (42.5)	65 (39.2)	199 (43.7)	0.60
Place of residence, *n* (%)				0.02
Rhône 69	166 (27.0)	57 (33.5)	109 (24.5)	
Other than Rhône 69	449 (73.0)	113 (66.5)	336 (75.5)	
Median Charlson index (IQR) without NEN	2 (1–4)	2 (1–4)	2 (1–4)	0.87
Perfomance status (ECOG) at diagnosis, *n* (%)				0.03
0-1	527 (85.7)	154 (90.6)	373 (83.8)	
2-4	88 (14.3)	16 (9.4)	72 (16.2)	
Genetic disorder[b], *n* (%)	19 (3.1)	10 (5.9)	9 (2.0)	0.01
Symptom (non-fortuitous finding), *n* (%)[a]	359 (58.4)	115 (67.6)	244 (54.8)	0.004
Primary tumour site, *n* (%)				<0.001
Duodenopancreas	229 (37.2)	69 (40.6)	160 (36.0)	
Small intestine	136 (22.1)	57 (33.5)	79 (17.8)	
Appendiceal	52 (8.5)	5 (2.9)	47 (10.6)	
Lung	48 (7.8)	17 (10.0)	31 (7.0)	
Other GI-NET	100 (16.2)	10 (5.9)	90 (20.2)	
Rectum	43 (7.0)	1 (0.6)	42 (9.4)	
Stomach	29 (4.7)	4 (2.4)	25 (5.6)	
Colon	16 (2.6)	3 (1.8)	13 (2.9)	
Gallbladder	6 (1.0)	1 (0.6)	5 (1.1)	
Oesophagus	4 (0.7)	0 (0.0)	4 (0.9)	
Anal canal	2 (0.3)	1 (0.6)	1 (0.2)	
Unknown and other	50 (8.1)	12 (7.1)	38 (8.5)	
Functioning status, *n* (%)	41 (6.7)	28 (16.5)	13 (2.9)	<0.001
Carcinoid syndrome	27 (4.4)	20 (11.8)	7 (1.6)	
Insulinoma	7 (1.1)	5 (2.9)	2 (0.4)	
Zollinger Elison	5 (0.8)	2 (1.2)	3 (0.7)	
Cushing syndrome	2 (0.3)	1 (0.6)	1 (0.2)	
Carcinoid heart disease, *n* = 544 (%)	3 (0.6)	2 (1.2)	1 (0.2)	0.13
Median size of primary in cm (IQR) *n* = 469	18 (10–30)	22 (15–32)	15 (9–30)	0.02
Multiple tumours, *n* = 545 (%)	64 (11.7)	33 (21.0)	31 (8.0)	<0.001
Median Ki67 in % (IQR)	3.5 (1.5–15.0)	5.0 (2.0–14.0)	3.0 (1.3–15)	0.77
WHO classifications, *n* (%)				0.002
NET G1 or typical carcinoid	261 (42.4)	56 (32.9)	205 (46.1)	
NET G2 or atypical carcinoid	186 (30.2)	75 (44.1)	111 (24.9)	
NET G3	39 (6.3)	11 (6.5)	28 (6.3)	
Undefined NET or carcinoid	48 (7.8)	11 (6.5)	37 (8.3)	
NEC	70 (11.4)	17 (10.0)	53 (11.9)	
MiNEN	11 (1.8)	0	11 (2.5)	
TNM stage, *n* (%)				<0.001
I	173 (28.1)	23 (13.5)	150 (33.7)	
II	99 (16.1)	27 (15.9)	72 (16.2)	
III	91 (14.8)	15 (8.8)	76 (17.1)	
IV	252 (41.0)	105 (61.8)	147 (33.0)	
Localization of metastases, *n* (%)				
Liver	199 (32.4)	84 (49.4)	115 (25.8)	<0.001
Distant lymph nodes	73 (11.9)	33 (19.4)	40 (9.0)	0.002
Bone	65 (10.6)	28 (16.5)	37 (8.3)	0.08
Peritoneum	49 (8.0)	20 (11.8)	29 (6.5)	0.01
Lung	26 (4.2)	8 (4.7)	18 (4.0)	0.72
Brain	11 (1.8)	2 (1.2)	9 (2.0)	0.71
Other	23 (3.7)	11 (6.5)	12 (2.7)	0.03

(*Continued*)

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Table 1 Continued.

