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Long-Term Results of Surgery for Small Intestinal Neuroendocrine Tumors at a Tertiary Referral Center

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Abstract
Background Small intestinal neuroendocrine tumors (SI-NETs) are uncommon, with an annual incidence of about 1 per 100,000 individuals. The primary tumor (PT) is generally small, but nevertheless the majority of patients have mesenteric lymph node metastases and liver metastases at diagnosis. Our aim was to identify prognostic factors for survival and to evaluate outcome after surgery in SI-NET patients.
Material and Methods We included 603 consecutive patients (325 men; age at diagnosis 63 ± 11 years [mean ± SD]) with histopathologically verified SI-NET, who were diagnosed between 1985 and 2010. Hospital charts were reviewed and were scrutinized for carcinoid heart disease (CHD), flush and/or diarrhea, proliferation by Ki-67 index, mesenteric lymph node metastases (m.lgllm), distant abdominal lymph node metastases (da.lgllm), liver tumor load (LTL), extra-abdominal metastases (EAM), locoregional resective surgery, as well as debulking of LTL, and adverse events after surgery.
Results Median overall survival (OS) was 8.4 years; 5-year OS was 67%, and 5-year relative survival was 74%. Independent prognostic factors by univariate and multivariate analysis were age at diagnosis, CHD, m.lgllm, da.lgllm, LTL, EAM, peritoneal carcinomatosis (PC), and proliferation. Locoregional resective surgery was associated with increased survival on crude and multivariate analysis. The 30-day mortality in our institution after initial locoregional resective surgery was 0.5% (1/205).
Conclusions For the first time, m.lgllm and da.lgllm, LTL, PC, and EAM are demonstrated to be independent prognostic factors by multivariate analysis. Locoregional removal of the PT/m.lgllm. was a positive prognostic factor by crude and adjusted analysis and may influence survival.

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Introduction

Small intestinal neuroendocrine tumors (SI-NETs) are the most common small bowel tumors. The annual incidence of SI-NETs has increased lasting recent decades and was in 2003 around 1/100,000 [1]. Small intestinal neuroendocrine tumors are recognized for their ability to produce serotonin and tachykinins; which may cause mesenteric fibrosis and the carcinoid syndrome, consisting of flush, frequent diarrhea, and, in advanced cases, right-sided heart failure. In contrast to small bowel adenocarcinoma, SI-NETs are also known for their advantageous survival, with 10-year overall, cause-specific, and relative survival rates of 36%, 80%, and 54%, respectively [2]. The primary tumor is often small, but SI-NETs, irrespective of primary tumor size, generally spread to mesenteric lymph nodes, and a majority of patients also display liver metastases at the time of diagnosis [1, 3]. The mesenteric metastases often grow larger than the primary tumor, and together with typical peritumoral fibrosis they have a tendency to infiltrate the mesenteric root and ultimately cause intestinal obstruction or vascular impairment [3]. Hence, SI-NETs

are often discovered during acute surgery for tumor-related intestinal obstruction or segmental small bowel ischemia [4].

Several prognostic factors are known to influence survival in SI-NETs; the presence of carcinoid heart disease and the number of liver metastases, as well as hormone values at referral, appear to have an effect on overall survival on univariate and multivariate analysis [5–7]. Studies also confirm the factor "age at diagnosis" to be independently prognostic for overall survival [2, 6, 8, 9]. Low tumor proliferation, or more specifically low Ki-67 index, is also associated with improved survival by both crude and adjusted analysis [5, 9–11] Other prognostic factors include WHO stage, primary tumor size, and calendar year of diagnosis [2, 5, 10].

Surgical removal of the primary tumor and mesenteric lymph nodes is indicated in patients without distant metastatic spread and has also been recommended in patients with liver metastases in order to prevent future complications caused by further growth of the mesenteric tumor [3, 12–14]. Continuing tumor growth, together with the associated fibrosis, may cause intestinal obstruction, segmental intestinal ischemia, and more extensive, sometimes incipient, venous ischemia, ultimately resulting in malnutrition and cachexia [3, 4, 9, 14–20]. In one recent study ($n = 360$) [9] of metastatic SI-NETs primary tumor surgery was a prognostic factor for overall survival when adjusting for age at diagnosis, proliferation, hormone levels, and therapy with somatostatin analogs and/or peptide receptor therapy. In another, somewhat smaller study ($n = 146$), there was no evident survival advantage of primary tumor surgery [8]. None of these studies specify the type of resective surgery performed to remove the primary tumor, and the extent of pathological mesenteric lymph nodes and their resection are also unknown [8, 9].

During the last 25 years the concept of debulking the liver tumor load has emerged in the treatment of SI-NET patients [21–23]. Debulking is used to palliate symptoms of the carcinoid syndrome and in an effort to improve long-term survival [22–26]. Live debulking is performed by a variety of methods; the most commonly used are hepatic resection, radiofrequency treatment, and liver embolization [23–25].

Biotherapy with somatostatin analogs and interferon are used to slow tumor progression. One prospective randomized trial demonstrates favorable progression-free survival using Sandostatin-LAR in NET patients [27], but survival benefits from the use of biotherapy have not been proven by randomized trials.

In The present retrospective study we have focused on clinical prognostic factors for overall and relative survival in the largest cohort ($n = 603$) of SI-NETs to date. We have also investigated the results and adverse events following surgery and debulking of liver metastases. Moreover we have used the new WHO classification for staging and grading for SI-NETs, and can thus present both overall and relative survival for each stage and grade of the SI-NET disease. The study is limited by referral bias to a tertiary center, but it is nevertheless the largest study available that supports previously demonstrated prognostic factors and brings new insights.

Patients and methods

We included 603 consecutive patients diagnosed and admitted to the Departments of Surgery or Endocrine Oncology at Uppsala University Hospital between 1985 and 2010. A database search was performed to find all patients with the (ICD-9/10) diagnostic codes for small intestinal tumor (152 C/C17.0-9) and/or carcinoid syndrome (259 C/E34.0). We included patients with a confirmed histopathological diagnosis of SI-NET made through microscopy and immunohistochemical staining of either liver biopsy material or surgical specimens. Specific staining for chromogranin A, synaptophysin, and serotonin confirmed the SI-NET diagnosis. Proliferation rate was estimated by Ki-67 index. Patients with a proliferation rate equal to or higher than a Ki-67 index of 20% at baseline (neuroendocrine carcinomas) and non-Swedish residents were excluded (owing to follow-up issues). Overall follow-up encompassed 6.9 ± 5.2 (mean $\pm$ SD) years, and the patients were followed until death or their last follow-up at the Departments of Surgery or Oncologic Endocrinology (until December 2010).

