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ORIGINAL SCIENTIFIC REPORT

Surgical Treatment of NEN of Small Bowel: A Retrospective Analysis

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Abstract

Background Neuroendocrine Neoplasms of the small intestine have been noticed more frequently over the past 35 years. They constitute about 25 % of all NENs and 29 % of all tumors of the small intestine. Due to the predominantly indolent nature and overall good prognosis, the benefit of surgical treatment is still debated.

Methods In a retrospective study, data of 83 surgically treated patients with neuroendocrine neoplasms of the small intestine, 48 males and 35 females with a median age of 62 years (range 25–86 years) were analyzed. Patient data were documented in the MaDoc database for neuroendocrine tumors of the University Medical Center of Mainz. IBM SPSS Statistics 20 was used for statistical analysis. Kaplan–Meier survival curves and Log-Rank tests, censoring patients at the time of last follow-up, were used to compare the overall survival depending on potential prognostic factors (stage, grade, surgical treatment).

Results At the time of diagnoses, the most common clinical symptoms were abdominal pain ($n = 31$, 37.3 %), bowel obstruction ($n = 11$, 13.3 %), bowel perforation and peritonitis ($n = 3$, 3.6 %), gastrointestinal bleeding ($n = 9$, 10.8 %), weight loss ($n = 11$, 13.3 %), and carcinoid syndrome ($n = 27$, 32.5 %). 65 patients (78.3 %) had lymph node metastasis and in 58 patients (69.9 %) distant metastasis were present. Segmental bowel resection (44) was the most common surgical procedure, followed by right hemi-colectomy (32) and explorative laparotomy (7). In most patients (78.9 %), lymphadenectomy (systematic/selective) was performed. The 5-year survival of patients who underwent a systematic or a selective lymphadenectomy differed significantly (82.2 vs. 40.0 %). The overall 3-, 5-, and 10-year survival rates were 88.2, 80.3, and 71.0 %, respectively.

Conclusion Mesenteric lymph node metastases are almost invariably present and have significant impact on patients' prognosis. Systematic lymphadenectomy prevents complications and improves the survival. Early surgical treatment should be the goal in order to prevent complications.

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Introduction

Neuroendocrine neoplasms (NENs) comprise a very heterogeneous and uncommon group of tumors. 25 % of all NENs are located in the small bowel (duodenum, jejunum, and ileum). Midgut NENs represent 29 % of all tumors of the small intestine [1] and are predominantly diagnosed at the age of 65 years. They can be associated with different clinical symptoms caused by the secretion of specific hormones or remain non-functioning. Clinical symptoms are absent or unspecific for a long time until the manifestation of liver metastasis or acute local complication like bowel obstruction, perforation, bleeding, or ischemia. About 50 % of the midgut NENs are diagnosed during an emergency laparotomy, e.g., due to bowel obstruction or ischemia (as consequence of mesenteric metastasis) or with the appearance of liver metastasis and clinical symptoms (Carcinoid Syndrome). Frequently, multifocal disease with mesenteric lymph node metastases at the time of diagnosis is observed [2]. However, due to the absence of symptoms and presuming a slow tumor progression, clinicians are frequently reluctant to recommend surgical resection of the primary tumor with mesenteric lymph node dissection, especially when liver metastases are present.

Laboratory tests (e.g., 5-hydroxy-indole-acetic-acid (5-HIAA), chromogranin A) and innovative imaging methods (e.g., octreotide-scan, 68Ga-DOTATOC-PET/CT and 18F-FDG-PET/CT) have significantly improved diagnosis and localization of midgut NENs. Nevertheless, in patients diagnosed in a non-emergency situation, preoperative prediction of the progression and/or the occurrence of complications is difficult due to the variable biological behavior of these tumors and the still remaining discrepancy between imaging modalities and the real intra-abdominal situation.

Recently, several prognostic factors were identified, which were associated with significant different survival rates. The Ki-67 index is the most important histopathologic marker associated with aggressive growth pattern of NENs. The WHO Classification of 2010 implemented the Ki-67 index in a grading system to distinguish between G1/G2 neuroendocrine tumors (NET, Ki-67 index: 0–20 %) and G3 neuroendocrine carcinomas (NEC, Ki-67 index: >20 %) [3]. Other prognostic factors are the presence of liver metastases, patient's age at diagnosis, and the size of the primary tumor [4].

