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► **To cite this version:**

Maroin Kalifi, Sophie Deguelte, Matthieu Faron, Pauline Afchain, Louis de Mestier, et al.. The Need for Centralization for Small Intestinal Neuroendocrine Tumor Surgery: A Cohort Study from the GTE-Endocan-RENATEN Network, the CentralChirSINET Study. *Annals of Surgical Oncology*, 2023, 30 (13), pp.8528-8541. 10.1245/s10434-023-14276-8 . hal-04490380

HAL Id: hal-04490380

<https://hal.science/hal-04490380>

Submitted on 2 Apr 2024

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The Need for Centralization for Small Intestinal Neuroendocrine Tumor Surgery: A Cohort Study from the GTE-Endocan-RENATEN Network, the *CentralChirSINET* Study

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ABSTRACT

Background. The concept of surgical centralization is becoming more and more accepted for specific surgical procedures.

Objective. The aim of this study was to evaluate the relationship between procedure volume and the outcomes of surgical small intestine (SI) neuroendocrine tumor (NET) resections.

Methods. We conducted a retrospective national study that included patients who underwent SI-NET resection between 2019 and 2021. A high-volume center (hvC) was defined as

a center that performed more than five SI-NET resections per year. The quality of the surgical resections was evaluated between hvCs and low-volume centers (lvCs) by comparing the number of resected lymph nodes (LNs) as the primary endpoint.

Results. A total of 157 patients underwent surgery in 33 centers: 90 patients in four hvCs and 67 patients in 29 lvCs. Laparotomy was more often performed in hvCs (85.6% vs. 59.7%; $p < 0.001$), as was right hemicolectomy (64.4% vs. 38.8%; $p < 0.001$), whereas limited ileocolic resection was performed in 18% of patients in lvCs versus none in hvCs. A bi-digital palpation of the entire SI length (95.6% vs. 34.3%, $p < 0.001$), a cholecystectomy (93.3% vs. 14.9%; $p < 0.001$), and a mesenteric mass resection (70% vs. 35.8%; $p < 0.001$) were more often performed in hvCs. The proportion of patients with ≥ 8 LNs resected was significantly higher (96.3% vs. 65.1%; $p < 0.001$) in hvCs compared with lvCs, as was the proportion of patients with ≥ 12 LNs resected (87.8% vs. 52.4%). Furthermore, the number of patients with multiple SI-NETs was higher in the hvC group compared

Gilles Poncet and Thomas Walter were joint last authors on this work.

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First Received: 24 April 2023

Accepted: 22 August 2023

Published online: 9 October 2023

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with the lvC group (43.3% vs. 25.4%), as were the number of tumors in those patients (median of 7 vs. 2; $p < 0.001$).

Conclusions. Optimal SI-NET resection was significantly more often performed in hvCs. Centralization of surgical care of SI-NETs is recommended.

Keywords Small intestine · Surgery · Neuroendocrine tumors · Centralization

Surgical resection of small intestine (SI) neuroendocrine tumors (NETs) is the cornerstone of curative treatment, and may also be indicated at the metastatic stage.^{1,2} Resection of SI-NETs is standardized and must follow some rules. First, since there are multiple SI-NETs in 30–50% of patients,³ an entire digital palpation of the SI is always required and is classically performed by laparotomy.⁴ Although the exteriorization of SI is mandatory for palpation, the laparotomy could be assisted by laparoscopy. Second, guidelines recommend removing at least 8 lymph nodes (LNs), however removing at least 12 LNs is currently under debate because the quality of the LN resection is associated with better overall survival (OS).^{5–10} Lastly, cholecystectomy must be systematically performed to prevent lithiasis complications and ischemic cholecystitis post liver embolization^{11,12} complications found particularly in patients presenting with metastatic disease for whom somatostatin analog treatment and embolization could be performed.

Strong and consistent associations between high procedural volume and improved clinical outcomes for pancreatotomy, esophagectomy, and hepatectomy have recently generalized the concept of centralization for complex surgical procedures in high-volume hospitals.^{13–16} There could be two explanations for the improved outcomes, i.e. the ‘practice makes perfect’ theory, which could be applied across the whole care management pathway (nurses, surgeon, oncologists, etc.), and the density of infrastructure, material, knowledge of specialists, and research.^{13,17} For interventions with a high morbidity rate, failure to rescue and 30-day mortality have often been used as quality assessment criteria.^{16,18} Herein, for SI-NET surgery, which is a low morbidity rate procedure, respect for the rules of oncological resection seems more relevant.⁴

To our knowledge, no studies have been published regarding centralization of SI-NET surgical care. Therefore, a multicenter, retrospective cohort study was conducted to investigate the impact of volume center on the quality of an oncological SI-NET resection, which is represented by the quality of the LN resection.

PATIENTS AND METHODS

Study Population

We identified patients treated in one of the 23 participant centers of the *Groupe d'étude des Tumeurs Endocrines* national database (GTE, N° CNIL 2219168, 5 January 2021). Patient data were extracted using the keywords ‘small intestinal (jejunum and ileum) primary tumors’ and ‘surgery of the primary tumor’. Patients who underwent resection of the primary tumor of an histologically confirmed SI-NET between January 2019 and December 2021, regardless of tumor grade and stage, and those who were admitted on an emergency basis but who had not undergone emergency resection within the first 24 h after admission, were included in the present study. The exclusion criteria were a duodenal NET, a previous history of SI-NET resection, an emergency resection within the first 24 h after admission (ischemic colitis/ileitis or peritonitis), and patients refusing to participate in this retrospective study. We also excluded patients for whom there was no, or too much, missing data, operative note, and/or pathological report.

Patients were treated within the ENDOCAN-RENATEN clinical network (constructed and supported by the GTE). This observational study followed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the *Hospices Civils de Lyon* (number 22-5544, 30 August 2021). Written information was provided to each patient included in the study. Their consent to participate was not required by French law but patients were informed about their right to withdraw their data from the cohort.