	Total population	Managed in the CoE	Just presented at the MDT of CoE	*P* value
	n = 615	170 (27.6%)	445 (72.4%)	
Median number of metastatic sites at diagnosis (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	<0.001
0	363 (59.0)	65 (38.2)	298 (67.0)	
1	128 (20.8)	55 (32.4)	73 (16.4)	
2	76 (12.4)	32 (18.8)	44 (9.9)	
≥3	48 (7.8)	18 (10.6)	30 (6.7)	

Neurofibromatosis type 1 *n* = 3, Neurofibromatosis type 1 *n* = 1.
[a]Available in 605 patients; [b]Multiple endocrine neoplasia type 1, *n* =13, tuberous sclerosis complex *n* = 2.
CoE, European Neuroendocrine Tumor Society (ENETS) Center of Excellence; MDT, Multidisciplinary Tumor Board; ECOG, eastern cooperative oncology group; G, grade; GI-NET, gastro-intestinal; IQR, interquartile range; LN, Lymph node; MiNEN, mixed neuroendocrine – non neuroendocrine neoplasm; NEC, poorly differentiated neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, (well differenciated) neuroendocrine tumour; WHO, World Health Organization.

Factors associated with conformity to CPG

The global conformity to both work-up and first treatment(s) received was 36.4% in the CoE group and 30.9% in the non-CoE group (Table 2). Factors significantly associated with higher conformity after univariate analysis were age <63 years old, Charlson index <2, performance status 0–1, presence of genetic syndrome, a well-differentiated tumour, a Grade 1 or 2 tumour, and a non-metastatic disease. After multivariate analysis, the management in the CoE, a younger age, the presence of genetic syndrome and a Grade 1 or 2 tumour remain significantly associated with higher conformity to both initial work-up and first received treatment (Table 4).

Table 2 Conformity with guidelines to the performed work-up and to first treatment(s) received, before and within the 12 months following diagnosis, and according to study groups.

	Conformity, *n*		Non conformity, *n*		Conformity with guidelines, *n* (%)		
	P-R	NP-NR	NP-R	P-NR	Managed in the CoE	Just presented at the MDT of CoE	*P* value
Laboratory test							
Chromogranin A (*n* = 613)	284	122	181	26	138 (81.2)	268 (60.5)	<0.001
5HIAA (*n* = 613)	128	389	69	27	153 (90.0)	364 (82.2)	0.02
Cardiac echography (*n* = 602)	101	435	60	0	161 (96.4)	375 (87.4)	0.001
Endoscopy (*n* = 603)	364	163	75	3	141 (85.5)	386 (88.1)	0.38
Imaging							
CT scan (*n* = 609)	511	60	35	3	165 (97.1)	406 (92.5)	0.04
MRI (*n* = 601)	300	157	124	20	130 (77.8)	327 (75.3)	0.52
Cerebral imaging (*n* = 598)	69	460	67	2	155 (92.8)	374 (86.8)	0.04
Functional Imaging							
Somatostatin Receptor Imaging (*n* = 613)	355	178	69	11	150 (88.2)	383 (86.5)	0.56
FDG PET (*n* = 578)	121	386	47	24	127 (80.4)	380 (90.5)	0.001
FDOPA PET (*n* = 613)	31	580	0	2	169 (99.4)	442 (99.8)	0.48
Global conformity of functional imaging (*n* = 613)	467		146		122 (71.8)	345 (78.2)	0.11
Expert pathological review (TENpath) (*n* = 515)	244	217	54	-	155 (98.7)	306 (85.5)	<0.001
Global conformity of work-up (*n* = 615)	196		419		63 (37.1)	133 (29.9)	0.09
Conformity for the first treatment received (*n* = 501)	456		45		158 (95.8)	298 (88.7)	0.01
Global conformity of both, work-up and first treatment(s) received (*n* = 502)	164		338		60 (36.4)	104 (30.9)	0.24