Patient charts were reviewed for symptoms, such as flush, diarrhea, and abdominal pain at baseline; carcinoid heart disease diagnosed by echocardiography; primary tumor stage; lymph node metastases; distant metastases; abdominal operations; liver debulking treatments; peptide receptor radioactive treatment (i.e., ^{177}lutetium-DOTA-Tyr3-octreotate); and medical treatment. A database was created in Excel 2008 for Mac (v.12; Microsoft, Redmond, WA).

Radiological imaging

Patients regularly underwent computed tomography (CT), both at baseline (abdominal CT within 6 months of diagnosis; $n = 562$), and during follow-up, in order to monitor tumor load and to evaluate treatment effect or disease progression. Presence of presumably metastatic mesenteric lymph nodes, distant abdominal lymph node metastases, extra-abdominal lymph node metastases, and number of liver metastases and extra-abdominal metastases (other than lymph nodes) at baseline and at the end of follow-up

were noted. Lymph nodes were deemed pathological if enlarged (largest diameter >1 cm), round-shaped, and accumulating intravenous contrast in a manner similar to the primary tumor and liver metastases as seen on CT images.

Liver tumor load was classified according to CT with the following partitions: no metastases; fewer than five metastases in one lobe; bi-lobar and/or between 5-10 metastases; and more than 10 hepatic metastases.

Nucleotide imaging

Somatostatin receptor scintigraphy and ^{11}C-5-hydroxy-tryptophan positron emission tomography were also performed, but the findings from these examinations were not recorded or reported in detail in this study, with the exception of those studies revealing apparent extra-abdominal tumor.

Pathology and Ki-67 index

Pathology reports were scrutinized for location ($n = 414$) and T-staging of the primary tumor ($n = 330$). Immunohistochemistry for Ki-67 was performed at the pathology department laboratory. Paraffin-embedded sections of 4 μm were used for immunohistochemistry. For antigen retrieval, sections were pre-treated with 45 min pressure boiling in a citrate buffer, pH 6.0. Immunohistochemistry was performed using an autostainer (DakoCytomation, Carpinteria, CA). Sections were incubated with an anti-Ki-67 antibody (DakoCytomation) diluted in antibody diluent (DakoCytomation), at room temperature for 60 min. The reaction product was revealed using Dako kit 50087 (DakoCytomation). Sections were counterstained with Mayer's haematoxylin. After this, a number of cells were counted and the Ki-67 index was given as a percentage of positive cells. WHO grade was classified with Ki-67 index; grade 1 = ≤ 2%, grade 2 = 3–20%, and grade 3 ≥ 20% according to Rindi et al. [28].

Hormone values

Serum chromogranin A (s-Cg A) and 5-hydroxy-indole-acetic acid (5-HIAA) in 24 h urine were regularly sampled from the patients at referral. Many patients had already undergone primary and mesenteric tumor surgery at referral, and in some cases had also started medical treatment. The s-Cg A and 5-HIAA values before surgery or before the beginning of medical treatment were available in only 125 (21%) and 163 (27%) patients, respectively. Given this fact, we did not further evaluate hormone values in relation to tumor stage, grade, and prognosis.

Surgical procedures

Laparotomy with or without resection was performed at least once in 517 of these patients, and 312 of them were operated on 1–3 times before referral to our institution. In total, 360 operations were done before referral: exploratory laparotomy $n = 38$, first locoregional resective surgery $n = 288$, and reoperative surgery, $n = 34$. Operative reports were scrutinized for evidence of apparent multiple primary tumors [3, 29], pathological mesenteric lymph nodes, liver metastases, and other intra-abdominal spread, such as peritoneal carcinomatosis and ovarian metastases. Furthermore, patients displaying mesenteric lymph node metastases at surgery were classified as radically resected or as having remaining mesenteric lymph nodes metastases after surgery.

At our institution the standard surgical approach for removal of the primary tumor and regional metastases (locoregional resective surgery) was a distal small bowel resection, often also including a right hemicolectomy (for more occasional jejunal tumors, only small bowel resection), combined with an extensive mesenteric dissection for removal of mesenteric lymph node metastases, taking care not to injure the proximal mesenteric vessels [29].

Debulking of liver metastases

Several different methods were used to treat liver metastases, both to palliate carcinoid symptoms and in an effort to improve survival. Liver surgery consisted of small atypical resections, larger wedge resections, as well as right or left hemihepatectomies. During the 1990 s hepatic artery embolizations/chemoembolizations (HAE/HACE) emerged as a treatment method for patients with large and/or bi-lobar tumor load.. These HAE/HACE procedures were accomplished with gelfoam (Spongostan or Ivalon) injected via a catheter into the hepatic artery, with or without supplementary chemotherapy. Similarly, radio-embolization debulking, a treatment that became available after 2000, was achieved through release of radioactive yttrium-90 microspheres into the hepatic artery. However, the most frequently used method for liver debulking at our institution since 2000 has been radiofrequency ablation, performed either via an ultrasound-guided percutaneous route, or via laparotomy, at times in combination with liver resections.

Medical treatment

Treatments with somatostatin analogs, interferon-alpha, and chemotherapy were recorded. Long- or short acting somatostatin analogs were given to most patients ($n = 497$), although some patients with no apparent

remaining tumor load and non-symptomatic patients were left without treatment. Interferon was given to most patients ($n = 477$) with remaining macroscopic or suspected microscopic disease, although elderly patients and patients with contraindications (i.e., ischemic heart disease, kidney failure, depression, or psoriasis) were more likely not to be offered this treatment. Chemotherapy was generally avoided, especially during recent years, as it has meager or no effect on low-proliferative SI-NETs [30, 31]. However, 29 patients in our cohort did receive chemotherapy. The most common chemotherapy protocols included streptomycin and 5-fluorouracil or Adriamycin.

Peptide receptor radioactive treatment

Both ^{111}indium-DTPA-octreotide and ^{90}yttrium-DOTA-Tyr3-octreotide have been used without convincing effect in our institution and are not in use anymore. However, radioactive ^{177}lutetium-DOTA-Tyr3-octreotate has emerged as a promising treatment option during the last decade. A total of 42 patients received lutetium treatments (1–5 per patient) during the studied time period.

Statistical analysis

Basic statistics

Parametric data are presented as means with standard deviations.

Survival analysis

All survival analyses were performed with Stata (Stata statistical software release 9, Stata Corp LP, College Station, TX). Overall survival (OS) curves were generated with the Kaplan-Meier method, and crude analysis of OS was computed with the log-rank test; $P < 0.050$ was considered statistically significant; 95% confidence intervals (96% CI) are given for survival estimates.

