Surgical Oncology 35 (2020) 336–343

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: http://www.elsevier.com/locate/suronc

Survival and disease recurrence in patients operated for small intestinal neuroendocrine tumors at a referral hospital

Oddry Folkestad [a], Hans H. Wasmuth [a,b], Patricia Mjønes [b,d], Reidun Fougner [e], Øyvind Hauso [b,c], Reidar Fossmark [b,c,*]

[a] Department of Gastrointestinal Surgery, St Olav's Hospital - Trondheim University Hospital, Trondheim, Norway
[b] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[c] Department of Gastroenterology and Hepatology, St Olav's Hospital - Trondheim University Hospital, Trondheim, Norway
[d] Department of Pathology, St Olav's Hospital - Trondheim University Hospital, Trondheim, Norway
[e] Department of Radiology, St Olav's Hospital - Trondheim University Hospital, Trondheim, Norway

ARTICLE INFO

Keywords:
Neuroendocrine tumours
Small intestine
Surgery
Clinical outcome
Patient survival

ABSTRACT

Background and objectives: Small intestinal neuroendocrine tumors (SI-NETs) are slow growing but have frequently metastasized at the time of diagnosis. Most patients are operated with either curative intent or with intent to prolong overall survival. In the current study we have examined overall and disease-free survival in patients operated for SI-NETs.
Methods: All patients with a histological diagnosis of SI-NET at St Olav's hospital in the period 1998–2018 were reviewed retrospectively. Patient, disease and treatment characteristics including European Neuroendocrine Tumor Society (ENETS) TNM staging classification, surgery type, time to recurrence and survival were recorded.
Results: A total of 186 patients were identified, whereof 54.3% male, median age at operation 68 years. The majority (n = 141 (75.8%)) underwent elective surgery and surgery was considered curative (radical) in 120 (64.5%) patients. Median estimated overall survival was 9.7 years (95% CI 7.6–11.8) for the entire population. Stage of disease, carcinoid heart disease, age, elective surgery, preoperatively known SI-NET, curative surgery and synchronous cancer were associated with survival in a multivariate analysis. Thirty-six of 120 (30%) patients had disease recurrence after a median follow-up time of 5.5 years, with a median estimated recurrence-free survival of 9.1 (5.4–12.9) years. Recurrence free survival was associated with age and synchronous cancer.
Conclusions: Patients with SI-NETs had long overall survival which seemed influenced by stage of disease, presence of carcinoid heart disease, an elective surgery, preoperatively known SI-NET, age and synchronous cancer. Appropriate preoperative diagnostic procedures and elective surgeries seem beneficial and should be aimed for.

1. Introduction

Neuroendocrine tumors (NETs) of the jejunum and ileum most often derive from serotonin-producing enterochromaffin cells and are referred to as small intestinal NETs (SI-NETs). The annual incidence of SI-NET has increased over the last decades with reported incidence rates of 0.32–1.12/100,000 in epidemiological studies [1–4]. However, in a large Swedish autopsy series in a population where the majority did not have a pre-mortem diagnosis of SI-NET, the prevalence was considerably higher and suggests that incidence may be above 0.5% [5,6].

The primary SI-NET is often small with median size reported to be ≤ 1.5 cm [7,8], but these tumors generally spread early to mesenteric lymph nodes, and many patients also present with liver metastases at the time of diagnosis [9,10]. Tumors ≥1.5 cm have usually metastasized at the time of discovery [8,11]. The primary tumor and mesenteric metastases are often accompanied by pronounced mesenteric desmoplasia which may cause intestinal or vascular obstruction. SI-NETs are thus often diagnosed during acute surgery for intestinal obstruction or segmental small bowel ischemia. Compared to other malignancies SI-NETs have an advantageous survival, with 5-year overall survival

* Corresponding author. Department of Gastroenterology and Hepatology, St Olav's hospital - Trondheim University Hospital, Prinsesse Kristinas gate 1, 7030, Trondheim, Norway.
E-mail address: reidar.fossmark@ntnu.no (R. Fossmark).

https://doi.org/10.1016/j.suronc.2020.09.015
Received 30 April 2020; Received in revised form 2 July 2020; Accepted 13 September 2020
Available online 18 September 2020

rates in the range 61–77% [12–14]. Patients with localized, regional disease and some patients with distant metastases are considered for surgery with curative intent [15]. Resection of the primary tumour and locoregional lymph node metastases improves outcome and may result in a 10-year disease specific survival rate of 100% in stage I and II patients, and a 10-year survival rate in stage III disease of more than 80% [10]. Recurrence rates after resection with curative intent range from 31% to 42% after an observation time of 5.5–7.1 years [7,16–18], and many patients have micrometastases to the liver that are too small to be detected by preoperative radiological imaging [12,19]. However, median overall survival for patients having undergone surgery has been reported to be 8.4 years [12].

The study aimed to assess the overall survival after surgical intervention and recurrence rate after presumed curative surgery for our cohort of patients with SI-NET, adjusted for factors that might affect the outcome.

2. Materials and methods

2.1. Patients

A retrospective analysis of patient records for patients with a histologically confirmed diagnosis of SI-NET in the jejunum or/and ileum was conducted. A total of 194 patients were identified from the archives of Department of Pathology at St Olav's hospital by searching for the SNOMED codes T64xxx (small intestinal tumour) and M824xx (NET) in the time period between January 1st' 1998 and May 31st' 2018. However, eight patients were only biopsied (endoscopic, percutaneous or during diagnostic laparoscopy) without subsequent bowel resection and were excluded from further review. The number of patients that were further reviewed was therefore 186, whereof 154 patients were operated at St Olav's hospital and 32 patients were operated at adjacent local hospitals. The analysis was approved by the Norwegian Centre for Research Data and the Regional Committee for Medical and Health Research Ethics, South-East Norway.

2.2. Radiological imaging

All patients underwent computed tomography (CT) preoperatively. Presence and size of assumed metastatic mesenteric lymph nodes, distant abdominal lymph node metastases, liver metastases and extra-abdominal metastases at baseline was noted. A preoperative SI-NET diagnosis was categorized as known in patients with histological evidence of SI-NET (typical NET findings in hematoxylin and eosin stained tissue sections and immunoreactivity for chromogranin A by immunohistochemical examination) or radiological imaging described by an expert radiologist (R Fougner) as suggestive of SI-NET (i.e. hypervascular tumors in the intestinal wall, hypervascular mesenterial mass with unsharp borders and desmoplastic reaction in the surroundings, often with calcification, enlarged hypervascular lymph nodes along the mesenterium, hypervascular liver metastases).