CoE, European Neuroendocrine Tumor Society (ENETS) Center of Excellence; MDT, Multidisciplinary Tumor board; P, performed; R, recommended; NP, not performed; NR, not recommended; 5HIAA, 5-Hydroxy-indolacetic acid; FDG, 18-Fluorodeoxyglucose; FDOPA, 18-fluoro-dihydroxyphenylalanine; TENpath, dedicated to Neuroendocrine neoplasm pathologist network; SRI, somatostatin receptor imaging.

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Table 3 Treatments performed within the 12 months following the diagnosis.

	Total population	Managed in the CoE	Just presented at the MDT of CoE	*P* value
Median time in days (IQR) from diagnosis to:				
First RENATEN MDT, *n* = 610	54 (28–100)	34 (20–69)	61 (33–108)	<0.001
First treatment, *n* = 443	20 (0–62)	36 (7–79)	7 (0–53)	0.02
SSA start in carcinoid syndrome, *n* = 27	31 (7–59)	42 (10–62)	24 (0–29)	0.13
Chemotherapy start in metastatic NEC, *n* = 36	15 (9–24)	14 (9–21)	15 (9–28)	0.72
Inclusion in a clinical trial, *n* = 610 (%)	82 (13.4)	46 (27.7)	36 (8.1)	<0.001
Place of first treatment, *n* = 525 (%)				<0.001
Rhône 69	302 (57.5)	143 (85.1)	159 (44.5)	
Other than Rhône	223 (42.5)	25 (14.9)	198 (55.5)	
Type of institution performing the first treatment, *n* = 525 (%)				<0.001
University public hospital	255 (48.6)	122 (72.6)	133 (37.3)	
Regional public hospital	99 (18.9)	14 (8.3)	85 (23.8)	
Private clinic	146 (27.8)	30 (17.9)	116 (32.5)	
Cancer Center	25 (4.8)	2 (1.2)	23 (6.4)	
First and second treatment within 12 months, *n* = 663[b] (%)				<0.001
Endoscopic resection of primary	56 (8.4)	3 (1.2)	53 (12.6)	
Surgery of primary	256 (38.6)	66 (27.1)	190 (45.2)	
Surgery of metastases	16 (2.4)	8 (3.3)	8 (2.0)	
Liver embolization	4 (0.6)	3 (1.2)	1 (0.2)	
Somatostatin analogues	98 (14.8)	56 (23.0)	42 (10.0)	
Chemotherapy	152 (22.9)	78 (32.1)	74 (17.6)	
Targeted therapy	1 (0.2)	1 (0.4)	0	
Peptide receptor radionuclide therapy	4 (0.6)	3 (1.2)	1 (0.2)	
Watch and wait without treatment	62 (9.4)	23 (9.5)	39 (9.2)	
No treatment, no follow-up	10 (1.5)	0	10 (2.38)	
Other[a]	4 (0.6)	2 (0.8)	2 (0.5)	

[a]Other: cardiac surgery (*n* = 2); palliative care (*n* = 2); [b]2 treatments considered for 142 patients.
CoE, European Neuroendocrine Tumor Society (ENETS) Center of Excellence; MDT, Multidisciplinary Tumor board; IQR, interquartile range; NEC, (poorly differentiated) neuroendocrine carcinoma; RENATEN, dedicated to Neuroendocrine neoplasm MDT; SSA, somatostatin analogues.

Table 4 Factors associated with conformity to both initial work-up and first received treatment.