Surgical therapy is indicated in cases of a Ki-67 index <20 % and represent the only curative treatment strategy if liver metastases are absent. Patients with an aggressive NEC (Ki-67 index >20 %) have a 5-year survival of only 50 % [5] and usually do not benefit from surgery unless complications demand palliative interventions.

At the time of diagnosis of G1/G2 small bowel NET, mesenteric lymph node metastases are usually present, which exceed the size of the primary tumor. The local effect of serotonin and growth factors causes desmoplastic alterations of the small bowel mesentery which may lead to intestinal obstruction, intestinal ischemia, or venous congestion (Fig. 1). It was hypothesized that surgical removal of the primary tumor (G1/G2) along with radical dissection of mesenteric lymph node metastasis can prevent those complications and is therefore recommended even in patients with liver metastases [6]. Moreover, several studies indicate that curative resection or debulking of liver metastasis may reduce symptoms and improve the long-term survival [7–10].

In our present study, we analyzed all patients with small bowel NEN treated in the University Medical Center Mainz from 1990 to 2014. Based on the ENETS classification system for small bowel NENs, we evaluated potential prognostic factors on the survival.

Especially, the outcome following the resection of the primary tumor, mesenteric lymph node dissection, and resection/debulking of hepatic metastases was analyzed.

Patients

In a retrospective study, all patients with NENs of the small bowel that were treated between 1990 and 2014 in the University Medical Center Mainz were identified and analyzed. We collected data of 89 patients treated in the time period in the Clinic of General, Visceral- and Transplantation Surgery, the Department of Endocrinology and Metabolic Diseases, and the Department of Nuclear Medicine of the University Medical Center University Mainz. In every patient, a primary NEN of the small bowel was diagnosed, located in the duodenum, the jejunum, or in the proximal and distal jejunum. Since NEN of the duodenum ($n = 6$) differs from the NEN of the jejunum and ileum and belong to the foregut NEN, those patients were excluded of the statistical analysis. We also identified 21 patients with liver metastasis of NEN of unknown primary site. Although a primary NEN of the small bowel was suspected in a number of these cases, we did not include those cases in our study. All patients had histological confirmation based on the immunohistochemical staining with neuroendocrine markers (Chromogranin A, Synaptophysin) and were graded using the Ki-67 index.

Documentation

For data acquisition and documentation, the software MaDoC particularly designed for NENs of the gastroenteropancreatic system was used. Clinical and biochemical

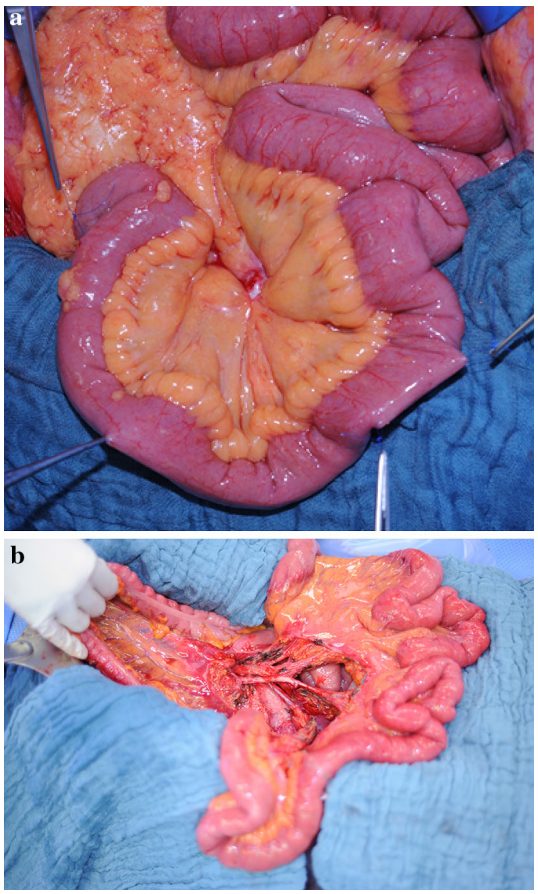


Fig. 1 Multifocal NET of the small intestine with central lymph node metastases and desmoplastic alterations of the mesenterium, before (**a**) and after (**b**) systematic lymphadenectomy