2.3. Surgical and non-surgical treatment

We recorded the type and method of surgical resection and whether it was an elective or emergency surgery. Surgery was defined as emergency if performed during an acute hospital admission. The operation was categorized as "curative" if the patient was without macroscopic tumour tissue at the end of surgery. Further treatment during follow-up was recorded, this included pharmacological treatment, embolization of liver metastases, surgical removal of metastases and peptide receptor radionuclide treatment (PRRT).

2.4. Disease stage and severity

Disease stage and severity at the time of diagnosis was assessed by the TNM-classification 8th edition [20] and the European Neuroendocrine Tumour Society (ENETS) staging system [15] based on radiological imaging, surgical reports and histopathological examination. ENETS classifies stage 0-IIIa as localized disease, stage IIIb as regional disease and stage IV as distant metastatic disease [15]. Tumor stage was defined as localized when the tumor was confined to the bowel wall, regional when there were metastases to locoregional lymph nodes, and distant disease when there were distant metastases to other organs, peritoneal spread, retroperitoneal spread or metastases to distant lymph nodes. The presence of carcinoid heart disease was recorded. Proliferation rates were estimated by the Ki-67 index in the histopathology reports and classified according to the World Health Organisation (WHO) grade (G1-3) [21].

2.5. Survival and disease recurrence

The patients were followed until they were registered as dead or until last follow-up visit, resulting in a median follow-up time of 4.7 years (0.0–20.0). CT scans were performed at intervals of 6–24 months, increasing with time after surgery according to evolving ENETS guidelines [22,23] in patients operated with curative intent, if disease recurrence was suspected during follow-up or to evaluate treatment effect or disease progression. Deaths were categorized as attributable to SI-NET or not based on information in the medical record about the clinical course of the SI-NET and other disease. Patients who died due do metastasis from SI-NET, tumor compression, carcinoid heart disease, acute bowel obstruction or other conditions attributable to advanced SI-NET disease, were listed as SI-NET related. In patients with insufficient information the cause of death was categorized as unknown.

2.6. Statistical analyses

Descriptive data are presented as frequency (n (%)) or median (range), as appropriate. Overall survival with comparisons between groups was analyzed by Kaplan-Meier with log-rank test. Variables considered to potentially influence survival or recurrence were included in univariate and multivariate analyses by using the Cox proportional hazards model. Hazard ratios (HR) with 95% confidence intervals (CIs) are presented. The Fishers exact test was used for comparisons of categorical variables between groups. Two-sided Mann-Whitney test was used for comparisons of numerical variables between two groups. P-values < 0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient demographics

There were 101 (54.3%) men and 85 (45.7%) women (Table 1). The median age at surgery was 68.0 years (31.1–91.1). The patients operated in an emergency setting were older than patients who underwent elective surgery (70.7 years vs. 65.0 years, $p < 0.05$).

3.2. Surgical procedures and indications for surgery

Laparotomy with resection that included the primary tumor was performed in all 186 patients. The standard surgical approach for removal of the primary tumor and regional metastases (locoregional resective surgery) was a bowel resection combined with an extensive mesenteric dissection for removal of mesenteric lymph node metastases. The most frequently performed procedures were resection of the small intestine (n = 112 (60.2%)), ileocolic resection (n = 33 (17.7%)) and right hemicolectomy (n = 35 (18.8%)). One patient underwent subtotal colectomy with a segmental resection of the small intestine. Minimal resection of the tumor, without a formal bowel resection of the small

Table 1
Patient demographics, disease characteristics and treatment during follow-up in patients operated for SI-NETs.

	Total (n = 186)	Elective operation (n = 141)	Emergency operation (n = 45)	p
Age, median (range)	68.0 (31–91)	68.0 (31–87)	70.0 (41–91)	<0.05
Male, n (%)	101 (54.3)	75 (53.2)	26 (57.8)	0.290
Preoperative SI-NET diagnosis known, n (%)	138 (74.2)	119 (84.4)	19 (42.2)	0.001
Preoperative SI-NET diagnosis unknown, n (%)	48 (25.8)	22 (15.6)	26 (57.8)	0.001
ENETS disease n (%)				
Localized	23 (12.3)	15 (10.6)	8 (17.8)	0.112
Regional	101 (54.3)	76 (53.9)	25 (55.6)	
Distant	61 (32.8)	50 (35.4)	11 (24.4)	
WHO grade*, n (%)				
G1	114 (61.3)	84 (59.6)	30 (66.7)	0.712
G2	59 (31.7)	45 (31.9)	14 (31.1)	
unknown	13 (7)	12 (8.5)	1 (2.2)	
Carcinoid heart disease, n (%)	7 (3.7)	7 (5)	0	0.129
Synchronous cancer, n (%)	27 (14.5)	21 (14.9)	6 (13.3)	0.796
Curative surgery, n (%)#	120 (64.6)	93 (66.0)	27 (60.0)	0.526
Recurrence, n (%)	36 (30.0)	27 (29.0%)	9 (33.3)	0.693
Deaths, n (%)	78 (41.9)	52 (36.9)	26 (57.8)	0.014
Due to surgical complications	4 (5.4)	0	4 (8.9)	<0.001
30-day mortality	4 (2.2)	0	4 (8.9)	
90-day mortality	8 (4.3)	2 (1.4)	6 (13.3)	
Treatment during follow-up, n (%)				
SSA	84 (45.2)	68 (42.2)	16 (35.6)	0.138
Interferon	17 (9.1)	15 (10.6)	2 (4.4)	0.211
TAE	17 (9.1)	15 (10.6)	2 (4.4)	0.203
Cytostatic treatment	5 (2.7)	4 (2.8)	1 (2.2)	0.815
PRRT	13 (7.0)	11 (7.8)	2 (4.4)	0.431
Liver surgery	6 (3.2)	6 (4.3)	0	0.161

*WHO grade available for n = 173. #Macroscopic tumour free after surgery. ENETS: European Neuroendocrine tumour Society; WHO: World Health Organization; G: grade; SSA: somatostatin analogue; TAE: trans arterial embolization of liver metastases; PRRT: peptide receptor radionuclide therapy.

intestine, was performed in five patients. A total of five patients also had liver resections performed with curative intent; two patients had liver resections performed at the same time as the SI-NET operation, while three patients had planned liver resections performed as a stage two surgery. A total of 120 patients (64.5%) had no known residual tumor load after their first operation and were considered curatively operated.