Data Collection

The following parameters were recorded at the time of surgery: age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale, symptomatic presentation, presence of carcinoid syndrome, carcinoid heart disease (CHD), number and location of metastatic sites, uptake on somatostatin receptor imaging (SRI), serum plasma chromogranin A (CgA) and urine 5-hydroxyindoleacetic acid (5HIAA) levels, and presence of a mesenteric mass, which was defined as a mass >2 cm in size in its largest dimension.¹⁹ According to the study by Lardièrre–Deguelte et al.,⁷ mesenteric mass invasion was classified into five stages based on its proximity to the trunk and/or branches of the superior mesenteric artery (SMA). Stage 0 indicates no visible mesenteric LNs suspicious of malignancy; stage I involves the proximity to the SI; and stage II indicates the involvement of the distal branches of the SMA. Stage III is further divided into two subclasses: stage III up refers to the involvement of the SMA trunk with less than three to

four free jejunal branches, and stage III down indicates the involvement of more than three to four free jejunal branches. Lastly, stage IV signifies the invasion of the first jejunal arteries.

We reported the type of SI resection, the surgical approach (laparoscopy or laparotomy), the realization of a lymphadenectomy and extensive lymphadenectomy (including the retropancreatic area), a cholecystectomy, palpation of the entire SI, length of hospital stay, death within 90 days after surgery, and the pathological results of the SI-NET resection. The R0 margin corresponded to microscopic free margin resection of all primary SI-NETs without regarding the presence of distant metastases.

In addition, we collected data from three questionnaires (when available in the medical files)—one developed before the study regarding the patients' satisfaction of their surgical care (electronic supplementary material [ESM] Table 1a, b); the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30; and the QLQ-GINET21 module specific for patients with gastrointestinal NETs (Appendix 1).²⁰ The specific scoring procedure described in the EORTC QLQ-C30 version 3.0 scoring manual was used.²¹

Study Objectives

The primary objective was to compare the rate of optimal LN resection (≥ 8) according to the volume center. Patients were categorized into two groups according to the volume center of SI-NET resection performed per year, i.e. more than five for high-volume centers (hvCs) and five or fewer resections for low-volume centers (lvCs). This cut-off was validated after discussion among members of the GTE Scientific Committee on 28 May 2021.

The secondary objectives were to compare the median number of resected LNs, the median LN ratio (LNR), the rate of extensive LN resection (retropancreatic area), the rate of bi-digital palpation of the SI total length, number of multiple SI-NETs, rate of cholecystectomy, and the rate of R0 resection (on the primary tumor and its regional LN/mesenteric mass, not on distant metastases) according to the volume center. Due to the study design (inclusion between January 2019 and December 2021), we did not evaluate local recurrence-free survival (RFS) or OS since surgery.

Statistical Analysis

Categorical variables were expressed as percentages and compared using the Chi-square test or Fisher's exact test when appropriate, while continuous variables were presented as median (interquartile range [IQR] Q1–Q3) and compared using the Mann–Whitney U test. Univariate analyses of factors associated with number of LNs ≥ 8 were performed by logistic regression; factors with a

p -value < 0.05 were introduced in a multivariate logistic regression. The association between volume center and number of LNs ≥ 8 was quantified using a linear mixed model. A p -value < 0.05 was considered statistically significant. All statistical analyses were performed using R package version 4.0.2.

According to a French single-center study,²² the proportion of surgeries that included ≥ 8 LNs was 100% in the European Neuroendocrine Tumor Society (ENETS) Center of Excellence (CoE) versus 74% outside the CoE. Based on these results, the minimal number of patients required for this national study was calculated according to the following prespecified hypotheses: $H_0 = 70\%$ of LNs ≥ 8 in lvCs and 90% of LNs in hvCs. Using, an α -risk of 5% and a power of 90%, 64 patients were required in each group.

RESULTS

Patient Characteristics at Diagnosis

A total of 439 patients who underwent an SI-NET resection were identified from the 23 ENDOCAN-RENATEN clinical networks of the national GTE database. Among these clinical networks, six agreed to participate, corresponding to 33 surgical centers and including 185 patients. A total of 157 patients who underwent an SI-NET resection in 33 different surgical centers between January 2019 and December 2021 were finally included—90 patients in 4 hvCs and 67 patients in 29 lvCs; 28 patients were excluded due to a lack of data (21 patients) or due to a resection performed within 24 h after admission (7 patients) (Fig. 1).

The median age was 66 years (IQR 58–72), 56.7% were male, and 94.3% had an ECOG PS score of 0–1. A total of 79.2% of patients had symptoms at surgery, mainly abdominal pain (33.7%) or diarrhea (29.2%); 18.8% had a carcinoid syndrome and only 5 patients (3.2%) had a CHD. Preoperative work-up showed multiple SI-NETs for 19.6% of patients, regional LNs for 87.4% of patients, and a mesenteric mass for 55.8% of patients; distant metastatic disease was found in 51.0% of patients, 41.5% in the liver, and 17% in the peritoneum. SRI, quantification of CgA, and urine 5HIAA levels were performed before surgery in 73.5%, 39.7%, and 50.7% of patients, respectively (Table 1).

Patients operated in an hvC had more frequent carcinoid syndrome than patients operated in an lvC (23.3% vs. 10.9%; $p = 0.049$). Preoperative cardiac ultrasound (63.3% vs. 15.8%; $p < 0.001$). Furthermore, preoperative SRI imaging (92.0% vs. 36.3%; $p < 0.001$), CgA quantification (57.5% vs. 8.2%; $p < 0.001$), and 5HIAA quantification (75.9% vs. 6.1%; $p < 0.001$) were more frequently performed in hvCs compared with lvCs (Table 1).