Variables	*n*	Univariate analysis		Multivariate analysis	
		Odd ratio (95% CI)	*P*-value	Odd ratio (95% CI)	*P*-value
Managed in the CoE, yes vs no	502	0.79 (0.54–1.17)	0.244	0.50 (0.30–0.84)	0.009
Period of diagnosis, first year vs second year	502	0.89 (0.61–1.29)	0.543		
Age, < vs ≥ median (63 years old)	502	0.39 (0.26–0.58)	<0.001	0.42 (0.26–0.79)	0.007
Women vs men	502	0.79 (0.55–1.15)	0.224		
Place of residence, other vs 69	502	1.26 (0.84–1.89)	0.263		
Charlson index, <2 vs ≥2	497	0.48 (0.33–0.71)	<0.001	1.30 (0.69–2.48)	0.419
Performance status, 0–1 vs >1	502	0.32 (0.16–0.65)	0.002	0.54 (0.23–1.25)	0.149
Symptoms at diagnosis, no vs yes	502	0.69 (0.48–1.01)	0.055	0.96 (0.60–1.56)	0.883
Genetic syndrome, no vs yes	502	4.72 (1.76–12.65)	0.002	5.57 (1.26–24.52)	0.023
Primary site, lung as reference	502				
Small intestine		0.74 (0.31–1.78)	0.503		
Duodenopancreas		0.53 (0.30–1.22)	0.136		
Unknown and others		0.37 (0.16–0.85)	0.020		
Functioning status, no vs yes	502	1.30 (0.67–2.56)	0.440		
Poorly vs well differentiated	502	14.20 (3.41–59.12)	<0.001	5.71 (0.93–35.02)	0.060
Tumour grade, Grade 3 as reference	468				
Grade 1		0.11 (0.05–0.27)	<0.001	0.24 (0.07–0.80)	0.021
Grade 2		0.17 (0.07–0.41)	<0.001	0.29 (0.09–0.95)	0.040
Metastatic disease, no vs yes	502	0.46 (0.31–0.70)	<0.001	0.83 (0.45–1.52)	0.544

CoE, European Neuroendocrine Tumor Society (ENETS) Center of Excellence.

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Table 5 Pancreatic and small-intestinal neuroendocrine tumour surgeries.

	Total population	Surgery performed in the CoE	Surgery not performed in the CoE	*P* value
Pancreatic neuroendocrine surgery				
Number of procedures, *n*	66	13	53	
Median time in days between diagnosis and surgery (IQR), *N* = 65	36 (0–141)	86 (25–176)	31 (0–118)	0.084
Type of procedure, *n* (%)				0.362
Left pancreatectomy	40 (60.6)	11 (84.6)	29 (54.7)	
Whipple resection	16 (24.2)	1 (7.7)	15 (28.3)	
Enucleation	5 (7.6)	1 (7.7)	4 (7.5)	
Other[a]	5 (9.0)	0	5 (9.4)	
Splenic preservation during left pancreatectomy, *N* = 40	18 (45.0)	11 (100)	7 (24.1)	0.010
Median number of lymph nodes resected (IQR), *N* = 57[b]	8 (5–12)	7 (6–10)	8 (5–13)	0.520
Patients with ≥13 lymph nodes resected, *n* (%)[b]	12 (19.4)	1 (7.7)	11 (22.9)	0.189
Mortality within 90 days, *n* (%)	2 (3.0)	0 (0)	2 (3.8)	0.588
Morbidity requiring new procedure within 90 days, *n* (%)	12 (18.2)	3 (23.1)	9 (18.0)	0.385
Negative margin resection, *n* (%), *N* = 66	62 (93.9)	13 (100.0)	49 (94.2)	0.358
Small intestinal neuroendocrine tumour (SI-NET) surgery				
Number of procedures, *n*	85	27	58	
Number of patients operated in 'emergency', *n* (%)	14 (16.4)	2 (7.4)	12 (20.7)	0.208
Median time in days between diagnosis and surgery (IQR)	26 (0–114)	105 (1–170)	0 (0–79)	<0.001
Cholecystectomy during the procedure, *n* (%), *N* = 64[c]	40 (62.5)	23 (95.8)	16 (40.0)	<0.001
Mortality within 90 days, *n* (%), *N* = 81	0 (0)	0 (0)	0 (0)	-
Morbidity requiring new procedure or a transfer to the ICU ward within 90 days, *n* (%), *N* = 81	3 (3.7)	0	3 (5.6)	0.212
Median number of lymph nodes resected (IQR), N=68[d]	22 (12–32)	35 (23–46)	15 (6–26)	<0.001
Patients with ≥8 lymph nodes resected, *n* (%), *N* = 68[d]	56 (82.4)	25 (100)	31 (73.8)	0.003
Patients with ≥12 lymph nodes resected, *n* (%), *N* = 68[d]	52 (76.5)	25 (100)	27 (64.2)	<0.001
Negative margin resection, *n* = 84 (%)	78 (92.8)	25 (92.6)	53 (93.0)	0.833
Median length of small intestine resection (IQR), *N* = 79	40 (16–66)	64 (39–96)	30 (13–49)	0.002
Multiple tumours, *n* (%)	28 (32.9)	13 (48.1)	15 (25.9)	0.042
Median number of SI-NET in multiple tumour (IQR)	4 (2–15)	15 (4–41)	3 (2–4)	0.024