data were collected retrospectively from hospital charts, pathology reports, and biochemistry laboratory records for each patient. MaDoC includes the documentation of prognostic factors like grade, Ki-67 index, lymph node and liver metastasis, extent of tumor spread based on the ENETS classification of 2007, tumor size, hormonal secretion, gender, age, and a number of additional variables. Therapeutic interventions and progression of the NENs were recorded in a follow-up chart. The database was authorized by our data protection officer and included 89 patients with NENs of the small bowel. All attempts were made to ensure the quality of data with all medical and electronic records accessible.

Clinical assessment

Reviewing the surgical report and the pathology report of each patient, we were able to differentiate patients with systematic or selective lymphadenectomy. Patients with ≥6 resected lymph nodes were allocated to the group systematic lymphadenectomy; if <6 lymph nodes were resected, we categorized the patients as selective lymph node dissection. The patients were followed in intervals between 3 and 6 month. Assessment of the 5-Hydroxyindoleacetic acid in 24 h-Urine and imaging procedures like CT, MRI, Ultrasonography, and Octreotide-Scintigraphy and DOTATOC PET/CT were used to exclude residual tumor foci. However, due to the long study period, not all imaging techniques were available at the beginning of the study.

Data analysis

For the statistical analysis, the software IBM SPSS Statistics 20 was used. Patients' follow-up was calculated from the time of diagnosis. In 38 patients, the diagnosis was made during or after the surgical intervention. In the other patients, the time interval during diagnosis and operation varied between 4 and 3760 days, with a median of 36 days. The disease-free survival was calculated until the date of the first recurrence (locoregional, lymph node, or distant metastasis) of the tumor. Recurrence was defined as newly identified disease by imaging or biochemical following a period of 6 months after successful primary treatment and lacking evidence of residual disease. Death due to all causes or date of last follow-up was used as the clinical end point. Overall survival analyses were performed with Kaplan–Meier calculations of relevant factors with potential impact on patient survival, e.g., tumor stage (ENETS), grading, and the resection strategy. Significant differences were calculated with the Chi-square test and the Log-Rank test. Covariates identified as having a significant influence on survival were included in a multivariate analysis using a Cox's proportional hazards model.

Results

Data of 83 patients with NENs of the small intestine [48 males and 35 females, median age of 59.9 years (range 25–85 years)] were retrospectively analyzed. Mean duration of follow-up from the time of diagnosis was 63.39 months. The distal ileum was the predominant localization ($n = 46$, 55.4 %), followed by the proximal ileum ($n = 19$, 22.9 %), the proximal jejunum ($n = 8$, 9.6 %), and the distal jejunum ($n = 10$, 12.0 %). 65 patients (78.3 %) had lymphatic metastasis and in 58 patients (69.9 %) distant metastasis were present (Table 1).

The median overall survival was 19.25 years; the overall survival rate was 88.2 % after 3, 80.3 % after 5, and 71.0 % after 10 years (Fig. 2a). In 35 patients (42.2 %), the tumor was removed with tumor-free resection margins (R0). 20 patients were classified R1 by the

Table 1 Demographics and overall survival rates of the 83 patients with NEN of the small intestine of the University Medical Center Mainz