The majority of the operations were elective (n = 141 (75.8%)). SI-NET disease was known preoperatively in 138 (74.2%) patients. Among patients who underwent elective procedures 119 (84.4%) patients had a preoperatively known SI-NET, while this was true for only 19 (42.2%) of the patients who underwent an emergency operation (p < 0.001). In 48 (25.8%) patients the SI-NET diagnosis was unknown before surgery. Twenty-six (54.2%) of 48 patients were operated in an emergency setting. In 17 (35.4%) patients the indication for surgery was an other synchronous cancer, in the majority of cases colorectal cancer. Fourteen of the patients with a preoperatively known other cancer were operated in an elective setting, while three patients had emergency operations due to bowel obstruction. Two (4.2%) patients were operated due to benign lesions in the colon and pancreas. Seventeen (35.4%) of 48 patients were operated due to acute bowel obstruction, six (12.5%) patients due to severe gastrointestinal bleeding, two (4.2%) patients due to chronic severe abdominal pain without fulminant bowel obstruction, while four (8.3%) patients were operated due to other benign diseases.

3.3. Disease stage and severity at time of diagnosis

Disease characteristics are presented in Table 1. Twenty-three (12.4%) patients had localized disease, 101 (54.3%) patients had regional disease and 61 (32.8%) patients had distant metastatic disease. All patients had histologically either G1 (n = 114 (61.3%)) or G2 (n = 59 (31.7%)) tumors. Seven (3.7%) patients had carcinoid heart disease.

The median number of resected lymph nodes was 5.0 (0–62) for the whole cohort (Table 2).

There were less lymph nodes resected in the emergency group, median 3.0 (0–62) vs. 6.0 (0–42) in the elective group (p = 0.095). The histological specimen contained at least one lymph node in 153 (82.2%) patients, and at least one positive lymph node was identified in 123 (66.1%) patients. Lymph nodes were found in 85.8% of the histological specimens in the elective surgery group vs. 71.1% in the emergency group (p = 0.025). Positive lymph nodes were also found more frequently in the elective group compared to the emergency group;

Table 2
Tumour pathology in patients operated for SI-NETs.

		Total (n = 186)	Elective operation (n = 141)	Emergency operation (n = 45)	p
T stage, n (%)					
1		12 (6.4)	9 (6.4)	3 (6.7)	0.82
2		42 (22.6)	32 (22.7)	10 (22.2)	
3		94 (50.5)	74 (52.5)	20 (44.4)	
4		34 (18.3)	24 (17)	10 (22)	
Unknown		4 (2.2)	2 (1.4)	2 (4.4)	
N stage, n (%)					
0		22 (11.8)	16 (11.3)	6 (13.3)	0.704
1		70 (37.6)	54 (38.3)	16 (35.6)	
2		76 (40.9)	60 (42.6)	16 (35.6)	
Unknown		18 (9.7)	11 (7.8)	7 (15.6)	
M stage, n (%)					
M0		124 (66.7)	90 (63.8)	34 (75.6)	0.199
M1a		38 (20.4)	32 (22.7)	6 (13.3)	
M1b		6 (3.2)	6 (4.3)	0	
M1c		17 (9.1)	12 (8.5)	5 (11.1)	
Unknown		1 (0.5)	1 (0.7)	0	
Multifocal primary tumors, n (%)		59 (31.7)	47 (33.3)	12 (26.7)	0.453
Lymph nodes					
≥1 node resected, patients (%)		153 (82.2)	121 (85.8)	32 (71.1)	0.025
≥1 node positive, patients (%)		123 (66.1)	99 (70.2)	24 (53.3)	0.038
Nodes evaluated per patient, median (range)		5.0 (0–62)	6.0 (0–42)	3.0 (0–62)	0.095
Nodes positive per patient, median (range)		1.0 (0–14)	1.0 (0–14)	1.0 (0–10)	0.038
Resection margins, n (%)[a]					
R0+R1		159 (85.5)	127 (90.1)	32 (71.1)	
R2	27 (14.5)	14 (9.9)	13 (28.9)	0.002	
R0	140 (75.3)	111 (78.7)	29 (64.4)		
R1	19 (10.2)	16 (11.3)	3 (6.7)		
R2	27 (14.5)	14 (9.9)	13 (28.9)	0.006	
Curative surgery[b]	120 (64.5)	92 (65.2)	27 (60.0)	0.524	

[a] For primary and mesenteric tumors.
[b] Macroscopic tumour free after surgery.

70.2% vs. 53.3% (p = 0.038). In 54.2% (n = 26) of the patients with a preoperatively unknown SI-NET at least one lymph node was found in the specimen versus 92% (n = 127) in the group with preoperative known SI-NET (p < 0.001). At least one positive lymph node was found in 35.4% (n = 17) of histological specimens of the patients with preoperatively unknown SI-NET vs. 76.8% (n = 106) in patients with preoperatively known SI-NET (p < 0.001).

3.4. Treatment during follow-up

Treatment during follow-up is presented in Table 1. Treatment with a long-acting somatostatin analogue was given to 84 (45.2%) patients; 68 (42.2%) patients in the elective group and 16 (35.6%) patients in the emergency group (p = 0.138). Interferon treatment was given to 15 patients (10.6%) in the elective group versus two (4.4%) patients in the emergency group (p = 0.203). The same 17 patients who were treated with interferon were also treated with transarterial embolization; 15 (10.6%) patients in the elective group versus two (4.4%) patients in the emergency group. Thirteen (7.0%) of 186 patients received treatment with PRRT; eleven (7.8%) and two (4.4%) patients in the elective and emergency group, respectively (p = 0.431).

3.5. Survival

Seventy-eight (41.9%) patients died during follow-up. Four (2.2%) patients (median age 81.5 (72.1–91.1) years) died within few days after emergency operations due to surgical complications. The 30-day mortality was 2.2% and the 90-day mortality was 4.3%. Thirty-three (42.3%) of 78 patients died due to SI-NET disease. Twenty-seven (14.5%) of 186 patients had an other synchronous cancer whereof 19 (10.2%) patients had colorectal cancer. Fifteen (19.2%) patients died from the synchronous cancer. The cause of death was unknown in 26 (14.1%) of 78 patients.

Median estimated overall survival was 9.7 years (95% CI 7.7–11.6) and five-year overall survival was 75.8%. Median estimated overall survival for localized, regional and distant disease stage was 11.6 years (95% CI 5.7–17.5), 11.3 years (95% CI 9.6–12.9) and 6.9 years (95% CI 4.1–9.6), respectively (Fig. 1). Five-year survival was 69.6%, 85.1% and 62.2% (p = 0.005) for localized, regional and distant disease, respectively. Nine out of 23 patients (39.1%) staged as localized SI-NET were operated for other synchronous intraabdominal cancers. The synchronous cancer affected survival in this patient group.