Relative survival (RS) was calculated as the ratio of the observed survival in the study population to the expected survival of the background population [32]. The expected mortality rates were assessed from gender-, age-, and period-specific life tables for Sweden. Relative survival analysis was performed with the statistical software package Stata, using the procedure strs, and further analyses were performed with the R statistical software package [33]. Relative survival analysis included the same variables as OS analysis. Survival estimates are given with 95% CI. Crude significance testing for RS was performed with a Poisson regression model truncated at 10-years follow-up.

Four different Cox proportional hazards models were used to study the adjusted effect of prognostic factors on OS. A value of $P < 0.05$ was considered statistically significant and 95% CI for hazard ratios are given. Correspondingly, four RS models calculating the excess mortality rate—i.e., the difference between the observed number of deaths and the expected number of deaths per person-year—were built into the Poisson regression model suggested by Dickman et al. and modeled for up to 10 years of follow-up [34]. Model estimates are presented as excess hazard ratios with 95% CI for the same prognostic factors as for OS models.

Results

Of the 603 patients in the present study, 325 (53.9%) were men. Age at diagnosis was 63.1 ± 11.3 years. Mean duration of follow-up from diagnosis was 6.9 ± 5.2 years, and 351 patients died during follow-up. Median OS was 8.4 years, 5-year OS was 67% (64%–71%), and 5-year RS was 74% (70%–79%) (Fig. 1). The patients' dates of diagnosis were equally dispersed over the entire study period.

Symptoms

At time of diagnosis, 455 (75%) patients complained of abdominal pain, 310 (51%) suffered from diarrhea, and 241 (40.0%) exhibited carcinoid flush (data missing, $n = 2$). A functional carcinoid syndrome consisting of diarrhea and/or flush was observed in 355 (59%) patients at diagnosis.

Carcinoid heart disease was observed in 60 (10%) patients at diagnosis, and during follow-up another 18

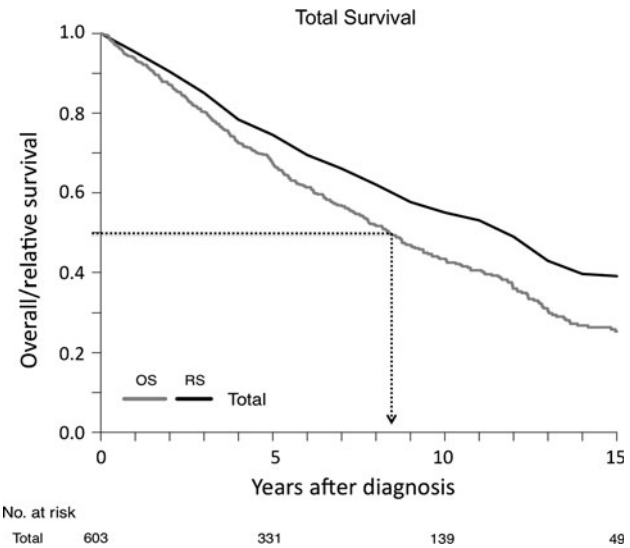

Fig. 1 Overall survival (OS) and relative survival (RS) for the entire patient cohort. Median overall survival (8.4 years) is indicated with a dotted arrow in the figure and number of patients at risk are shown beneath the figure

patients developed carcinoid heart disease after mean 3.4 ± 4.1 years.

WHO-stage and grade

Pathology reports were scrutinized for staging of the primary tumor, which was located in the small bowel in 410 cases and in the cecum in four cases (pathology reports not available despite resection, $n = 79$). The four primary tumors located in the cecum were all positive for chromogranin A, synaptophysin, and serotonin on immunohistochemical staining and therefore were classified as SI-NET tumors. Six tumors were staged as T1, 50 were T2, 134 were T3, and 140 were T4 (data in reports not sufficient for T-staging, $n = 84$). A total of 269 patients (65%) had solitary primary tumors, and 145 (36%) patients had multiple submucosal tumor nodules in the small intestinal wall, generally close to the primary tumor, and in most cases likely to represent local lymphatic spread [29].

Mesenteric lymph-node metastases were discovered in 528 (88%) of all patients at diagnosis. Of the 517 patients that underwent laparotomy, 482 (93%) had a variable number of pathological mesenteric lymph nodes identified by palpation or verified by histopathology. Forty-six (57%) of 86 nonoperated patients had enlarged mesenteric lymph nodes on CT imaging (CT performed at baseline, $n = 81$). Enlarged distant-abdominal (i.e., retroperitoneal/para-aortal or in association to the hepatoduodenal ligament) lymph nodes were recognized in 99 (18%) of the 562 patients that were examined by CT at baseline.

Liver metastases were observed in 366 (61%) patients at diagnosis by laparotomy, ultrasound, or CT (data missing, $n = 2$). At baseline CT imaging ($n = 562$), 238 patients had no liver metastases, whereas 80 patients had fewer than five metastases in one lobe, 105 patients had bi-lobar and/or between 5–10 metastases, and 139 patients had more than 10 liver metastases. Ninety-nine (42%) patients without liver metastases at diagnosis developed liver metastases during follow-up.

The 517 patients that underwent laparotomy were scrutinized for intra-abdominal tumor spread (other than mesenteric lymph node metastases and liver metastases), which was revealed in 111 patients at first laparotomy by reviewing operation charts and pathology reports. Peritoneal carcinomatosis was the most frequently recorded intra-abdominal manifestation ($n = 103$, 17% [representing 20% of all patients undergoing operation]), followed by ovarian ($n = 26$, 4.3%), pancreatic ($n = 3$, 0.5%), and splenic metastases ($n = 3$, 0.5%).

Extra-abdominal lymph node metastases were observed in 24 (4.0 %) of all patients at diagnosis, and 37 (6.1%) patients displayed extra-abdominal metastases (other than metastatic lymph nodes) at diagnosis. Several patients had multiple sites of extra-abdominal spread; the most common were lymph node ($n = 24$) and bone metastases ($n = 23$). All but two of the patients with extra-abdominal tumor spread at diagnosis also displayed liver metastases. During follow-up, extra-abdominal spread was diagnosed in another 70 (12%) patients.