TABLE 1 Preoperative characteristics of patients included in the high- and low-volume groups

Variables	<i>N</i>	All [<i>n</i> = 157]	High-volume C [<i>n</i> = 90]	Low-volume C [<i>n</i> = 67]	<i>p</i> -value
Age, years (median [IQR])	157	66 [58–72]	64 [56–69]	69 [60–76]	0.004
Male	157	89 (56.7)	44 (48.9)	45 (67.2)	0.027
ECOG PS scale					0.840
0–1		148 (94.3)	85 (94.4)	63 (94.1)	
≥2		9 (5.7)	5 (5.6)	4 (5.9)	
Symptoms at surgery	154	122 (79.2)	70 (78.7)	52 (80.0)	0.601
Abdominal pain		52 (33.7)	31 (34.8)	21 (32.3)	0.0832
Diarrhea		45 (29.2)	23 (25.8)	22 (33.8)	0.336
Metastasis symptoms		21 (13.6)	13 (14.6)	8 (12.3)	0.729
Asthenia		69 (44.8)	39 (43.8)	30 (46.1)	0.912
Weight loss		22 (14.3)	13 (14.6)	9 (13.8)	0.947
Carcinoid syndrome	154	28 (18.8)	21 (23.3)	7 (10.9)	0.049
Cardiac ultrasound performed	157	66 (44.9)	57 (63.3)	9 (15.8)	< 0.001
Carcinoid heart disease	154	5 (3.2)	4 (4.4)	1 (1.6)	0.314
Multiple SI tumors	153	30 (19.6)	22 (24.4)	7 (11.1)	0.043
Regional lymph nodes	143	125 (87.4)	83 (96.5)	42 (73.6)	0.003
Mesenteric mass	138	67 (48.6)	47 (53.4)	20 (40.0)	0.130
Lardière–Deguelte’s classification	59				< 0.001
Classified		59 (37.6)	56 (62.2)	3 (4.4)	
≥III down		21(35.6)	20 (35.7)	1 (33.3)	
Number of distant metastatic sites	147				0.004
0		72 (49.0)	36 (42.3)	36 (58.1)	
1		47 (32.0)	37 (43.5)	10 (16.1)	
2		17 (11.6)	10 (11.8)	7 (11.3)	
≥3		11 (7.4)	7 (8.2)	4 (6.5)	
Location of metastatic sites	147				
Liver metastases		61 (41.5)	44 (51.8)	17 (27.4)	0.022
Peritoneum		25 (17.0)	15 (17.6)	10 (16.1)	0.853
Distant lymph nodes		9 (6.1)	3 (3.5)	6 (9.7)	0.071
Bone		7 (4.7)	3 (3.5)	4 (6.4)	0.295
Other		7 (4.7)	7 (8.2)	0	0.034
SRI	132				
Performed before surgery		97 (73.5)	81 (92.0)	16 (36.3)	< 0.001
Uptake on SRI		92 (94.9)	76 (93.8)	16 (100)	0.308
CgA	136				
Performed before surgery		54 (39.7)	50 (57.5)	4 (8.2)	< 0.001
CgA in ULN (median [IQR])	136	132 [58.5–272.5]	135.5 [58.5–277]	89.5 [72.5–1724.5]	0.429
5HIAA sample not performed	136				
Performed before surgery		69 (50.7)	66 (75.9)	3 (6.1)	< 0.001
5HIAA (median [IQR])	136	54 [22–122]	54 [22.5–121.5]	30 [25–175]	0.914

Data are expressed as *n* (%) unless otherwise specified

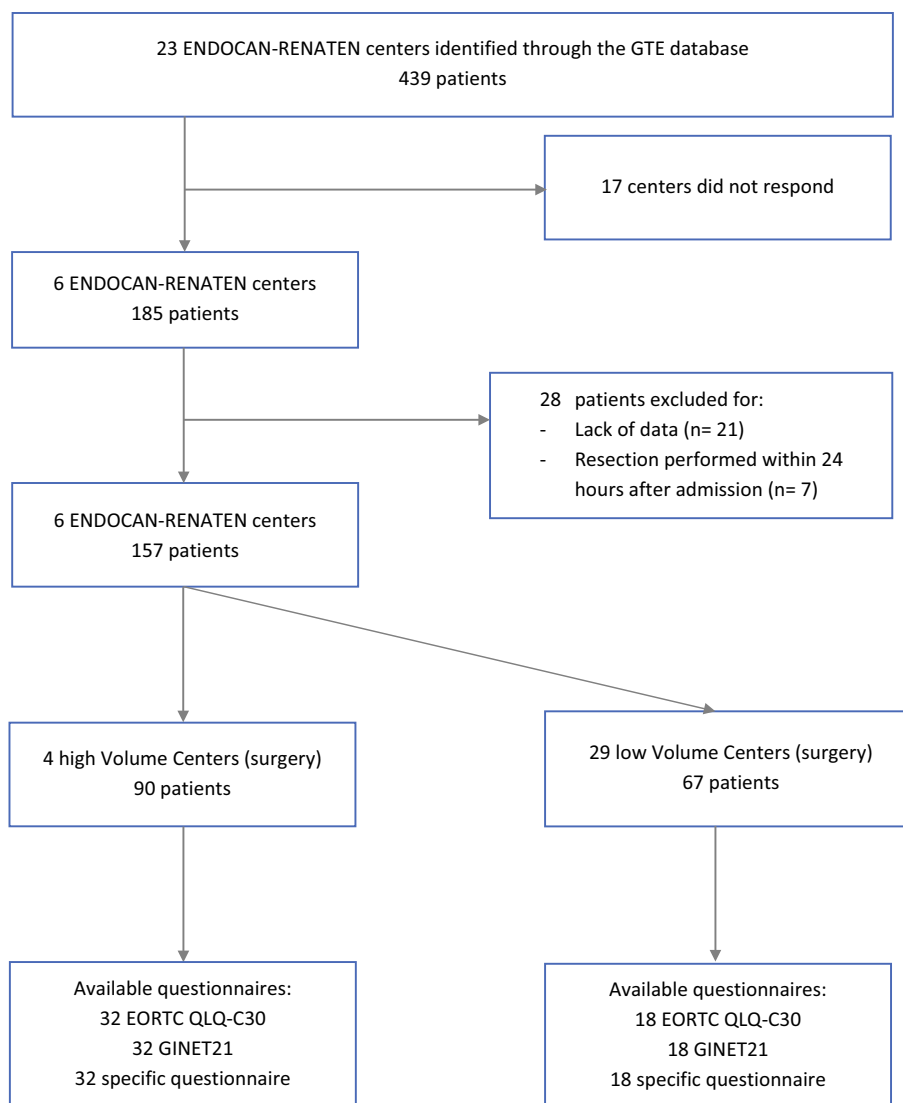
CgA chromogranin A, ECOG PS Eastern Cooperative Oncology Group Performance Status, IQR interquartile range, SI small intestinal, SRI somatostatin receptor imaging, ULN upper limit of normal, 5HIAA 5-hydroxyindoleacetic acid