Patients with G1 tumors had a median estimated survival of 10.0 years (95% CI 7.2–12.9) vs. 9.5 years (95% CI 5.3–13.7) for patients with G2 tumors (p = 0.78). The five-year survival for patients with G1 or G2 tumors was 76.3% for both groups.

A higher proportion of patients who were operated in an emergency setting died during follow-up compared to patients who were operated in an elective setting (26 of 45 (57.8%) vs. 52 of 141 (36.9%), p = 0.014). Median estimated survival of patients who were operated in an elective setting was 10.2 years (95% CI 8.2–12.3) vs. 6.8 years (CI 95% 5.3–8.4) for the patients in the emergency group (p = 0.005) (Fig. 2), while the five-year survival was 78.7% and 66.7%, respectively.

Patients with a preoperatively known SI-NET diagnosis had a median estimated survival of 10.2 years (95% CI 8.1–12.3), while the median estimated survival of the patients with preoperatively unknown SI-NET was 7.3 years (95% CI 4.0–10.6), (p = 0.032). Five-year overall survival rates were 79.0% and 66.7%, respectively (Fig. 3).

Median estimated survival for patients who were considered tumour free after operation was 11.5 years (9.8–13.2 years), compared to 6.2 years (95% CI 3.2–9.3 years) (p < 0.001) for those with residual tumour load. Five-year survival was 85.8% and 57.6% (p < 0.001), respectively (Fig. 4).

In a Cox proportional hazard regression model, age at surgery, elective surgery, disease stage, radical surgery, known SI-NET at time of surgery, carcinoid heart disease and synchronous cancer at the time of operation, were independently associated with overall survival (Table 3).

3.6. Surgery with curative intention and disease recurrence

A total of 120 (64.5%) patients had curative intent surgery. Thirty-six of these patients (30.0%) had recurrence after curative intent surgery after a median follow-up time of 5.5 years (0.0–20.0). The recurrence was found in the liver alone in 20 (55.6%) of the 36 patients whereas ten (27.8%) patients had recurrence in both the liver and other

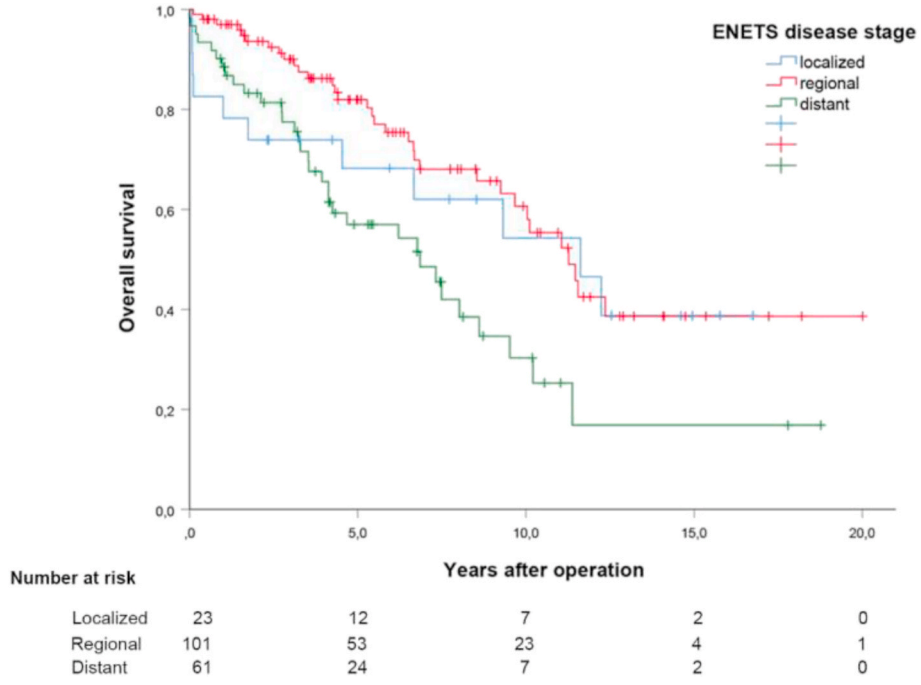

Fig. 1. Overall survival in patients operated for small intestinal neuroendocrine tumors, stratified by ENETS disease stage.

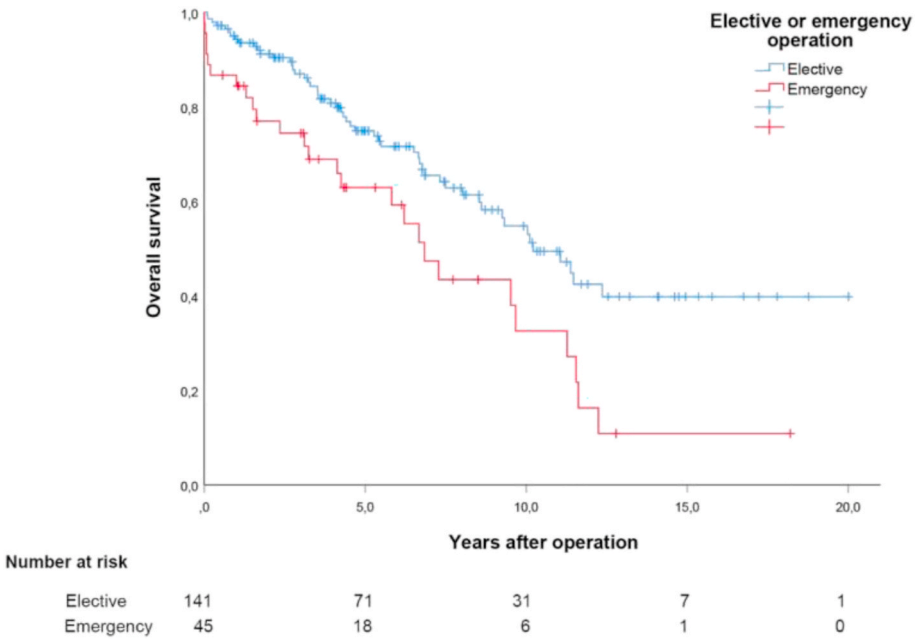

Fig. 2. Overall survival in patients operated for small intestinal neuroendocrine tumors, stratified by whether an elective versus emergency operation was performed.