Patient characteristics	Number	Overall survival		
	(*n*/ %)	3-year (%)	5-year (%)	10-year (%)
Gender				
Female	35/42.2			
Male	48/57.8			
Age at diagnosis				
<50	18/21.7			
50–59	16/19.3			
60–69	30/36.1			
70–79	16/19.3			
>79	3/3.6			
ENETS stage				
I	3/3.6	66.7	–	–
II	9/10.8	71.4	57.1	57.1
III	13/15.7	100.0	90.0	67.5
IV	58/69.9	89.1	76.2	76.2
Tumor diameter				
0 to <1 cm	6/7.2	83.3	83.3	83.3
1 to < 2 cm	35/42.2	89.5	80.8	65.5
2 to < 3 cm	22/26.5	82.1	82.1	82.1
3 to < 4 cm	13/15.7	73.3	73.3	73.3
≥4 cm	6/7.2	100.0	100	100.0
Lymph node metastasis				
No	18/21.7	92.2	82.1	73.9
Yes	65/78.3	72.8	62.4	62.4
Distant metastasis				
Yes	58/69.9	89.1	76.2	76.2
No	25/30.1	88.2	82.4	62.4
Hormone secretion				
Yes	39/47.0	91.1	82.8	77.3
No	44/53.0	85.2	77.8	63.4
Grade (ENETS)				
1	35/42.2	97.1	92.9	92.9
2	35/42.2	95.8	84.5	73.9
3	12/14.6	40.9	30.7	0.0
Surgery				
Segmental resection Jejunum	15/18.0	88.9	76.2	50.8
Segmental resection Ileum	29/35.0	90.9	90.9	81.8
Right Hemi-colectomy	32/38.6	92.5	81.9	81.9
Exploration	7/8.4	57.1	42.9	42.9
Lymphadenectomy				
Systematic	52/86.7	85.4	82.2	70.5
Selective	8/13.3	100.0	40.0	40.0
Resection of hepatic metastasis				
Overall	37/100.0			
Hemihepatectomy	5/13.5	80.0	50.0	–
Segmentectomy	7/18.9	100.0	85.7	–
Atypical resection solitary	16/43.3	100.0	87.5	81.25
Atypical resection multiple	7/18.9	85.7	85.7	57.1
Other type of resection	2/5.4	50.0	0.0	0.0
Result of hepatic resection				
R0/R1	30/51.7	93.7	88.5	88.5
R2 (debulking)	7/12.1	71.4	38.1	38.1
Not resected	21/36.2	84.0	84.0	84.0

pathology report and in 28 patients only a R2-resection was possible. Recurrent disease was observed in 26 patients (74.3 %). The tumor-free survival was 69.5, 55.1, and 46.6 % at 3, 5, and 10 years, (median tumor-free survival 128 months) (Fig. 2b). Only 9 patients with NEN of the small intestine were disease-free at the time of the last follow-up.

Univariate survival analysis of prognostic factors such as ENETS stage, tumor diameter, functional activity, grade (referring to the Ki-67 index), and type of surgical resection was performed. Due to the limited number of patients, we combined stage IIa and IIb as well as stage IIIa and IIIb of the ENETS classification system to create four different groups (stage I to IV). The overall survival of those different groups is depicted in Fig. 3. One of the three patients diagnosed with stage I disease died within 3 years after the diagnosis. The 5- and 10-year survival rates could not be calculated for this group. The 3-, 5-, and 10-year overall survival of 9 patients with stage II disease were 71.4, 57.1, and 57.1 %. 13 patients with stage III had an overall survival of 100.0 % after 3 years, 90.0 % after 5 years, and 67.5 % after 10 years. Most patients ($n = 58$, 69.9 %) were diagnosed with stage IV and demonstrated a 3-, 5-, and 10-year overall survival of 89.1, 76.2, and 76.2 %. Comparison of stage specific patient survival revealed no significant differences (Log-Rank test: $p = 0.466$).

The primary tumor size was ≤3 cm in 63 patients (75.9 %) and >3 cm in the remaining patients. Comparison of these two groups revealed no significant difference in the overall survival (Fig. 4; Log-Rank test $p = 0.885$). In 26 patients (31.3 %), multifocal NEN of the small bowel were diagnosed.