[a]Other: isthmectomy (*n* = 4), unknown (*n* =1); [b]Enucleations not considered; [c]Seven patients previously underwent cholecystectomy before the SI-NET surgery, emergency surgeries not considered; [d]Emergencies and NA not considered.
CoE, European Neuroendocrine Tumor Society (ENETS) Center of Excellence; IQR, interquartile range; MDT, Multi-disciplinary Tumor board; NET, neuroendocrine tumour.

Focus on pancreatic and small-intestinal surgeries

A total of 66 patients underwent a pancreatic surgery, which more frequently consisted of a left pancreatectomy: 11 out of 13 (84.6%) in the CoE and 29 out of 53 (54.7%) outside the CoE. The spleen was conserved in all cases in the CoE and in 24.1% of cases in the non-expert centres. There was only one Whipple resection performed in the CoE; however, the median number of resected lymph nodes (LN) was the same in both groups. There were no significant differences in post-operative morbidity and mortality nor in the R0 resection rate (Table 5).

A total of 85 patients underwent a SI-NET surgery, 27 performed in the CoE and 58 outside. Fourteen patients (16.4%) underwent the surgery within the week of the first symptoms, classified as 'emergency': two for perforation, one for digestive hemorrhage refractory to arterial embolization, eight for occlusive syndrome, and three for sub-occlusive syndrome. Regardless of emergencies, conformity to CPG was higher for surgeries performed in the CoE vs outside: higher rate of cholecystectomy (95.8% vs 40.0%) and higher median number of resected LN (35 vs 15). Similarly, all (100%) lymphadenectomies included more than 12 LN in the CoE vs 64.2% outside. The length of SI resection was twice as long in the CoE (median of 64 cm vs 30 cm), and specialized surgeons found multiple SI-NET in 48.1% of patients whereas surgeons outside the CoE found 25.9% of patients with multiple SI-NETs; among them, the median number of tumours was also significantly higher (median of 15 vs 3) (Table 5).

Focus on appendiceal NET

As presented in Table 1, appendiceal NET were most often managed outside of the centre of excellence (47 vs

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5 in the CoE). The diagnosis was usually performed the same day (46/52) as its treatment (identified incidentally on appendectomy pathological specimens). Even if the group is small, treatment conformity reached 100%. Work-up was non-conforming in 19 cases (36.5%): when no additional exploration was needed, chromogranin A was unnecessarily measured in four cases; also, for 13 tumours which were at risk of spreading, SRI imaging or chromogranin A had not been performed.

Discussion

The Lyon-CoE-MDT managed more than 300 patients with a new NEN diagnosis yearly, but fewer than a third were seen in the CoE-clinics within 6 months following their diagnosis. Patients initially managed by the CoE more often lived closer to the CoE, presented a better performance status, and were more often included in a clinical trial. Around one-third had their full work-up conforming to CPG, while the conformity was greater than 85% for the first administered treatment. The global conformity was higher after multivariate analysis for patients initially managed in the CoE, for younger patients, for those with a genetic syndrome, and for those with a NET-G1 or 2 tumours. Lastly, the conformity of the pancreatic and small intestinal surgeries to the CPG was higher when performed in the CoE.