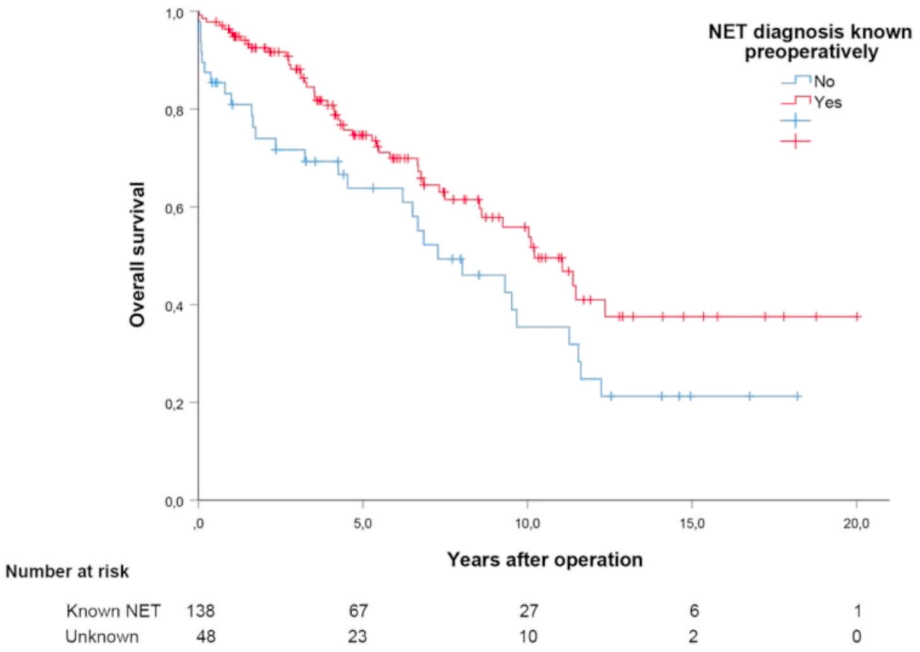

Fig. 3. Overall survival in patients operated for SI-NET, stratified by a preoperatively known SI-NET diagnosis or not.

organs. Recurrence was found in mesenteric lymph nodes alone in three (8.3%) patients, in retrocrural or retroperitoneal lymph nodes in two (5.6%) patients and a new primary tumour in the small intestine was found in one patient (2.8%).

The rate of curative intent resection did not differ between patients operated by elective vs. emergency procedures (66.0% vs. 60.0%, p = 0.526).

Median estimated recurrence free survival was 9.3 years (95% CI 7.4–11.2) and the five-year recurrence free survival was 79.2%. Median estimated recurrence free survival was 10.0 years (95% CI 7.8–12.3) for G1 tumors vs. 6.3 years (95% CI 4.7–7.9) for G2 tumors (p = 0.152). Five-year recurrence free survival was 80.8% for G1 tumors vs. 78.9% for patients with G2 tumors.

In a Cox proportional hazard regression analysis of recurrence free survival, a synchronous cancer (HR 2.81 (95% CI 1.30–6.10), p = 0.009) and age (HR 1.03 (95% CI 1.00–1.06), p = 0.009) were independently associated with disease recurrence (Table 4).

4. Discussion

Most patients with SI-NET have regional or distant metastatic disease at the time of diagnosis, in the current patient study as well as in other studies. In this patient study 54.3% had regional disease while 32.8% had distant metastases to the liver or other distant sites. A median estimated overall survival of 9.7 years was found, which is comparable to the median survival of 8.4 years in patients operated in Uppsala,

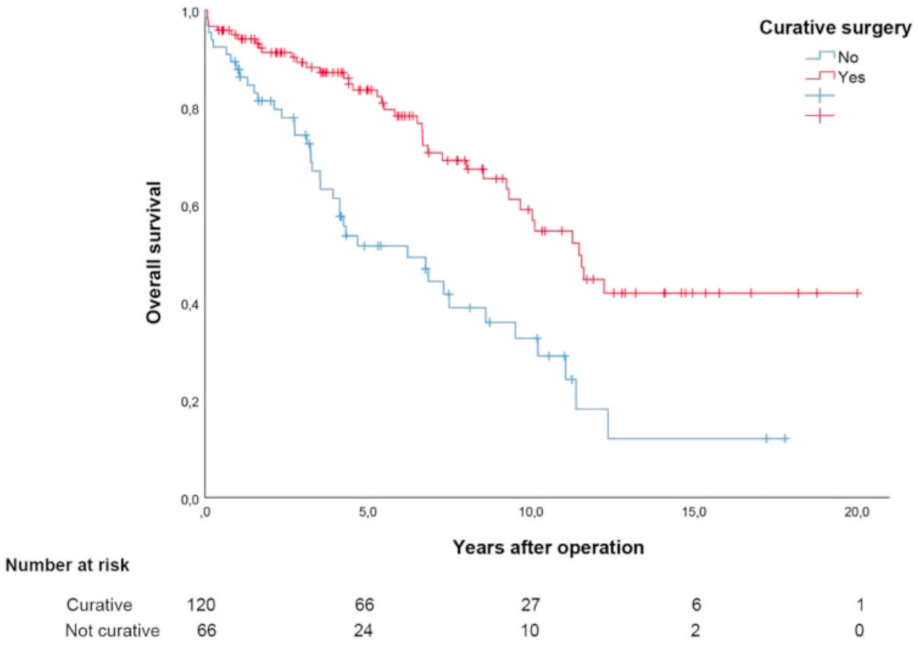

Fig. 4. Overall survival in patients operated for SI-NETs stratified by whether or not they were macroscopically tumour free after surgery (curative surgery).

Table 3
Univariate and multivariate Cox regression analysis of variables associated with overall survival in patients operated for SI-NETs.

Variable	Univariate		Multivariate	
	Hazard-ratio [95% CI]	p	Hazard -ratio [95% CI]	p
Carcinoid heart disease	3.89 [1.77–8.85]	0.001	7.64 [2.87–20.35]	0.000
Emergency surgery	1.95 [1.22–3.13]	0.005	2.15 [1.09–4.28]	0.028
ENETS stage	1.56 [1.08–2.25]	0.018	2.01 [1.07–3.79]	0.030
Synchronous cancer	2.27 [1.31–3.94]	0.004	2.01 [1.02–3.97]	0.045
WHO grade	1.15 [0.69–1.92]	0.597	1.35 [0.75–2.44]	0.321
Sex	1.33 [0.85–2.07]	0.215	1.13 [0.68–1.11]	0.629
Age	1.06 [1.04–1.09]	0.000	1.10 [1.07–1.14]	0.000
Single vs multiple tumors	1.03 [0.95–1.11]	0.464	0.95 [0.50–1.78]	0.860
Lymph nodes in the specimen	0.99 [0.96–1.02]	0.419	0.87 [0.97–1.03]	0.382
R0 resection	1.59 [1.21–2.08]	0.001	0.82 [0.53–1.27]	0.382
Operated at St Olavs Hospital	1.31 [0.75–2.30]	0.349	0.80 [0.38–1.70]	0.566
Diagnosis known preoperatively	0.61 [0.38–0.96]	0.034	0.47 [0.22–0.99]	0.049
Curative surgery[a]	0.39 [0.25–0.60]	0.000	0.25 [0.10–0.64]	0.004

ENETS: European Neuroendocrine Tumour Society; WHO: World Health Organization.
[a] Macroscopic tumour free after surgery.