In 38 patients (45.8 %), the NEN was diagnosed postoperatively. In those patients an emergency situation prompted the decision for exploratory laparotomy. Clinical features were abdominal pain ($n = 31$, 37.3 %), bowel obstruction ($n = 11$, 13.3 %), bowel perforation with peritonitis ($n = 3$, 3.6 %), and gastrointestinal bleeding ($n = 9$, 10.8 %). Intraoperative a tumor of the small intestine was discovered causing the clinical symptoms. Due to the emergency situation, the resection did usually not include extended lymphadenectomy. In the final

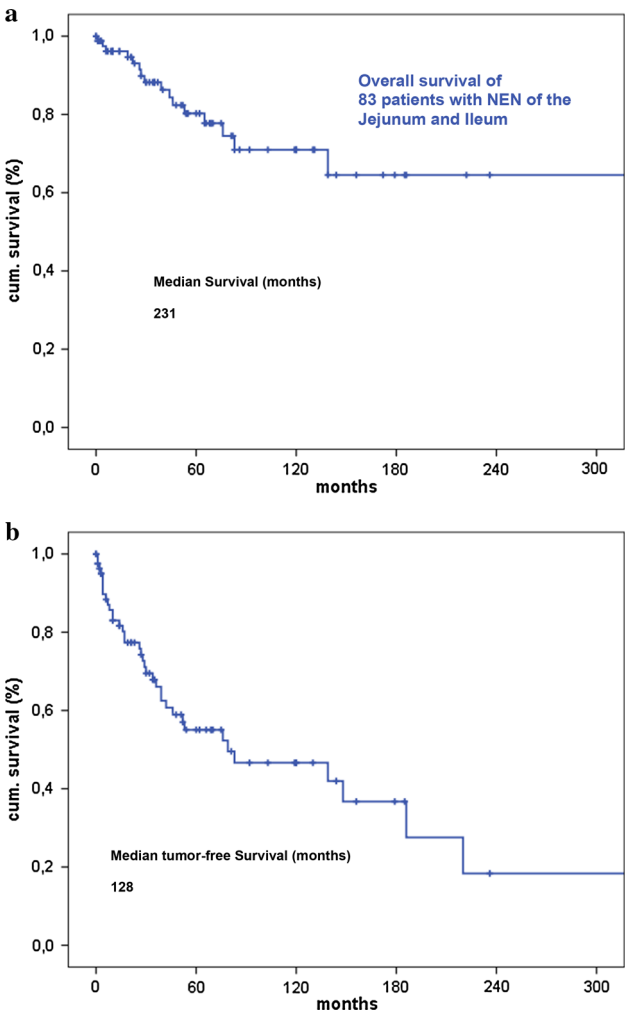
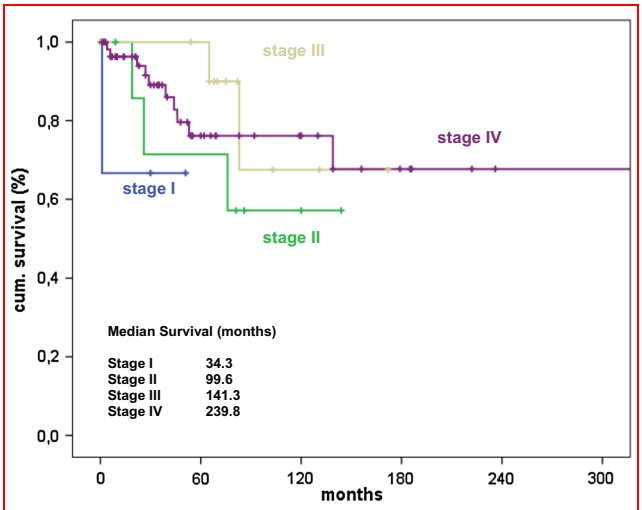


Fig. 2 **a** Kaplan–Meier survival curve of 83 patients with NEN of the small intestine. Death or date of last follow-up was the clinical end point. (3-year survival: 88.2 %, 5-year survival: 80.3 %, 10-year survival: 71.0 %). **b** Kaplan–Meier curve presenting the tumor-free survival of patients in which an R0 resection could be performed. Recurrence of the disease was the clinical endpoint. (3-year tumor-free survival: 69.5 %, 5-year tumor-free survival: 55.1 %, 10-year tumor-free survival: 46.6 %)