Table 1 TNM staging proposal according to Rindi et al. [21]

Disease stage	T-primary tumor	N-regional nodes	M-distant metastases
Stage I	T1–2	N0	M0
Stage II	T3–4	N0	M0
Stage III	Any T	N1	M0
Stage IV	Any T	Any N	M1

Regional nodes mesenteric lymph nodes; *distant metastases* metastasis at any distant site (including non-regional lymph nodes)

Patients were also staged according to the current WHO criteria (2010; Table 1). Five-year OS was 100% for stage I ($n = 3$) and stage II ($n = 15$). For stage III, 5-year OS was 86% ($n = 181$), and for stage IV it was 57% ($n = 397$). In 7 patients, WHO stage was left undecided because of missing data. In total 18 patients were stage I–II at time of diagnosis, and none of these experienced tumor recurrence, nor did any of these patients have elevated hormone values (s-Cg A, 5-HIAA; $n = 13$) during a follow-up of 7.8 ± 4.0 years.

The proliferation marker Ki-67 was analyzed in 299 patients, thus allowing WHOgrading. The 299 patients were analyzed 1–4 times, and the highest index available for each patient was chosen for grading. Patients with a Ki-67 index exceeding 20% at baseline were excluded from the study, as previously mentioned (neuroendocrine carcinomas). WHO grade 1 was most common, accounting for 203 (68%) of all patients. Eighty-nine (30%) patients were WHO grade 2, and seven (2.3%) patients were WHO grade 3. Seven patients with WHO grade 3 based on their highest Ki-67 index, were initially indexed as WHO grade 1 ($n = 5$) or WHO grade 2 ($n = 2$).

Survival analysis of prognostic factors at diagnosis

Overall and relative survival figures, as well as univariate survival analyses regarding gender, age, symptoms, lymph node status, distant metastatic status, WHO stage, and WHO grade are presented in Table 2 (see also Figs. 2, 3). WHO stage and mesenteric lymph nodes were significant prognostic factors for OS, but they could not be modeled for RS because a subgroup with RS that exceeds survival of the general population does not allow such a model to converge (i.e., patients without known lymphatic spread, stage I–II; Table 3). The parameter "flush/and or diarrhea" was significant on crude analyses, but not by multivariate

Table 2 Overall and relative survival rates as well as crude analysis of survival according to the Mantel-Cox (OS) or Poisson regression model (RS) for patient characteristics

Patient characteristics	OS			RS		
	5-year	10-year	*P* Value	5-year	10-year	*P* value
Gender			0.865			0.378
Male	68 (63;73)	43 (37;49)		77 (70;82)	56 (48;64)	
Female	67 (61;73)	44 (38;52)		72 (66;78)	54 (46;62)	
Age at diagnosis			<0.001			<0.001
<50	87 (80;95)	76 (66;87)		88 (78;94)	78 (65;87)	
50–59	81 (74;88)	61 (52;71)		83 (75;89)	66 (55;75)	
60–69	70 (64;77)	38 (31;47)		76 (68;82)	46 (37;56)	
70–74	54 (44;66)	27 (17;41)		63 (49;74)	40 (24;58)	
>75	36 (27;48)	11 (5;25)		50 (36;64)	26 (10;52)	
Flush and/or diarrhea			0.022			0.005
Yes	63 (58;68)	40 (34;46)		69 (63;75)	50 (42;57)	
No	74 (68;80)	49 (42;57)		82 (75;88)	63 (53;72)	
Carcinoid heart disease			<0.001			<0.001
Yes	37 (26;51)	20 (12;34)		41 (28;54)	26 (14;41)	
No	71 (67;75)	46 (42;51)		78 (74;83)	58 (52;64)	
Pathological mesenteric lglll.[a]			0.005			Not done[b]
Yes	72 (68;77)	47 (42;53)		79 (74;84)	58 (52;65)	
No	90 (80;100)	80 (65;98)		100 (80;107)	105 (75;119)	
Pathological distant-abdominal lgll.			<0.001			<0.001
Yes	58 (49;69)	25 (17;38)		66 (53;76)	33 (21;47)	
No	70 (66;75)	47 (42;53)		77 (72;82)	60 (53;66)	
Pathological extra-abdominal lgll.			0.256			Not done[c]
Yes	74 (58;94)	28 (13;58)		81 (5596)	36 (14;62)	
No	67 (63;71)	44 (40;49)		74 (7079)	56 (50;62)	
Liver tumor load			<0.001			<0.001
No metastases	83 (78;88)	58 (51;66)		92 (86;97)	74 (64;83)	
<5 metastases in one lobe	69 (59;80)	43 (31;58)		77 (64;87)	57 (40;73)	
5–10 or bilobar metastases	56 (47;67)	28 (20;40)		63 (51;73)	36 (24;49)	
>10 metastases	50 (42;59)	29 (20;39)		55 (45;64)	36 (25;47)	
Peritoneal carcinomatosis[a]			<0.001			<0.001
Yes	52 (43;63)	32 (23;44)		58 (46;68)	41 (28;53)	
No	79 (75;83)	54 (48;60)		86 (82;91)	66 (59;73)	
Extra-abdominal metastases			<0.001			<0.001
Yes	37 (23;57)	17 (7;43)		41 (23;59)	24 (8;46)	
No	69 (66;73)	45 (41;50)		77 (72;81)	57 (51;63)	
WHO stage			<0.001			Not done[b]
I–II	100 (100;100)	100 (100;100)		113 (113;113)	135 (135;135)	
III	86 (81;91)	58 (50;67)		95 (88100)	74 (62;84)	
IV	57 (52;62)	34 (29;40)		63 (57;69)	43 (37;50)	
WHO grade			<0.001			<0.001
1	82 (76;88)	65 (57;75)		89 (82;94)	78 (66;88)	
2	54 (44;67)	41 (30;56)		61 (47;73)	51 (35;67)	
3	51 (23;100)	26 (5;100)		58 (14;90)	31 (2;79)	

Results are presented as percentages (95% confidence interval)

[a] During first operation instead of at diagnosis (only patients operated on)

[b] Model does not converge (negative excess hazard)

[c] Non-proportional excess hazards (few patients in one subgroup)

lgll. lymph nodes

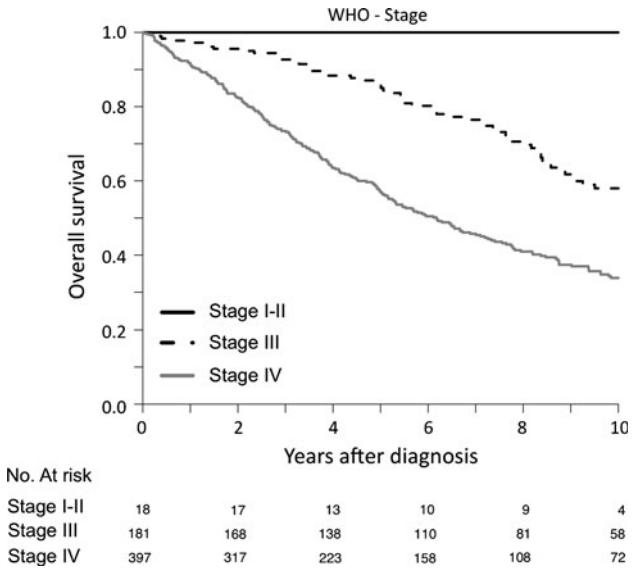

Fig. 2 Overall survival (OS) from time of diagnosis for WHO stage. Number of patients at risk in each group (stage I–II, III,IV) are shown beneath the figure