Table 4
Univariate and multivariate Cox regression analysis of variables associated with recurrence free survival in patients who were macroscopic tumour free after operation for small intestinal neuroendocrine tumors.

Variable	Univariate		Multivariate	
	Hazard-ratio [95% CI]	p	Hazard -ratio [95% CI]	p
Synchronous cancer	2.51 [1.38–4.58]	0.003	2.81 [1.30–6.10]	0.009
ENETS stage	1.40 [0.82–2.40]	0.217	1.81 [0.82–4.02]	0.145
WHO grade	1.79 [1.03–3.10]	0.040	1.51 [0.83–2.76]	0.177
≥1 lymph node in specimen	1.34 [0.74–2.43]	0.335	1.51 [0.51–4.20]	0.433
Emergency surgery	1.24 [0.71–2.18]	0.447	1.22 [0.62–2.40]	0.571
≥1 positive lymph node in specimen	1.30 [0.77–2.22]	0.328	1.20 [0.52–2.77]	0.663
Single vs multiple tumors	1.09 [0.63–1.89]	0.767	1.14 [0.60–2.17]	0.686
Age	1.03 [1.01–1.06]	0.009	1.03 [1.00–1.06]	0.009
Sex	1.13 [0.68–1.87]	0.635	0.91 [0.49–1.69]	0.758
Diagnosis known preoperatively	0.86 [0.51–1.45]	0.559	0.50 [0.24–1.03]	0.059

ENETS: European Neuroendocrine Tumour Society; WHO: World Health Organization.

Sweden [12], and overall survival of 9.3 years in Oslo, Norway, where 89% of the patients underwent resection of the primary tumour [24]. ENETS stage and WHO grade are both accepted prognostic factors [15] which are used in clinical practice. In this cohort ENETS stage was significantly associated with survival, whereas WHO grade was not. In a multivariate analysis which also included age and ENETS stage, carcinoid heart disease was found to be the strongest negative prognostic factor with a HR 7.6, which is similar to findings in other patient cohorts [12,24,25]. Interestingly, both elective surgery and a preoperatively known SI-NET were discovered to be independent positive prognostic factors. Such circumstances are of particular importance as they to some extent may be influenced by the treating physicians. Patients who underwent elective surgery had longer median survival compared to patients who were operated with an emergency procedure (10.2 vs. 6.8 years, $p < 0.005$ in univariate analysis). A study by Eriksson et al. found reduced survival in patients who had elective surgery compared to emergency surgery, however, 74% of the patients had stage IV disease, whereas 76% of the patients undergoing emergency surgery had stage I-IIIb disease [26]. This illustrates the value of multivariate analyses to

assess determinants of prognosis. Studies of other gastrointestinal cancers have demonstrated that emergency surgery is associated with increased mortality, as observed for instance in colorectal cancer [27]. The role of timing of surgery in SI-NETs has been studied to some extent and Manguso et al. did not find that timing seemed to affect overall survival [7]. However, Lewis et al. [28] found that both emergency operation and inferior lymph node harvest were associated with inferior long-term survival in colorectal cancer, as also observed in this cohort, and lymph node harvest is one factor that could explain how timing of surgery could affect survival.

Patients with a preoperatively known SI-NET had longer median estimated overall survival than patients with unknown diagnosis before surgery (10.2 years vs. 7.3 years, $p = 0.032$ in univariate analysis), whereas recurrence free survival did not differ between these groups. The observations suggest that a more targeted diagnostic work-up, including cross-sectional imaging, could improve planning of surgery and outcome.

The value of debulking surgery in NETs has been studied and debated for decades [29,30]. Surgical removal of tumor recurrences or ablative treatment of liver metastases during follow-up was only performed in a minority of our patients. Although observational studies suggest that liver debulking or liver directed treatment may prolong survival, such studies are prone to selection bias and when using propensity score matched comparisons, liver directed therapies do not seem to increase survival [31].

The value of extensive lymph node dissection during surgery has been studied for many cancers. In the study of Manguso et al. [7] positive lymph nodes were found in 90% and 74.9% of the specimens after elective and emergency procedures, respectively. In the present study lymph nodes were found in 121 (85.8%) of 141 histologic specimens in the elective surgery group versus 32 (71.1%) of 45 in the emergency group ($p = 0.025$), as an indication of a more extensive surgical procedure in the elective setting. Positive lymph nodes were also found more frequently in specimens after elective than emergency procedures (70.2% vs. 53.3%, $p = 0.038$). Although the proportions are lower than reported by others [7], the differences are of comparable magnitude and the findings suggest that insufficient lymph node harvest during emergency surgeries could affect long-term survival. A recent study suggests that at least eight lymph nodes should be resected for more accurate staging and determination of prognosis [32].

In 14.5% of the patients in this cohort the SI-NETs were found during surgery for an other synchronous abdominal cancer, mainly colon cancer, and the non-neuroendocrine cancers affected overall survival significantly. The increased risk of second primary malignancies in patients with gastrointestinal NETs is well documented with colorectal cancer and breast cancer as the second primary malignancies with highest absolute risks, but also with an increased incidence compared to the background population [33,34]. In a Swedish population based autopsy study 48% of individuals with SI-NET had other malignancies, with colorectal cancer as the most prevalent - found in 10% of individuals with SI-NET [5]. The same authors found that patients with SI-NET had twice as high risk for developing colon cancer compared to controls [5]. Haugvik et al. reported that a family history of any cancer and a family history of colorectal cancer was associated with an increased risk of SI-NET. The relative contribution of genetic predisposition and life-style factors is not known [35].