We estimated that the Lyon-CoE-MDT covers around 66% of NEN patients. Indeed, assuming a NEN incidence of 6.98/100,000 inhabitants (14) among the population of 6.66 million inhabitants in the Rhône-Alpes area, we expected to have 465 new patients yearly. For comparison, in sarcomas, another rare cancer, Blay and coworkers estimated in 2017 the coverage of the NETSARC network to be 81.6% (14). Therefore, around one third of NEN patients were probably not considered in the present study. We may suppose that patients unseen by the CoE have a less severe NEN disease; indeed, in the epidemiologic data, primaries from the rectum/appendix/stomach, known to often be localized and low grade, are more common (15). In our study, the pancreas and small intestine primaries represented the majority of the cohort, as was the case in other expert centre and/or high volume centres (12, 16). Further efforts are necessary to increase systematic presentation of NEN patients at a RENATEN MDT. Indeed, discussing a patient's management in specialized NEN MDT often leads to complementary functional imaging or revision of histological data, which frequently results in significant changes in patients' management (13, 17, 18, 19).

We observed that patients referred to the CoE more often had 'complex diseases'; indeed, patients more often presented a primary other than rectum/appendix/gastric, a stage IV disease, and a Grade 2 tumour. These factors have been identified in previous studies as requiring specific diagnostic investigations and tailored therapeutic approaches (12, 13), which are more likely to be performed in a CoE. For instance, we pointed out in the present study that appendiceal NET, often localized and Grade 1, were perfectly managed according to clear guidelines, when they were only presented in the dedicated MDT. Geographical proximity also influences the place of management; indeed, more patients in the CoE group lived in the same area as the CoE (Rhône 69). Ideally, complexity of the disease should be the primary factor in deciding whether a patient is managed in a CoE. There might be a need to develop patients' pathways to ensure equality of care across the area. In addition, we observed a greater proportion of patients accessing clinical trials in the CoE group; facilitating access to clinical trials is another role of NEN CoE that promotes the development of CPG with a better level of evidence (19).

Diagnosis to treatment time varied greatly between patients, but we observed a significantly longer diagnosis to treatment time for patients in the CoE group, where a quarter of the patients were treated more than 2 months after their diagnosis. The course of the disease being predominantly favourable in NEN (15), most patients do not require urgent treatment. However, there are some treatments, such as those for poorly differentiated carcinomas or those for carcinoid syndrome, which represent emergency situations. We did not observe any significant difference between the two groups in terms of diagnosis to treatment time for these two cases. We should mention here that for carcinoid syndromes, time from first symptoms, and not diagnosis, might have been a more accurate way of measuring this parameter. Besides a quick treatment, another objective to consider for patients with carcinoid syndromes is CHD screening. We did notice a greater proportion of patients with carcinoid syndromes being screened for CHD in the CoE. We should, however, consider that the sample size of patients with carcinoid syndrome in the non-CoE group was small ($n = 7$). Regarding metastatic NEC, it is encouraging to observe a relatively short median time between diagnosis and first chemotherapy in and outside the CoE (14 days vs 15 days). There is no diagnosis to first chemotherapy time clearly indicated in the literature; however, a quick start is recommended as performance status deterioration may occur and preclude further therapy (6, 20). A delay

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longer than 21 days did not seem acceptable to us; this was the main reason for non-conforming treatments (Supplementary Table 2).