Surgery and Pathological Results

The median overall number of SI-NET resections per year and per center was 6.6 (IQR 2–17), 1 (IQR 1–3) in lvCs, and 17 (IQR 7.3–17) in hvCs. The median time from

diagnosis to surgery was 128 days (IQR 61.5–201.5). In 54 lvC cases (80.6%) and 50 hvC cases (55.6%) [*p* = 0.001], the pathological diagnosis was unknown preoperatively and was performed on surgical specimen. For 74.6% of patients, the surgical approach used was laparotomy, and the most

FIG. 1 Study flowchart.
EORTC European Organisation
for Research and Treatment of
Cancer



frequent types of surgery were right hemicolectomy (53.5%) and SI segmental resection (39.5%); the median length of SI resection was 90 cm (IQR 50–180). In addition, a cholecystectomy was performed in 59.9% of patients and a bi-digital palpation was performed in 69.4% of patients; multiple tumors were palpated in 35.7% of patients. R0 resection was obtained in 94.2% of patients (Table 2).

In hvCs, 85.6% of patients underwent surgery by laparotomy and 14.4% by laparoscopy, whereas in lvCs, 40.3% were operated by laparoscopy ($p < 0.001$). The emergency surgeries performed within 1 week after admission were more frequent in lvCs than in hvCs (38.3% vs. 10.9%; $p < 0.001$). Right hemicolectomies were more frequently performed in hvCs (64.4% vs. 38.8%; $p < 0.001$). Limited ileocolic resection was never performed in hvCs, but was performed in 18.0% of patients in lvCs.

The median length of SI resection was 10 cm longer in lvCs than in hvCs ($p = 0.001$). Cholecystectomy (93.3% vs.

14.9%; $p < 0.001$) and bi-digital palpation of the entire SI length (95.6% vs. 34.3%; $p < 0.001$) were more often performed in hvCs than lvCs, and mesenteric mass was more often resected in hvCs (70.0% vs. 35.8%; $p < 0.001$). In hvCs, surgeons found multiple SI-NETs in 43.3% of patients compared with 25.4% of patients in lvCs ($p = 0.009$). Among these patients, the median number of tumors confirmed on pathological specimens was also significantly higher in patients in hvCs compared with patients in lvCs (7 vs. 2; $p < 0.001$) (Table 2).

Quality of the Lymph Node Resection

In hvCs compared with lvCs, the proportion of resected LNs ≥ 8 was significantly higher (96.3% vs. 65.1%; $p < 0.001$), as was the proportion of LNs ≥ 12 (87.8% vs. 52.4%; $p < 0.001$). An extensive lymphadenectomy was also more frequently performed in hvCs than lvCs (64.6%

TABLE 2 Operative and postoperative characteristics of patients included in the high- and low-volume groups

Variables	N	All [n = 157]	High-volume C [n = 90]	Low-volume C [n = 67]	p-value
Time from diagnosis to surgery, days (median [IQR])	103	128 [61.5–201.5]	154 [92–222.5]	67 [27–93]	< 0.001
Surgical approach	157				< 0.001
Laparotomy		117 (74.6)	77 (85.6)	40 (59.7)	
Laparoscopy		40 (25.4)	13 (14.4)	27 (40.3)	
Emergency surgery	157	30 (19.1)	12 (10.9)	18 (38.3)	< 0.001
Type of surgery	157				< 0.001
Right hemicolectomy		68 (43.3)	47 (52.2)	21 (31.3)	
Right hemicolectomy prolonged with SI resection		16 (10.2)	11 (12.2)	5 (7.5)	
SI segmental resection		62 (39.5)	32 (35.5)	30 (44.8)	
Ileocolic resection		11 (7.0)	0 (0)	11 (18.0)	
Cholecystectomy	157	94 (59.9)	84 (93.3)	10 (14.9)	< 0.001
Length of SI resection, cm (median [IQR])	69	90 [50–180]	90 [50–195]	80 [35–100]	0.001
Bi-digital palpation of the SI total length	157	109 (69.4)	86 (95.6)	23 (34.3)	< 0.001
Multiple tumors	157	56 (35.7)	39 (43.3)	17 (25.4)	0.009
Number of SI-NETs in patients with multiple tumors (median [IQR])	157	4 [2–12]	7 [3–16]	2 [2–7]	< 0.001
R0 margin resection	157	148 (94.2)	85 (94.4)	63 (94.0)	0.912
Resection of a mesenteric mass	157	87 (55.4)	63 (70.0)	24 (35.8)	< 0.001
Ki67, % (median [IQR])	154	2.4 [1–4.9]	3.0 [1–5]	2.0 [1–4]	0.331
WHO classifications	154				0.002
NET-G1		74 (48.1)	33 (37.1)	41 (63.0)	
NET-G2		79 (50.3)	56 (62.9)	23 (35.4)	
NET-G3		1 (0.6)	0	1 (1.6)	
LN resection					
Number of LNs resected (median [IQR])	145	20 [11–30]	28 [17.5–39.5]	12 [6–18.5]	< 0.001
Patients with ≥8 LNs resected	145	120 (82.8)	79 (96.3)	41 (65.1)	< 0.001
Patients with ≥12 LNs resected	145	105 (72.4)	72 (87.8)	33 (52.4)	< 0.001
Extensive lymphadenectomy	145	59 (40.6)	53 (64.6)	6 (9.5)	< 0.001
Number of positive lymph nodes (median [IQR])	145	4 [2–6]	4 [2–6]	3 [1–5]	0.012
Lymph node ratio (median [IQR])	145	0.21 [0.07–0.9]	0.1 [0.07–0.31]	0.27 [0.1–0.48]	0.036