After a median follow-up of 5.5 years disease recurrence was diagnosed in 30% of the patients who were considered tumor free after surgery. Others have observed that with even longer follow-up time, recurrence is diagnosed in the majority of patients with SI-NETs [36]. Tumor biological characteristics, including the tendency to early micrometastases to lymph nodes and the liver [19,37,38], may explain such clinical observations. Nevertheless, numerous non-randomized studies suggest that patients who are macroscopically tumor free after surgery have a survival benefit. Although a preoperatively known SI-NET diagnosis tended to be associated with recurrence free survival in the multivariate analysis (HR 0.50), neither elective surgery nor a preoperatively known SI-NET were factors significantly associated with recurrence free survival in the present patient cohort. In fact, patient age and a synchronous cancer were the only factors that were significantly associated with recurrence free survival. Risk factors for disease recurrence have been studied by Le Roux et al. who found that emergency operation, preoperatively unknown diagnosis of SI-NET, distant mesenteric lymph-node metastases and multiple primary tumors were associated with shorter disease free survival in a multivariate analysis [16]. Patients operated in an emergency setting had a four times higher risk of recurrence and inadequate perioperative exploration was significantly higher in the emergency group [16]. Manguso et al. have compared outcomes after elective versus emergency surgery for SI-NETs and found more frequent recurrences in patients operated in an emergency setting (41.6%) vs. patients operated with elective procedures (33.6%) [7].

Strengths of this study include the long-term and almost complete follow-up of the patient cohort, as well as an evaluation of not only survival, but also disease recurrence. Analyses based on large patient registries are often limited by the lack of information about disease recurrence, a factor which is particularly important when evaluating outcome of surgery in the relatively indolent SI-NETs. The study was limited by its retrospective design and patients were thus not randomized with respect to the various factors that could affect outcome. Although multivariate analyses were performed residual confounding cannot be ruled out.

5. Conclusions

This study shows that overall survival in the studied cohort of SI-NET patients is comparable to the outcome reported from other Western centers. Disease stage according to ENETs classification, carcinoid heart disease, synchronous cancer, preoperatively known SI-NET, elective surgery, curative surgery and age were all associated with overall survival, whereas synchronous cancer and age were associated with recurrence free survival. Thorough preoperative diagnostic procedures and achieving peroperative locoregional control seem beneficial.

Funding

None.

Declaration of competing interest

None.

Acknowledgment

The work received funding from St Olav's Hospital - Trondheim University Hospital, Trondheim, Norway.

References

[1] T. Ito, H. Sasano, M. Tanaka, R.Y. Osamura, I. Sasaki, W. Kimura, K. Takano, T. Obara, M. Ishibashi, K. Nakao, R. Doi, A. Shimatsu, T. Nishida, I. Komoto, Y. Hirata, K. Nakamura, H. Igarashi, R.T. Jensen, B. Wiedenmann, M. Imamura, Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan, J. Gastroenterol. 45 (2) (2010) 234–243.

[2] J.C. Yao, M. Hassan, A. Phan, C. Dagohoy, C. Leary, J.E. Mares, E.K. Abdalla, J. B. Fleming, J.N. Vauthey, A. Rashid, D.B. Evans, One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States, J. Clin. Oncol. 26 (18) (2008) 3063–3072.

[3] O. Hauso, B.I. Gustafsson, M. Kidd, H.L. Waldum, I. Drozdov, A.K. Chan, I. M. Modlin, Neuroendocrine tumor epidemiology: contrasting Norway and North America, Cancer 113, (10) (2008) 2655–2664.

[4] K. Landerholm, S. Falkmer, J. Jarhult, Epidemiology of small bowel carcinoids in a defined population, World J. Surg. 34 (7) (2010) 1500–1505.

[5] J. Eriksson, O. Norlen, M. Ogren, H. Garmo, C. Ihre-Lundgren, P. Hellman, Primary small intestinal neuroendocrine tumors are highly prevalent and often multiple before metastatic disease develops, Scand. J. Surg. 1457496919874484 (2019).

[6] T. Berge, F. Linell, Carcinoid tumours. Frequency in a defined population during a 12-year period, Acta Pathol. Microbiol. Scand. 84 (4) (1976) 322–330.

[7] N. Manguso, A. Gangi, N. Nissen, A. Harit, E. Siegel, A. Hendifar, F. Amersi, Long-term outcomes after elective versus emergency surgery for small bowel neuroendocrine tumors, Am. Surg. 84 (10) (2018) 1570–1574.

[8] J. Soga, Carcinoids of the small intestine: a statistical evaluation of 1102 cases collected from the literature, J. Exp. Clin. Canc. Res. 16 (4) (1997) 353–363.

[9] I.M. Modlin, K.D. Lye, M. Kidd, A 5-decade analysis of 13,715 carcinoid tumors, Cancer 97 (4) (2003) 934–959.

[10] H. Jann, S. Roll, A. Couvelard, O. Hentic, M. Pavel, J. Muller-Nordhorn, M. Koch, C. Rocken, G. Rindi, P. Ruszniewski, B. Wiedenmann, U.F. Pape, Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome, Cancer 117 (15) (2011) 3332–3341.

[11] J.P. Boudreaux, D.S. Klimstra, M.M. Hassan, E.A. Woltering, R.T. Jensen, S. J. Goldsmith, C. Nutting, D.L. Bushnell, M.E. Caplin, J.C. Yao, S. North American Neuroendocrine Tumor, The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum, Pancreas 39 (6) (2010) 753–766.

[12] O. Norlen, P. Stalberg, K. Oberg, J. Eriksson, J. Hedberg, O. Hessman, E.T. Janson, P. Hellman, G. Akerstrom, Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center, World J. Surg. 36 (6) (2012) 1419–1431.

[13] R. Garcia-Carbonero, J. Capdevila, G. Crespo-Herrero, J.A. Diaz-Perez, M. P. Martinez Del Prado, V. Alonso Orduna, I. Sevilla-Garcia, C. Villabona-Artero, A. Beguiristain-Gomez, M. Llanos-Munoz, M. Marazuela, C. Alvarez-Escola, D. Castellano, E. Vilar, P. Jimenez-Fonseca, A. Teule, J. Sastre-Valera, M. Benavent-Vinuelas, A. Monleon, R. Salazar, Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE), Ann. Oncol. 21 (9) (2010) 1794–1803.

[14] P.F. Quaedvlieg, O. Visser, C.B. Lamers, M.L. Janssen-Heijen, B.G. Taal, Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients, Ann. Oncol. 12 (9) (2001) 1295–1300.

[15] B. Niederle, U.F. Pape, F. Costa, D. Gross, F. Kelestimur, U. Knigge, K. Oberg, M. Pavel, A. Perren, C. Toumpanakis, J. O'Connor, D. O'Toole, E. Krenning, N. Reed, R. Kianmanesh, Vienna consensus conference, p., ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum, Neuroendocrinology 103 (2) (2016) 125–138.

[16] C. Le Roux, C. Lombard-Bohas, C. Delmas, S. Dominguez-Tinajero, P. Ruszniewski, E. Samalin, J.L. Raoul, P. Renard, E. Baudin, M. Robaskiewicz, E. Mitry, G. Cadiot, Groupe d'etude des Tumeurs, E., Relapse factors for ileal neuroendocrine tumours after curative surgery: a retrospective French multicentre study, Dig. Liver Dis. 43 (10) (2011) 828–833.