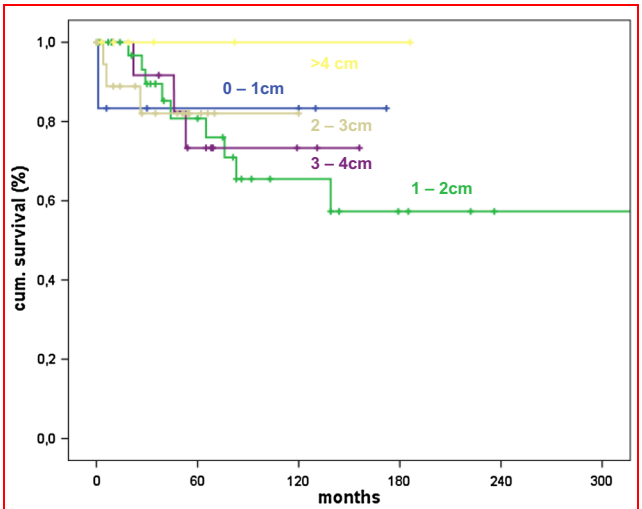
pathological report, the tumor was classified as neuroendocrine neoplasm.

39 patients (46.9 %) had functioning NENs. Symptoms included the classic carcinoid syndrome ($n = 27$, 32.5 %) and diarrhea ($n = 27$, 32.5 %). The patient group with functioning NENs had 3-, 5-, and 10-year survival rates of 91.1, 82.8, and 77.3 %. Patients with non-functioning NENs showed comparable 3-, 5-, and 10-year survival rates of 85.2, 77.8, and 63.4 %. There was no significant difference of the overall survival rates between functioning and non-functioning NENs (Fig. 5, Log-Rank test $p = 0.607$).



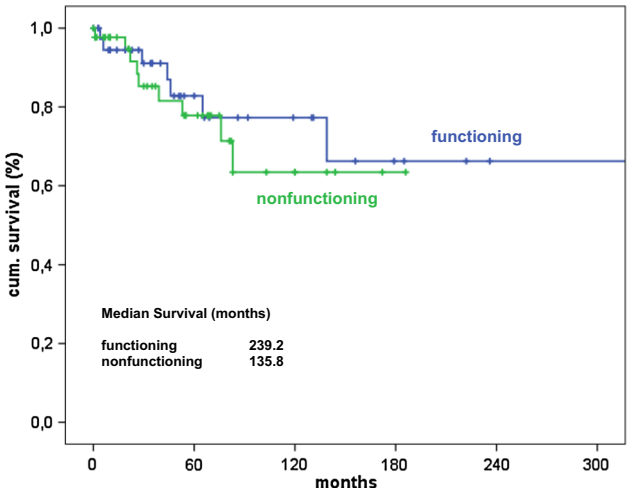
	3 year survival	5 year survival	10 year survival
I (3 patients)	66.7	-	-
II (9 patients)	71.4	57.1	57.1
III (13 patients)	100.0	90.0	67.5
IV (58 patients)	89.1	76.2	76.2

Fig. 3 Kaplan–Meier survival curve according to the ENETS stages. (Log-Rank test: $p = 0.466$)



	3 year survival	5 year survival	10 year survival
0 – 1cm: (6 patients)	83.3	83.3	83.3
>1 – 2cm: (35 patients)	89.5	80.8	65.5
>2 – 3cm: (22 patients)	82.1	82.1	82.1
>3 – 4cm: (13 patients)	91.7	73.3	73.3
>4cm: (6 patients)	100.0	100.0	100.0

Fig. 4 Kaplan–Meier survival curve according to the tumor diameter as prognostic factor. (Log-Rank test: $p = 0.885$)