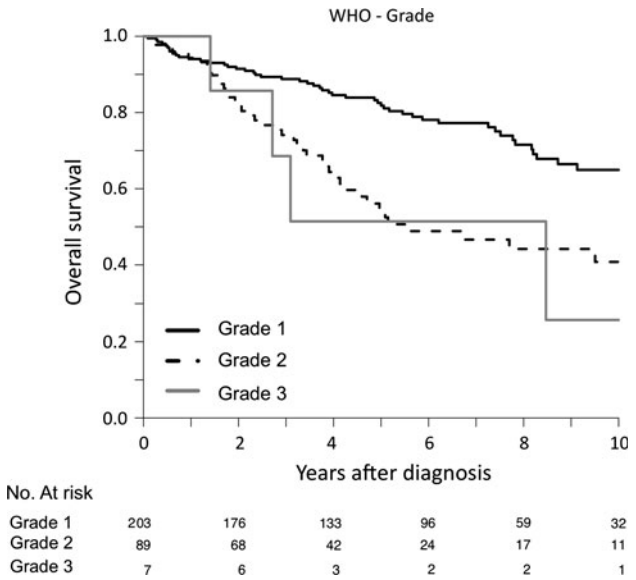

Fig. 3 Overall survival (OS) from time of diagnosis for WHO-grade. Number of patients at risk in each grade (1, 2, 3) are shown beneath the figure

analyses (Tables 2, 4). Calendar year of diagnosis did not affect OS or RS by crude analysis (figure not shown; OS $P = 0.522$, RS $P = 0.742$).

Three different multivariate models for OS and RS were built. WHO stage was not brought into any multivariate analyses to avoid interaction with other variables (lymph node status, liver tumor load), and "extra-abdominal lymph node metastases" was excluded because there were very few cases in one group, leading to uncertainty in the data.

In the first model, we investigated prognostic factors that were readily available in all patients; gender, age at diagnosis, symptoms, carcinoid heart disease, distant abdominal lymph nodes, liver tumor load, and extra-abdominal metastases, and we included all patients with complete data ($n = 562$; Table 4).

In the second model (table not shown), we aimed for testing also for WHO grade, but as this parameter was only available from the late 1990 s, we only included patients diagnosed from 1998 to 2009 ($n = 308$). Complete data for all prognostic factors used in the first model, as well as WHO grade, were available in 260 patients.

In the third model (table not shown) we wanted to perform an adjusted analysis targeting peritoneal carcinomatosis and mesenteric lymph node status, which were findings at operation. Thus, this model included the same parameters as the first model but excluded all patients that were not operated on (patients with complete data, $n = 481$). The parameter "mesenteric lymph nodes" was only included in the OS model, as the excess mortality model was not able to compute a RS that exceeded 100% (survival for cancer subgroup better than the matched population; figure not shown).

Significant negative prognostic factors for OS and RS on crude and multivariate analysis in all three multivariate models included old age at diagnosis, carcinoid heart disease, and liver tumor load (Table 3) High WHO grade (grade 2–3 versus grade 1, hazard ratio [± 95% CI]; 1.83 [1.09–3.08]), peritoneal carcinomatosis (hazard ratio [± 95% CI]; 1.76 [1.26–2.45]), and pathological mesenteric lymph nodes (hazard ratio [± 95% CI]; 3.92 [1.44–10.7]) were also shown to be negative prognostic factors for OS and RS in the second and third multivariate models, respectively. Enlarged distant abdominal lymph nodes and extra-abdominal metastases were prognostic factors on crude analysis, and also in the multivariate models where all patients were included (Table 3), but not in the model where only patients from 1998–2009 were included and where the parameter WHO grade was included (table not shown).

Treatment

Primary tumor and mesenteric lymph node surgery

Eighty-six patients never underwent operation, either because the patient refused or because of poor general health, advanced carcinoid heart disease, advanced age, or metastatic disease with lack of abdominal symptoms and/or radiologically undetectable mesenteric tumor. The remaining 517 patients underwent laparotomy 1–4 times (liver resections excluded), with the intent to resect tumor

Table 3 Multivariate Cox-regression model (overall survival, OS) and Poisson regression model (relative survival, RS) for all patients with complete data

Prognostic factor	HR	95% CI	*P* value	EHR	95% CI	*P* value
Sex						
Male	1.00	(ref.)		1.00	(ref.)	
Female	0.80	(0.63,1.04)	0.091	0.82	(0.59,1.12)	0.213
Age group, years						
<50	1.00	(ref.)		1.00	(ref.)	
50–59	1.77	(0.96,3.28)	0.068	1.66	(0.83,3.32)	0.151
60–69	3.68	(2.10,6.48)	<0.001	3.36	(1.78,6.35)	<0.001
70–74	6.20	(3.40,11.29)	<0.001	5.15	(2.55,10.37)	<0.001
75+	11.28	(6.20,20.53)	<0.001	9.02	(4.43,18.36)	<0.001
Flush and/or diarrhea						
No	1.00	(ref.)		1.00	(ref.)	–
Yes	1.05	(0.79,1.39)	0.736	1.07	(0.73,1.56)	0.743
Carcinoid heart disease						
No	1.00	(ref.)	–	1.00	(ref.)	–
Yes	2.52	(1.76,3.61)	<0.001	2.75	(1.83,4.14)	<0.001
Distant-abdominal lgll.metastases						
No	1.00	(ref.)	–	1.00	(ref.)	–
Yes	1.47	(1.09,1.99)	0.012	1.55	(1.08,2.24)	0.019
Liver tumor load						
No metastases	1.00	(ref.)	–	1.00	(ref.)	–
<5 metastases	1.58	(1.05,2.38)	0.028	2.11	(1.18,3.76)	0.011
5–10 metastases	2.55	(1.79,3.62)	<0.001	3.48	(2.11,5.75)	<0.001
>10 metastases	2.89	(2.04,4.09)	<0.001	4.13	(2.52,6.74)	<0.001
Extra-abdominal metastases						
No	1.00	(ref.)	–	1.00	(ref.)	–
Yes	2.10	(1.35,3.28)	0.001	2.37	(1.44,3.90)	<0.001