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *LN* lymph node, *SI* small intestinal, *NETs* neuroendocrine tumors, *WHO* World Health Organization

vs. 9.5%; $p < 0.001$). Moreover, a higher median number of resected LNs (28 vs. 12; $p < 0.001$) was observed in hvCs (Table 2). The number of resected LNs seems to be proportionally related to the number of SI-NET resections performed per center per year (10.5 increase by 10 additional SI-NET resections per center; 95% CI -2.4 to 2.3 ; $p = 0.11$) (Fig. 2). In univariate analysis, number of resected LNs ≥ 8 was associated with patients operated in hvCs (vs. lvCs), younger patients, female, patients operated by laparotomy, no emergency surgery, and right hemicolectomy. In multivariate analysis, patients operated in hvCs (vs. lvCs; odds ratio [OR] 4.42, 95% CI 1.49–13.88; $p = 0.008$), female (vs. male; OR 3.80, 95% CI 1.20–14.43; $p = 0.022$) and patients operated by laparotomy (vs. laparoscopy; OR 3.78, 95% CI 1.17–12.98; $p = 0.027$) remain significantly associated with ≥ 8 LNs (Table 3).

Patient-Reported Outcomes and Quality of Life

Among the 157 patients, 50 (32%) had information in their medical files corresponding to the three questionnaire items in both groups (ESM Fig. 1)—32 in hvCs and 18 in lvCs. Regarding patients' satisfaction for their surgical care, 74.2% of hvC patients and 44.4% of lvC patients were reassured 'a lot' by being cared for in the surgical center; 77.4% of hvC patients and 66.7% of lvC patients were satisfied 'a lot' with their perioperative hospitalization; and 74.2% of hvC patients and 55.6% of lvC patients were satisfied 'a lot' with their follow-up at their surgical center (ESM Fig. 1a). Patient-reported outcomes (PROs) regarding the general symptoms were similar between both groups, except for reports of a lot of fear and anxiety (6.5% of hvC patients vs. 22.2% of lvC patients) [ESM Fig. 1b]. PROs regarding

FIG. 2 Number of resected LNs according to the number of surgeries performed per year per center. *LNs* lymph nodes

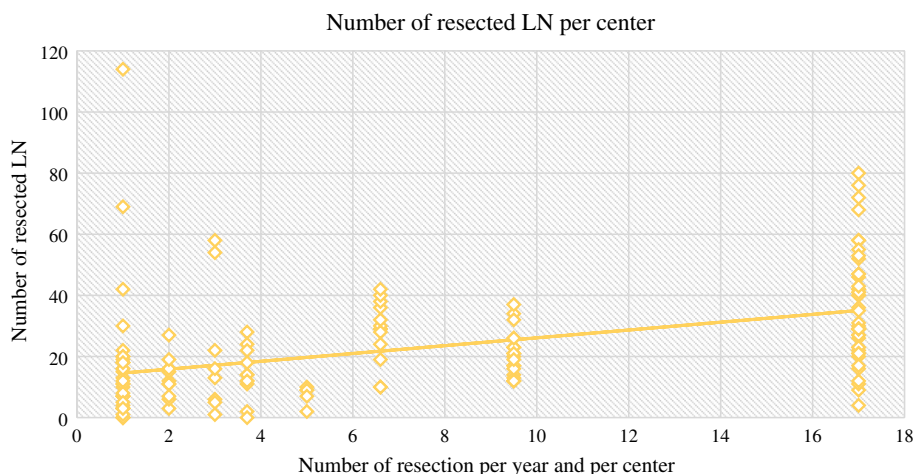


TABLE 3 Factors associated with resection of ≥ 8 lymph nodes

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Patients operated in an lvC vs. an hvC	8.96 (3.45–23.30)	< 0.001	4.42 (1.49–13.88)	0.008
Age, > vs. \leq median	2.49 (1.02–6.08)	0.041	1.87 (0.65–5.58)	0.245
Male vs. female	3.55 (1.25–10.14)	0.010	3.80 (1.20–14.43)	0.022
Laparoscopy vs. laparotomy	4.12 (1.67–10.12)	0.002	3.78 (1.17–12.98)	0.027
Emergency surgery, yes vs. no	3.96 (1.53–10.25)	0.006	3.16 (0.91–11.39)	0.071
Right hemicolectomy, no vs. yes	3.17 (1.18–8.48)	0.015	1.58 (0.45–5.97)	0.479
ECOG PS scale, ≥ 2 vs. 0–1	1.64 (0.31–8.63)	0.575		
Symptoms at surgery, yes vs. no	1.88 (0.52–6.82)	0.308		
Carcinoid syndrome, no vs. yes	1.69 (0.47–6.17)	0.402		
Distant metastatic disease, no vs. yes	1.87 (0.72–4.86)	0.193		

OR odds ratio, CI confidence interval, hvC high-volume center, lvC low-volume center, ECOG PS Eastern Cooperative Oncology Group Performance Status

the transit/exemption were also very similar for both groups; 25.8% of patients in hvCs reported ‘a lot of accelerated transit’, and approximately 9.7% reported ‘a lot of bloating’ (ESM Fig. 1c). PROS regarding the healing process were also similar for both groups; 67.7% and 72.2% of patients in hvCs and lvCs, respectively, were satisfied with their scar and had no healing problems. In addition, <10% of patients reported a postoperative incisional hernia (ESM Fig. 1d).