[17] K. Landerholm, N. Zar, R.E. Andersson, S.E. Falkmer, J. Järhult, Survival and prognostic factors in patients with small bowel carcinoid tumour, Br. J. Surg. 98 (11) (2011) 1617–1624.

[18] M. Ter-Minassian, J.A. Chan, S.M. Hooshmand, L.K. Brais, A. Daskalova, R. Heafield, L. Buchanan, Z.R. Qian, C.S. Fuchs, X. Lin, D.C. Christiani, M.H. Kulke, Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database, Endocr. Relat. Canc. 20 (2) (2013) 187–196.

[19] R. Fossmark, T.M. Balto, T.C. Martinsen, J.E. Gronbech, B. Munkvold, P.G. Mjones, H.L. Waldum, Hepatic micrometastases outside macrometastases are present in all patients with ileal neuroendocrine primary tumour at the time of liver resection, Scand. J. Gastroenterol. 54 (8) (2019) 1003–1007.

[20] J. Brierley, M.K. Gospodarowicz, C. Wittekind, TNM Classification of Malignant Tumours, eighth ed., John Wiley & Sons, Inc., Chichester, West Sussex, UK ; Hoboken, NJ, 2017.

[21] I.D. Nagtegaal, R.D. Odze, D. Klimstra, V. Paradis, M. Rugge, P. Schirmacher, K. M. Washington, F. Carneiro, I.A. Cree, Board, W. H. O. C. o. T. E., the 2019 WHO classification of tumours of the digestive system, Histopathology 76 (2) (2020) 182–188.

[22] B. Niederle, U.F. Pape, F. Costa, D. Gross, F. Kelestimur, U. Knigge, K. Oberg, M. Pavel, A. Perren, C. Toumpanakis, J. O'Connor, D. O'Toole, E. Krenning, N. Reed, R. Kianmanesh, ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum, Neuroendocrinology 103 (2) (2016) 125–138.

[23] U.F. Pape, A. Perren, B. Niederle, D. Gross, T. Gress, F. Costa, R. Arnold, T. Denecke, U. Plockinger, R. Salazar, A. Grossman, ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas, Neuroendocrinology 95 (2) (2012) 135–156.

[24] D.S. Bergestuen, L. Aabakken, K. Holm, M. Vatn, E. Thiis-Evensen, Small intestinal neuroendocrine tumors: prognostic factors and survival, Scand. J. Gastroenterol. 44 (9) (2009) 1084–1091.

[25] J.E. Moller, P.A. Pellikka, A.M. Bernheim, H.V. Schaff, J. Rubin, H.M. Connolly, Prognosis of carcinoid heart disease: analysis of 200 cases over two decades, Circulation 112 (21) (2005) 3320–3327.

[26] J. Eriksson, H. Garmo, P. Hellman, C. Ihre-Lundgren, The influence of preoperative symptoms on the death of patients with small intestinal neuroendocrine tumors, Ann. Surg Oncol. 24 (5) (2017) 1214–1220.

[27] O.H. Sjo, S. Larsen, O.C. Lunde, A. Nesbakken, Short term outcome after emergency and elective surgery for colon cancer, Colorectal Dis. 11 (7) (2009) 733–739.

[28] A. Lewis, G. Akopian, S. Carillo, H.S. Kaufman, Lymph node harvest in emergent versus elective colon resections, Am. Surg. 78 (10) (2012) 1049–1053.

[29] B. Wangberg, G. Westberg, U. Tylen, L. Tisell, S. Jansson, O. Nilsson, V. Johansson, T. Schersten, H. Ahlman, Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction, World J. Surg. 20 (7) (1996) 892–899, discussion 899.

[30] S. Partelli, D.K. Bartsch, J. Capdevila, J. Chen, U. Knigge, B. Niederle, E.J. M. Nieveen van Dijkum, U.F. Pape, A. Pascher, J. Ramage, N. Reed, P. Ruszniewski, J.Y. Scoazec, C. Toumpanakis, R. Kianmanesh, M. Falconi, Antibes consensus conference, p., ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours, Neuroendocrinology 105 (3) (2017) 255–265.

[31] O. Norlen, P. Stalberg, J. Zedenius, P. Hellman, Outcome after resection and radiofrequency ablation of liver metastases from small intestinal neuroendocrine tumours, Br. J. Surg. 100 (11) (2013) 1505–1514.

[32] M.Y. Zaidi, A.G. Lopez-Aguiar, M. Dillhoff, E. Beal, G. Poultsides, E. Makris, F. Rocha, A. Crown, K. Idrees, P. Marincola Smith, H. Nathan, M. Beems, D. Abbott, J.R. Barrett, R.C. Fields, J. Davidson, K. Cardona, S.K. Maithel, Prognostic role of lymph node positivity and number of lymph nodes needed for accurately staging small-bowel neuroendocrine tumors, JAMA Surg. 154 (2) (2019) 134–140.

[33] A.K. Clift, P. Drymousis, A. Al-Nahhas, H. Wasan, J. Martin, S. Holm, A. Frilling, Incidence of second primary malignancies in patients with neuroendocrine tumours, Neuroendocrinology 102 (1–2) (2015) 26–32.

[34] N. Zar, H. Garmo, L. Holmberg, P. Hellman, Risk of second primary malignancies and causes of death in patients with adenocarcinoma and carcinoid of the small intestine, Eur. J. Canc. 44 (5) (2008) 718–725.

[35] S.P. Haugvik, I. Basim Ibrahim, P. Hedenstrom, R. Valente, A.J. Hayes, D. Siuka, I. P. Gladhaug, G. Capurso, Smoking, alcohol and family history of cancer as risk factors for small intestinal neuroendocrine tumors: a systematic review and meta-analysis, Scand. J. Gastroenterol. 52 (8) (2017) 797–802.

[36] U.F. Pape, U. Berndt, J. Muller-Nordhorn, M. Bohmig, S. Roll, M. Koch, S. N. Willich, B. Wiedenmann, Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours, Endocr. Relat. Canc. 15 (4) (2008) 1083–1097.

[37] W.E. Gibson, R.S. Gonzalez, J.M.M. Cates, E. Liu, C. Shi, Hepatic micrometastases are associated with poor prognosis in patients with liver metastases from neuroendocrine tumors of the digestive tract, Hum. Pathol. 79 (2018) 109–115.

[38] D. Elias, J.H. Lefevre, P. Duvillard, D. Goere, C. Dromain, F. Dumont, E. Baudin, Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think, Ann. Surg. 251 (2) (2010) 307–310.