HR hazard ratio; *EHR* excess hazard ratio; *CI* confidence interval

Table 4 Overall and relative survival rates as well as crude analysis of surviving using Mantel-Cox (OS) or Poisson regression model (RS) for surgical treatment of primary tumor and mesenteric lymph node metastases

Surgery for primary tumor and mesenteric lymph nodes	OS			RS		
	5 -year	10 -year	*P* Value	5 -year	10 -year	*P* Value
Resective surgery			<0.001			<0.001
Surgery	75 (72;80)	51 (46;56)		82 (78;86)	63 (56;69)	
Exploratory laparotomy only	37 (21;62)	16 (6;43)		43 (21;66)	23 (6;50)	
No surgery	28 (19;40)	6 (2;16)		34 (22;46)	10 (3;22)	
Mesenteric lgllm. after surgery[a]			0.001			0.003
Radically resected	77 (72;82)	52 (46;59)		84 (78;89)	63 (55;71)	
Remaining mesenteric lgllm.	63 (56;71)	38 (31;48)		70 (61;78)	48 (38;59)	

Results are presented as percentages (95% confidence interval)

[a] Patients without lymph node metastases excluded

or to treat complications of the abdominal tumor load. A total of 672 abdominal operations were undertaken, 312 of which were performed in our institution (liver resections for SI-NET and SI-NET unrelated surgery excluded).

Exploratory laparotomy with or without intestinal bypass (bypass $n = 17$, ileostoma $n = 2$) was the initial treatment in 38 patients. Seventeen of these 38 patients underwent reoperative surgery 1–3 times during follow-up,

14 of them undergoing locoregional tumor resection at the reoperation. Indications for the first reoperation were tumor reduction (TR, $n = 8$), acute intestinal obstruction (AIO, $n = 4$), subacute intestinal obstruction (SAIO, $n = 4$), and abdominal pain (AP, $n = 1$).

In total, 493 patients underwent locoregional resective surgery of primary tumor and/or the mesenteric lymph node metastases. Mesenteric lymph-node dissection was attempted during locoregional resective surgery in 405 patients, and 293 of these patients were macroscopically radically resected regarding their mesenteric lymph node metastases. Indications for the first locoregional resective surgery were as follows:: TR ($n = 285$), AIO ($n = 87$), SAIO ($n = 99$), small bowel ischemia (SBI, $n = 14$), intestinal hemorrhage ($n = 5$), and bowel perforation ($n = 3$).

After their first locoregional resective surgery, 107 patients underwent reoperation due to the abdominal tumor load 1–3 times. After the first locoregional resective surgery or a subsequent locoregional reoperative procedure, 313 patients were classified as radically resected regarding their mesenteric metastases, and 168 patients had remaining pathologically enlarged mesenteric lymph nodes.

We analyzed the rate of major complications at our institution separately from complications after surgery elsewhere.

At referring hospitals, the morbidity rate after locoregional resective surgery and exploratory laparotomy ($n = 326$) was 5.8 % ($n = 19$). Mortality after surgery at referring hospitals could not be investigated.

The morbidity rate at our institution after the first locoregional resective surgery (primary tumor and in general extensive mesenteric dissection) ($n = 205$) was 7.8 % ($n = 16$). Total surgery-related 30-day mortality at our institution was 1.6 % (5/312), 30-day mortality after the first locoregional resective surgery was 0.5 % (1/205), and after elective reoperative locoregional resective surgery it as 2.0% (1/49).

Debulking of liver metastases

A total of 465 patients either had liver metastases at baseline ($n = 366$) or developed them during follow-up ($n = 99$). Of those 465 patients, 162 were subjected to various forms of liver debulking. At the end of follow-up, 25 (17%) patients in the treatment group demonstrated no signs of tumor on CT (CT within the final 6 months of follow-up, $n = 151$), whereas five (2.1%) patients in the non-treated group had no detectable liver tumor according to CT (CT within the final 6 months of follow-up, $n = 237$). During the studied time period, 53 patients underwent liver resection once, and four patients underwent liver resection twice. Eight patients underwent hemihepatectomy, 16 patients had segmentectomies or larger wedge resections, and 33 patients had one or several small atypical resections. Major postoperative complications were bile leakage ($n = 1$), and intra-abdominal bleeding that required surgical re-intervention ($n = 2$). One of the patients who experienced a massive bleeding episode after hemihepatectomy died of postoperative complications.

Sixty-eight of our 603 patients were treated with radiofrequency ablation (RFA), and a total of 159 ablation sessions (1–6 sessions per patient) were recorded. Two patients suffered from colonic perforations, and they died within 30 and 90 days after the ablation procedures, respectively.

A total of 113 HAE/HACE were performed in 71 patients (1–6 times per patient). Post–embolization cholecystitis was seen in one of the 37 patients with remaining gallbladder, one patient suffered from a hepatic abscess, and one patient developed acute intestinal ischemia due to abnormal vascular anatomy (with origin of hepatic artery from the mesenteric trunk). No patient died within 90 days after HAE/HACE.

Ethanol injections ($n = 7$) and radioembolization with yttrium-90 microspheres ($n = 12$) were also used sporadically. One patient died of liver failure within 90 days after radioembolization with yttrium-90 microspheres.

Survival analysis regarding abdominal tumor surgery and debulking of liver metastases

Overall survival and RS after diagnosis in the patients who underwent locoregional resective surgery, those who had exploratory laparotomy only, and those who were not operated on differed on univariate analysis (Table 4, Fig. 4). Both OS and RS were also higher in the patients whose metastatic mesenteric lymph nodes were grossly radically removed than in the patients with remaining pathological mesenteric lymph nodes (Table 5).

We used a multivariate model to target possible survival benefits of locoregional resective surgery (table not shown). In this model we included the same parameters as in our first multivariate model for prognostic factors (Table 3) but also added the parameter "locoregional resective surgery" ($n = 562$, table not shown). Locoregional resective surgery was associated with a decreased hazard ratio (95% CI) 0.46 (0.33; 0.65, $P > 0.001$), and a decreased excess hazard ratio 0.41 (0.27; 0.62, $P < 0.001$) when patients "not operated on" were used as the standard of reference (HR 1.0, EHR 1.0).

The OS and RS from time of diagnosis were calculated for various liver debulking procedures, and only patients with liver metastases at diagnosis or during follow-up only were included in this analysis (Table 5).