PROS regarding quality of life (QoL) in the EORTC QLQ-C30 showed no difference between both groups for overall health status. According to the GI-NET21 modules, there was a trend toward more endocrine-, gastrointestinal-, and treatment-related symptoms for hvC patients (Appendix 1).

DISCUSSION

The present study investigated for the first time the impact of procedure volume on surgical care for SI-NETs, based on a cut-off of five SI-NET resections per center, per year.

A significant relationship between volume center and optimal SI-NET surgery was identified, according to number of resected LNs ≥ 8 (ENETS recommendations).²³ The frequency of resected LNs ≥ 8 or ≥ 12 and extensive lymphadenectomy was significantly higher in hvCs versus lvCs. Furthermore, the number of patients identified with multiple primary SI-NETs and the number of resected primary SI-NETs were also higher in hvCs, and cholecystectomy was also more often performed in hvCs.

In the present study, younger patients, females, patients with a carcinoid syndrome, and those with more distant metastases were more often operated in hvCs, which may be due to more patient transfers from lvCs to hvCs, especially for patients with carcinoid syndrome or distant metastases. The pathological diagnosis was unknown preoperatively in the majority of cases in both groups, but more frequently in lvCs. The mesenteric mass and its retractile aspect is quite specific in SI-NETs but not seen in desmoid tumor, lymphoma, or metastatic LNs from other cancers. In the case of clinical symptoms such as carcinoid syndrome, the

hypervascular aspect of liver metastases, or the uptake of lesions at SRI, physicians must recognize a diagnosis of SI-NET and surgeons need to perform an optimal surgery. Herein, emergency resections performed after the first 24 h after admission were more frequently performed in lvCs than in hvCs. Despite similar symptoms at admission, a lower time between diagnosis and surgery was found in lvCs, which could be the consequence of a minimal preoperative workout in lvCs. The main emergency presentations were mesenteric ischemia and occlusive syndrome on retractile mesenteritis, but without severity criteria that would require surgery within 6–12 h (necrosis, perforation, peritonitis, etc.), which are rare (only seven cases herein). Of note, in the present study, we chose an arbitrary cut-off of 24 h, rather than 6 or 12 h, in order to consider all these situations, such as patients who underwent surgery between 12 and 24 h because more time was needed for internal reasons related to each structure. As the quality of SI-NET surgery is higher in hvCs as well as the quality of the preoperative work-up (SRI, cardiac ultrasound, quantification of CgA and 5HIAA), the lvC should start medical treatment of the occlusive syndrome or venous ischemia as soon as possible and transfer the patient to an hvC to initiate work-up and mapping of SI-NET local invasion.⁴ When severity criteria are present, a minimal resection and offloading stoma are mandatory without approaching mesenteric vessels, followed by a second intervention after a work-up, which could be proposed in better local conditions in hvCs.⁴ Using these two approaches in favor of a transfer to an hvC, centralization of SI-NET surgery with the aim of improving its quality would be feasible, even when the patient is initially taken care of in an lvC. We believe that this is particularly relevant when proximal mesenteric masses are present and require management, in an lvC, that is probably too complex. Finally, in light of a recent meta-analysis showing severe morbidity of 7%, a certain impact of hospital volume on postoperative outcomes was suggested.²⁴

Implementing centralized care is a challenge for health-care policies, mainly due to financial and structural constraints. Recently, centralization was the subject of a debate about two main parameters. First, although high procedure volume was the most used criterion in scientific literature regarding centralization, for some authors high hospital volume is thought to be a better criterion.^{14,25,26}

Second, the methodology to determine the cut-off values for the annual caseload varies among studies (spline model method, Chi-square automatic interaction detector [CHAID] method, etc.) considering the specificity of every surgical procedure.^{18,27} The cut-off could also be determined arbitrarily after committee validation,²⁸ when the incidence of the surgical procedures is very low, as in the present study. The five annual resections per year cut-off is a good compromise these days in France, according to the incidence of SI-NET surgery and its feasibility (SI-NET surgery is often not an urgent procedure requiring a complete work-up with enough time to arrange a transfer to an hvC). Using this cut-off, only four centers were considered hvCs; taking 10 as a cut-off, this was only two centers (data not shown). A recent study brought to light the difficulties encountered in France regarding the implementation of surgical care centralization for pancreatectomies, despite its high incidence, because of the inconsistent geographical distribution of hvCs, which were dispersed and limited in number.²⁹ Centralization in The Netherlands, a relatively small country in size, was successful, having increased resection rates and survival¹⁵ based on a cut-off of 20 patients per year thanks to a policy that benefits hvCs.³⁰ The cut-off must be discussed in each country according to its demography and size, the frequency of the surgical procedure, and its capacity to centralize these procedures.

Beside the centralization of patients in hvCs, educational programs have also had an important impact on the improvement of surgical management of SI-NETs. These surgical training programs have proven benefits in various fields, for instance in trauma and oncology,^{31,32} but not yet for the surgical management of SI-NETs. These educational programs, such as those organized by ENETS with dedicated sessions or surgical societies, are important to develop. However, the difficulty is to involve general gastrointestinal surgeons from lvCs who are dealing with a few cases each year, while surgeons need to follow educational programs for more frequent digestive surgeries such as colorectal or pancreatic cancer.