In the present study, conformity with NEN CPG was high. Taken individually, each item of work-up presented a high degree of conformity, usually more than 85% across groups. Similarly, conformity to the first received treatment remained high (>88%) in both groups. Indeed, all patients were presented at the MDT and this multidisciplinary approach correlates with better consistency with CPG (18, 19). However, taken together, the 'global' initial work-up conformity was rather low, even in the CoE (37.1%), highlighting the difficulty of establishing consensual guidelines in the NEN field. For instance, although chromogranin A, hepatic MRI and FDG-PET scan are often recommended, experts disagree on their utility in some cases. This is the first study, to our knowledge, to assess factors influencing conformity to CPG regarding NEN patients. In sarcomas, another group of rare and heterogeneous tumours, it was found that management in a CoE improved conformity to CPG (7, 8); we report here a comparable result for NEN. Moreover, many studies linked better survival to early involvement of a specialized team for sarcoma management (11, 15, 21, 22, 23). Regarding NEN, only one recent retrospective study indicated a link between centre volume and patient's survival (16). More studies have, on the other hand, examined the impact of a specialized NEN MDT, leading to significant changes in patients' management for 21–51% of those studied (12, 13); interestingly, Zandee and coworkers reported fewer changes after specialized MDT for gastroduodenal, appendiceal and rectal NET (13), which in the present study were managed less often in the CoE.

Our study is the first one to compare NET surgeries outside vs inside a CoE. It was not designed to observe survival improvement in patient outcome, as diagnoses were recent; however, CPG are based on studies that suggest benefits in patient outcome. Indeed regarding SI surgery, the number of patients with more than eight resected lymph nodes is significantly greater in the CoE (92.6 vs 66.1%); although the optimal extent of the lymphadenectomy is not clearly defined, resection of more than eight lymph nodes has been associated with better overall survival (21). Similarly, a significantly lower number of multifocal tumours observed in patients operated outside the CoE suggests that, during surgeries, primaries have been missed, leading undeniably towards suboptimal oncological results. Regarding pancreatic NET, systematic splenectomy during left pancreatectomy is rarely justified and may lead to septic and hematological complications (22); splenic preservation was higher in the CoE. Moreover, we observed a similar median number of resected lymph nodes (seven vs eight) whereas we would have expected a higher number in the non-expert group since there were significantly more Whipple resections in this group. Currently, CPG recommend referral to expert centres for especially difficult cases such as extensive lymphadenectomy, debulking surgery or in case of genetic syndrome (3, 23). According to our findings, we might consider systematic referral to CoE, and so centralization, of NET surgeries; indeed, non-specialized surgeons may only manage a few cases of NET surgeries within their career, which can be very challenging.

Besides being retrospective, our study has some limitations. Although it included a great number of patients, our study is monocentric; this study does not evaluate the CPG according to the 62 ENETS CoE throughout Europe, nor the 23 RENATEN centres throughout the French national territory. Moreover, we decided to include any type of NEN discussed at the MDT. Considering the heterogeneity of NEN, it is challenging to define common criteria to compare quality of care (24). Finally, an estimated one-third of our region's NEN patients are left out of our study; comparing conformity to CPG of those patients not even presented at the CoE-MDT would be interesting.

In conclusion, our study suggests that conformity to CPG remains high for both work-up and treatment of NEN patients independently of the place of treatment. Because of the widespread observance of the CPG outside the CoE, not all patients need to be managed in the CoE, which is neither feasible for medico-economic reasons nor adequate for patients' quality of life. Referral to the CoE should be considered for more complex cases such as metastatic diseases, G2 tumours or carcinoid syndromes or to allow access to clinical trials. Finally, we should encourage centralization of NET surgery.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0097.

Declaration of interest

C M: none; K M B: none; M J: none; L M: none; A T: none; V H: none; M P: none; G P: Ipsen, Novartis; J F: Ipsen; L F: Ipsen, GE; F B C: none; M A: none; C L B: Ipsen, Novartis; T W: Novartis, Ipsen, Keocyt, Sirtex.

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Statement of ethics

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) and its ethical committee, on the 6th of 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 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, else it was sent to them by mailing at their last known address. Data extracted from the medical charts were restricted to participants in the project group. The results were presented in an aggregate manner so that no individual may be identified.

Author contribution statement

C M and T W designed the study; C M, K M B, L M, A T, V H, C L B, and T W collected the data (prospective database); C M and T W conducted the descriptive statistical analyzes; C M and T W interpreted the data and wrote the first draft of the manuscript. M J, L M, V H, M P, G P, J F, L F, F B C, M A, C L B, and T W care of patients within the ENETS CoE of Lyon. All authors have read the manuscript and agree to its submission.

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