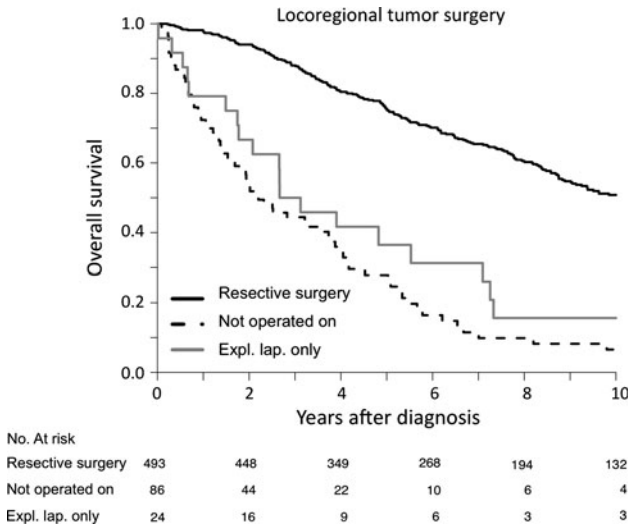

Fig. 4 Overall survival (OS) from time of diagnosis for locoregional resective surgery. Resective surgery = locoregional resection of primary tumor and/or mesenteric lymph nodes, expl. lap. only = exploratory laparotomy only and not operated on = patients not operated on. Number of patients at risk in each group are shown beneath the figure

Survival analysis regarding biotherapy, chemotherapy, and peptide receptor radioactive therapy

Treatment with somatostatin analogs was a negative prognostic factor for OS and RS by univariate analysis (Table 5). In contrast, patients who received interferon treatment fared better than patients without this treatment on univariate analysis (Table 5). Chemotherapy treatment did not affect OS by crude analysis but had a negative impact on RS (not shown in table; OS $P = 0.13$, RS $P = 0.03$). Patients that received peptide receptor radioactive therapy (^{177}lutetium-DOTA-Tyr3-octreotate) fared better than non-treated patients by univariate analysis (Table 5).

Discussion

Small intestinal neuroendocrine tumors are in a majority of patients spread to both lymph nodes and liver at diagnosis [14]. Despite this, relatively favorable 5-year OS and RS of 68% and 75%, were encountered in our series, comparable to results from the Swedish cancer registry of patients diagnosed 1991–2000, showing 5-year OS of 65% and RS 77% [2]. The OS of the SI-NET disease has not improved during the last decades according to a large U.S. study based on the SEER database [35]. However, that database is not complete and has to be considered as biased in information. In contrast, studies based on the Swedish National Cancer Registry have demonstrated improved relative and cause-specific survival over the last decades [2, 36]. In the present study we could not note such a trend, possibly due to referral bias of patients with more advanced disease or co-morbidities during recent years to our tertiary center.

Moreover, mesenteric lymph nodes (only modeled for OS), distant abdominal lymph nodes, liver tumor load, peritoneal carcinomatosis, and extra-abdominal metastases, are to our knowledge for the first time demonstrated to be independent prognostic factors for OS and RS on multivariate analysis. It should, however, be noted that the parameters "distant abdominal lymph nodes" and "extra-abdominal metastases" were non-significant in the multivariate model where WHO grade was included, although this may be due to fewer patients and shorter follow-up diminishing the power of the model. Age, carcinoid heart disease, and WHO grade are confirmed as independent prognostic factors for OS and for the first time shown to be prognostic factors for RS [6, 7, 10].

Older SI-NET patients, especially patients older than 74 years of age at diagnosis, featured a shorter relative

Table 5 Overall and relative survival rates for different methods of liver debulking, medical treatment, and radioactive receptor treatment (PRRT)

Treatment	OS		RS	
	5-year	10-year	5-year	10-year
Debulking of liver metastases[a]				
Liver surgery	86 (77;96)	67 (53;94)	90 (77;98)	76 (56;90)
Radiofrequency ablation	94 (88;100)	75 (63;89)	98 (88;102)	84 (67;95)
Hepatic artery embolization	74 (65;85)	41 (30;55)	78 (65;87)	46 (32;59)
Radioembolization	83 (64;100)	69 (45;100)	87 (49;100)	74 (31;96)
No debulking	53 (47;59)	28 (23;34)	60 (53;66)	38 (30;46)
Biotherapy and radiotherapy				
Somatostatin analog	65 (61;69)	41 (36;46)	72 (67;76)	51 (45;57)
Interferon	71 (67;75)	47 (42;52)	77 (72;81)	57 (51;63)
PRRT (lutetium)	93 (85;100)	75 (61;92)	97 (82;102)	82 (61;95)

[a] Only patients with liver metastases at diagnosis or follow-up

survival and a high excess mortality rate on multivariate analysis, both in the present study and in previous studies published from the Swedish cancer registry [2, 36]. This fact may be interpreted in at least two different ways; either the excess mortality of older SI-NET patients is due to their SI-NET or SI-NET-related complications in a higher degree than in younger patients, or they harbor confounding negative prognostic factors for survival that are absent in the general population in a higher degree than in younger patients with SI-NETs.

Gender was not a prognostic factor for OS or RS, which corresponds to findings from the Swedish cancer registry, and also with Ahmed et al. [2, 9, 36], although two studies ($n = 167$, and $n = 67$) have found female gender to be a negative prognostic factor for survival by crude and multivariate analysis, respectively [37, 38].

Carcinoid heart disease (5- year OS 37%, RS 45%) was an independent negative prognostic factor for survival, and the median survival (2.3 years) was similar to a study of 200 patients with carcinoid heart disease diagnosed 1981–2000 (median survival 2.6 years) and to previous studies from our group [7, 39]. Thus, carcinoid heart disease is one of the strongest negative prognostic factors for survival in SI-NETs.

A functional carcinoid syndrome appears when hormones are released into the circulation, but is usually not present until the patient exhibits liver metastases or large retroperitoneal lymph nodes, as the first passage metabolism of the liver detoxifies hormones that originate from the bowel tumor [4]. Symptoms of the carcinoid syndrome, in our study defined as flush and/or diarrhea, affected the OS and RS on crude but not by adjusted analysis, presumably due to confounders, such as presence of liver tumor or distant-abdominal lymph node metastases in patients presenting with the carcinoid syndrome.