In addition, the present study highlighted that optimal SI-NET surgery was not clinically impacted by the length of the resected SI (median difference of 10 cm between hvCs and lvCs), with no impact on patient satisfaction regarding their surgical procedure or on their QoL. However, these results

must be interpreted with caution as less than one-third of patients provided information in the questionnaires. Assessing the satisfaction of surgical procedure is difficult using general EORTC QoL scales because these scales mix several aspects of the disease and the life of the patients, in addition to the procedure itself. The trend towards more symptoms in hvCs, found using the specific GI-NET21 modules, could be expected as patients in this group had a carcinoid syndrome significantly more often. We therefore designed a questionnaire dedicated to the feelings of the patients following their SI-NET surgery. This questionnaire showed that patients were satisfied to undergo surgery and follow-up in an hvC, even if it is likely that several of them lived some distance away from the hvC (data not collected). Moreover, although there were significantly more laparotomies and right hemicolectomies in hvCs, thus leading to longer scars (data not collected), the satisfaction reported by patients regarding their healing and their scars was similar in hvCs and lvCs. Further PRO data in larger populations are needed to confirm these preliminary results.

This study had several limitations. First, among 23 centers, because they were lacking in time, only 6 centers responded to our call and accepted to participate. Nevertheless, we were able to include a sufficient number of patients according to our statistical hypothesis. Second, postoperative complications were not collected as this was not feasible retrospectively without important bias and the risk of missing data, especially in lvCs. Moreover, lower postoperative complications (such as superficial wound infection, anastomotic leak, readmission, etc.) were expected in hvCs. Third, there might be bias regarding the number of resected LNs found in the pathology report. The pathologist in an hvC may spend more time sorting through the mesenteric fat to identify LNs. The retrospective nature of the present study did not allow this to be evaluated, but it needs to be considered for interpretation of the primary objective. Lastly, the design of this study did not allow evaluation of the local RFS or OS from the date of surgery since the included patients had undergone surgery between 2019 and 2021. However, it is well demonstrated that the quality of LN resection is associated with OS and relapse,^{5,33} as the number of resected LNs is one of the most powerful markers of OS.^{9,34} Further studies with longer follow-up are needed to evaluate the real oncological impact of surgery performed in hvCs.

CONCLUSION

Optimal SI-NET resection was significantly more often performed in hvCs. The centralization of surgical care of SI-NETs is recommended.

APPENDIX 1A

Patient reported outcome (PRO) on quality of life (QoL), EORTC QLQ-C30 and GI-NET21 modules, of patients who have undergone a SI-NET surgery. Values are reported in median (Q1-Q3)

Variables	hvC, n=38	lvC, n=12
<i>Global health status/QoL</i>		
Global health status/QoL (revised)	50 (42–83)	58 (42–83)
<i>Functional scales</i>		
Physical functioning (revised)	93 (80–100)	87 (72–100)
Role functioning (revised)	100 (83–100)	100 (58–100)
Emotional functioning	75 (50–100)	92 (50–100)
Cognitive functioning	100 (83–100)	100 (83–100)
Social functioning	83 (67–100)	83 (58–100)
<i>Symptom scales/items</i>		
Fatigue	33 (22–44)	17 (0–56)
Nausea and vomiting	0 (0–0)	0 (0–0)
Pain	0 (0–33)	0 (0–33)
Insomnia	0 (0–0)	0 (0–8)
Appetite loss	0 (0–33)	0 (0–8)
Constipation	0 (0–0)	0 (0–0)
Diarrhea	33 (0–67)	33 (0–33)
Financial difficulties	0 (0–0)	0 (0–0)
<i>QLQ-GINET21</i>		
Endocrine Symptoms	33 (0–47)	11 (0–50)
Gastrointestinal symptoms	27 (13–40)	13 (7–33)
Treatment-related symptoms	17 (0–33)	17 (0–33)
Social functioning of the new module	33 (22–55)	22 (11–61)
Disease-related worries	44 (15–69)	22 (19–50)

A high score for a functional scale represents a high/healthy level of functioning, but a high score for a symptom scale/item represents a high level of symptomatology/problems

hvC High volume center, lvC low volume center, QoL quality of life

APPENDIX 1B: EORTC QLQ-C30 (THE USED FRENCH VERSION)**QUESTIONNAIRE SUR LA QUALITE DE VIE
EORTC QLQ-C30 version 3**

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

Vos initiales :

Date de naissance :

La date d'aujourd'hui :

Au cours de la semaine passée	Pas du tout	Un peu	Assez	Beaucoup
1. Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provision chargé ou une valise ?	1	2	3	4
2. Avez-vous des difficultés à faire une LONGUE promenade ?	1	2	3	4
3. Avez-vous des difficultés à faire un PETIT tour dehors ?	1	2	3	4
4. Etes-vous obligée de rester au lit ou dans un fauteuil la majeure partie de la journée ?	1	2	3	4
5. Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux W.C. ?	1	2	3	4
6. Etes-vous limitée d'une manière ou d'une autre pour accomplir, soit votre travail, soit vos tâches habituelles chez vous ?	1	2	3	4
7. Etes-vous totalement incapable de travailler ou d'accomplir des tâches habituelles chez vous ?	1	2	3	4
Au cours de la semaine passée	Pas du tout	Un peu	Assez	Beaucoup
8. Avez-vous eu le souffle court ?	1	2	3	4
9. Avez-vous eu mal ?	1	2	3	4
10. Avez-vous eu besoin de repos ?	1	2	3	4
11. Avez-vous eu des difficultés pour dormir ?	1	2	3	4
12. Vous êtes-vous sentie faible ?	1	2	3	4
13. Avez-vous manqué d'appétit ?	1	2	3	4

14. Avez-vous eu des nausées (mal au cœur) ?	1	2	3	4
15. Avez-vous vomi ?	1	2	3	4
16. Avez-vous été constipée ?	1	2	3	4
Au cours de la semaine passée	Pas du tout	Un peu	Assez	Beaucoup
17. Avez-vous eu de la diarrhée ?	1	2	3	4
18. Etiez-vous fatiguée ?	1	2	3	4
19. Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision ?	1	2	3	4
21. Vous êtes-vous sentie tendue ?	1	2	3	4
22. Vous êtes-vous fait du souci ?	1	2	3	4
23. Vous êtes vous sentie irritable ?	1	2	3	4
24. Vous êtes vous sentie déprimée ?	1	2	3	4
25. Avez-vous eu des difficultés pour vous souvenir de certaines choses ?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gênée dans votre vie FAMILIALE ?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gênée dans vos activités SOCIALES (par exemple sortir avec des amis, aller au cinéma...)	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers ?	1	2	3	4

POUR LES QUESTIONS SUIVANTES, VEUILLEZ REpondRE EN ENTOURANT LE CHIFFRE ENTRE 1 ET 7 QUI S'APPLIQUE LE MIEUX A VOTRE SITUATION.

29. Comment évalueriez-vous l'ensemble de votre ETAT PHYSIQUE au cours de la semaine passée ?

1 2 3 4 5 6 7
Très mauvais Excellent

30. Comment évalueriez-vous l'ensemble de votre QUALITE DE VIE au cours de la semaine passée ?

1 2 3 4 5 6 7
Très mauvais Excellent

APPENDIX 1C: EORTC QLQ – GI.NET21 (THE USED FRENCH VERSION)

FRENCH

**EORTC QLQ – GI.NET21**

Les patients rapportent parfois les symptômes ou problèmes suivants. Pourriez-vous indiquer, s'il vous plaît, si, au cours de la semaine passée, vous avez été affecté(e) par l'un de ces symptômes ou problèmes. Entourez, s'il vous plaît, le chiffre qui correspond le mieux à votre situation.

Au cours de la semaine passée:	Pas du tout	Un peu	Assez	Beaucoup	
31. Avez-vous eu des bouffées de chaleur?	1	2	3	4	
32. Avez-vous remarqué, ou d'autres vous ont-ils fait remarquer que vous aviez le visage congestionné/rouge?	1	2	3	4	
33. Avez-vous eu des sueurs nocturnes?	1	2	3	4	
34. Avez-vous ressenti une gêne dans l'abdomen?	1	2	3	4	
35. Vous êtes-vous senti(e) ballonné(e)?	1	2	3	4	
36. Avez-vous été gêné(e) par des gaz?	1	2	3	4	
37. Avez-vous eu des acidités ou des brûlures d'estomac?	1	2	3	4	
38. Avez-vous eu des difficultés à manger?	1	2	3	4	
39. Avez-vous éprouvé des effets secondaires de votre traitement? (si vous n'êtes pas sous traitement, veuillez entourer N/A)	N/A	1	2	3	4
40. Les injections répétées vous ont-elles causé une gêne quelconque? (si vous ne recevez pas d'injection, veuillez entourer N/A)	N/A	1	2	3	4
41. Avez-vous eu peur que la tumeur réapparaisse dans d'autres parties du corps?	1	2	3	4	
42. Vous êtes-vous inquiété(e) d'une perturbation de votre vie familiale?	1	2	3	4	
43. Vous êtes-vous fait du souci pour votre santé dans l'avenir?	1	2	3	4	
44. Dans quelle mesure votre maladie ou votre traitement ont-ils affecté vos proches?	1	2	3	4	
45. Une perte de poids vous a-t-elle gênée?	1	2	3	4	
46. Une prise de poids vous a-t-elle gênée?	1	2	3	4	
47. Les résultats des tests vous ont-ils préoccupé? (si vous n'avez subi aucun test, veuillez entourer N/A)?	N/A	1	2	3	4
48. Avez-vous ressenti des douleurs dans les muscles ou les os?	1	2	3	4	
49. Avez-vous été limité(e) dans vos capacités de voyager?	1	2	3	4	
Au cours des <u>quatre</u> dernières semaines:					
50. Avez-vous eu des difficultés à obtenir des informations adéquates à propos de votre maladie et de votre traitement?	1	2	3	4	
51. La maladie ou son traitement ont-ils eu un impact défavorable sur votre vie sexuelle? (si non applicable, veuillez entourer N/A)	N/A	1	2	3	4

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at <https://doi.org/10.1245/s10434-023-14276-8>.

ACKNOWLEDGMENT The authors thank the patients and their association (Association des patients porteurs de tumeurs endocrines diverses [APTED]) for their participation in this study. They also thank the ENDOCAN-RENATEN clinical network, a French organization for neuroendocrine neoplasm management, constructed and supported by the Groupe d'Etude des Tumeurs Endocrines (GTE).

AUTHOR CONTRIBUTIONS MK and TW designed the study, and SD, MF, PA, LdM, KA, and TL collected the data. TW conducted the statistical analyses. MK, AP, GP, and TW interpreted the data and wrote the first draft of the manuscript, while MK, AP, GP, TW, SD, MF, PA, KA, LM, and TL coordinated care of patients within the ENDOCAN-RENATEN network. All authors have read the manuscript and agree to its submission.

FUNDING This study did not receive any specific grants from funding agencies in the public, commercial, or non-for-profit sectors; however, patients were identified from the French national database of the GTE, which is partially supported by IPSEN Pharma.

DISCLOSURE Louis de Mestier has received consulting and congress fees from AAA/Novartis, Ipsen, Viatrix; consulting and research fees from Esteve; and consulting fees from Mayoly and SIRTex. Thierry Lecomte has received personal fees from IPSEN, Keocyte and AAA, outside the submitted work. Thomas Walter has received fees from Novartis, Ipsen, Keocyt, and Terumo. Maroin Kalifi, Sophie Deguelte, Matthieu Faron, Pauline Afchain, Arnaud Pasquer, Fabien Subtil, Khalid Alghamdi, and Gilles Poncet have no disclosures to declare.

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