Peritoneal carcinomatosis is present in 10%–33% of gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients, which corresponds with our findings for SI-NETs [40–42]. A former study from our own institution of patients diagnosed 1980–1990 showed a peritoneal carcinomatosis prevalence of 25% [14]. The reason for diversity in prevalence for peritoneal carcinomatosis could be due to referral patterns, number of patients operated on, and site of origin. For example, SI-NETs seem to have a higher prevalence than duodenal or pancreatic NETs [41]. In contrast to our results, one study of GEP-NETs found no survival disadvantage for patients presenting with peritoneal carcinomatosis [41]. In contrast, one study of SI-NETs shows that untreated peritoneal carcinomatosis may cause 40% of all deaths in patients displaying peritoneal carcinomatosis, supporting the fact that this feature may indeed influence survival [40].

We have for the first time demonstrated RS figures for WHO grade and stage, and we were able to visualize a difference in OS and RS between grade 1 and grade 2 SI-NETs, and also to present survival differences between the different WHO stages (I–II versus III versus IV). Using the same WHO staging system, other authors have found 5-year cause-specific survival for stage III (97%), and stage IV (84%) [10] (OS and RS not published), which is equal (stage III) or superior (stage IV) to RS in our series (stage III; 95% and stage IV; 63%). However, RS rates and cause-specific survival rates for SI- NETs have been reported to differ even within the same cohort [2], and consequently these figures are not entirely comparable. Different age profiles, referral patterns, and/or treatment regimes may be other underlying reasons for differences between cohorts. Interestingly, none of the patients subjected to locoregional surgery with apparent stage I–II ($n = 18$) in our study had a recurrence during follow-up, which rendered a 100% OS indicating possible curative resection in these patients, which has also been noted by Jann et al. for 10 of their patients with stage I–II SI-NET (cause-specific survival) [10]. Thirteen of the 18 stage I–II SI-NETs were incidentally detected at operation for unrelated disease, and SI-NETs without mesenteric tumor spread reaching clinical significance should be considered rare. Therefore, when staging a patient as I–II, it is imperative that radical primary tumor surgery and thorough mesenteric dissection with removal of lymph nodes has been performed, and that laparotomy and follow-up with radiological imaging have excluded metastases.

Conflicting results regarding locoregional resection of the primary and mesenteric tumor in metastatic SI-NET have been published, and uncertainties as to what type of surgical procedures have been performed complicate the picture [8, 9]. Our group has recommended an active strategy with early prophylactic locoregional tumor removal, with the intent to prevent or delay abdominal complications from the growth of the mesenteric tumor disease [3, 14, 16, 43]. In agreement with the UKINETS study [9] and others [24, 44, 45], surgical removal of the primary (and mesenteric) tumor was a positive prognostic factor for survival on both crude and multivariate analysis. Remaining mesenteric lymph node metastases seem to have a negative impact on survival, and can be associated with increased risk of abdominal complications, due to progressive tumor growth and fibrosis, which may ultimately cause intestinal obstruction, intestinal ischemia, and a state of malnutrition [3, 4, 14].

Patients with liver metastases who underwent liver resection, liver embolization, and radiofrequency ablation had a respectable OS from date of diagnosis of 86%, 74%, and 94%, respectively. The second largest study of SI-NET tumors reported 78% OS for hepatic surgery and 53% OS

for HAE (radiofrequency ablation not done), although these numbers are not entirely comparable to ours, as these survival figures are from date of diagnosis of liver metastases [9]. Moreover, it is known that debulking by liver resection, radiofrequency ablation, and/or HAE can accomplish palliation of symptoms, decrease in hormone levels, in some series decent progression-free survival [23–25] However, most patients treated with debulking of liver metastases will experience residual or recurrent liver metastases (83% according to follow-up by CT in our study), provided follow-up is long enough [26]. Treatment of liver metastases from SI-NETs should therefore in general be considered as palliative, although exceptions do occur with patients being seemingly cured after long-term follow-up. Debulking procedures can be considered as safe if some pitfalls are avoided. Special attention is warranted for percutaneous radiofrequency ablation of lesions close to the liver capsule, as colon injury and subsequent perforation can occur; these lesions may instead be treated by small liver resections, or with intraoperative/laparoscopic radiofrequency ablation.

Response rates for interferon in NET (neuroendocrine tumors) ranges from 0% to 27% in various trials, and one randomized trial has shown comparable response rates for interferon, somatostatin analogs, and a combination of the two [46, 47]. Our patients treated with interferon had a 5-year OS of 71%, and we believe that is indicated as monotherapy or in combination with somatostatin analogs in SI-NET patients who tolerate the treatment. Drawbacks include adverse effects such as hyperthyroidism, immunosuppression, and depression. Contraindications for interferon include severe heart disease, kidney failure, and liver failure.

Patients treated with somatostatin analogs in our series showed a OS of 65%, which may be considered as good as mainly patients with more advanced disease (and carcinoid symptoms) are allocated to this treatment by selection bias. Treatment with long-acting somatostatin analogs is also considered to offer marked improvement of life-quality in patients with symptoms of the carcinoid syndromeIt may also prevent development or progression of the carcinoid heart disease. One prospective randomized trial [27] has shown prolonged progression-free survival in patients allocated to a treatment protocol with long-acting somatostatin analogs (Sandostatin LAR), and treatment with this drug is indicated in most patients with remaining disease, as well as in those with absence of the carcinoid syndrome.

Peptide receptor radioactive treatment with ^{177}Lu-octreotate has been demonstrated to provide partial remission or stable disease (28%), and apparently prolonged survival compared to historical controls [48], and although our study did not analyze this treatment in detail, our patients that received lutetium had a favorable 5-year survival of 93% (85–100) from time of diagnosis.

A retrospective cohort study, such as ours, has the disadvantage of "confounding by indication" when studying effects of treatment, because it is difficult to distinguish between treatment effect and biased patient selection. Despite efforts to adjust for known prognostic factors by multivariate analyses, unknown disease-specific and unidentified co-morbidities will remain, and thus possibly influence patient survival. We refrained from use of crude and multivariate models including the different medical and liver debulking treatments, as interpretation can be complicated when treatments are multiple and commence at and encompass different time periods. Randomized controlled prospective trials are hence needed to formulate traditional evidence-based criteria for medical and surgical treatment of SI-NETs and survival. However, such trials are difficult to conduct, due to the scarcity of patients and the indolent course of the disease. Treatment effect on survival has at present only been investigated with retrospective cohort analyses, despite the disadvantages with this study design. The evidence base for treatment-effect of SI-NETs is therefore commonly based on such studies and on secondary outcomes such as symptom palliation, hormone values, or disease progression.

In conclusion, we have presented new prognostic factors and have also confirmed known prognostic factors for survival in SI-NET patients. Moreover, patients who underwent locoregional resective surgery, at which the primary tumor and pathological mesenteric lymph nodes were removed, fared better by crude and multivariate analysis regarding survival.

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