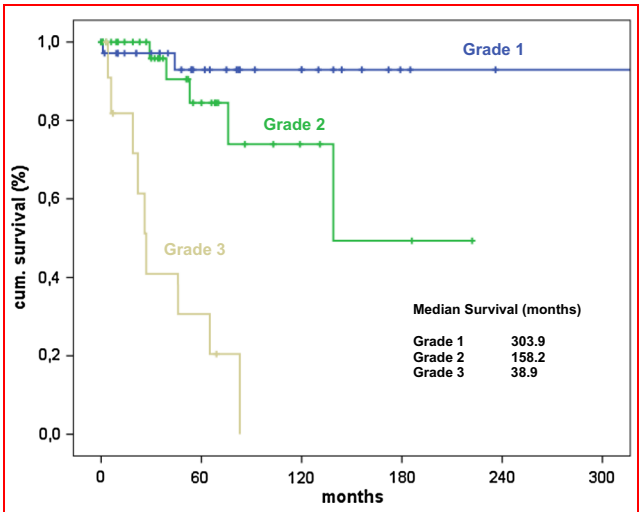


	3 year survival	5 year survival	10 year survival
functioning: (patients 39)	91.1	82.8	77.3
non-functioning: (patients 44)	85.2	77.8	63.4

Fig. 5 Hormonal activity as prognostic factor (Log-Rank test: $p = 0.607$)

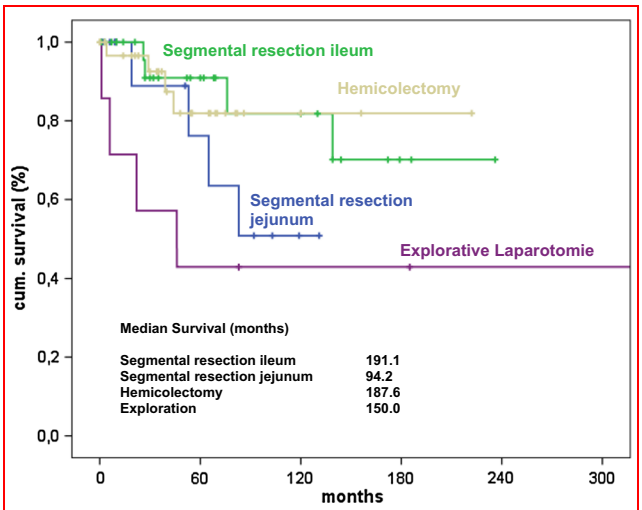
The proliferation marker Ki-67 was analyzed in 63 patients (75.9 %), thus allowing ENETS grading. WHO grade 1 was most common, accounting for 36 (43.4 %) of all patients. 35 (42.2 %) patients were grade 2 and 12 (14.5 %) patients were WHO grade 3. Patients with grade 1 and a Ki-67 index $\leq$2 had overall survival rates of 97.1 % after 3, 92.9 % after 5, and 92.9 % after 10 years. The patient group with grade 2 NET had survival rates of 95.8 % after 3, 84.5 % after 5, and 73.9 % after 10 years. A very poor survival was associated with grade 3 NEC resulting in survival rates of 40.9 % after 3 years and 30.7 % after 5 years. None of the patients with NEC and a Ki-67 index >20 % survived 10 years (Fig. 6). The ENETS grading system divided the patient cohort into three groups with significantly different prognoses (Log-Rank $p < 0.001$).

With regard to the treatment of the primary tumor and mesenteric lymph node metastasis, all 83 patients with NEN underwent surgery. In 7 patients, the primary NEN remained unresected (explorative laparotomy) because of the advanced tumor stage. Segmental bowel resection (44) of the ileum (29) and the jejunum (15) represented the most frequent surgical procedure, followed by right hemi-colectomy (32) (Fig. 7). The most favorable long-term overall survival was observed after right hemi-colectomy with a 10-year survival rate of 81.9 %. Following segmental bowel resection, the 10-year survival rates were 81.8 % for the ileum and 50.8 % for the jejunum. As expected the worst 10-year survival of 42.9 % was associated with explorative laparotomy.



	3 year survival	5 year survival	10 year survival
1 (35 patients)	97.1	92.9	92.9
2 (35 patients)	95.8	84.5	73.9
3 (12 patients)	40.9	30.7	0.0

Fig. 6 Grade as prognostic factor for the overall survival (Log-Rank test: $p < 0.001$)



	3 year survival	5 year survival	10 year survival
Segmental resection			
Ileum (29 patients)	90.9	90.9	81.8
Jejunum (15 patients)	88.9	76.2	50.8
Hemicolectomie (32 patients)	92.5	81.9	81.9
Exploration (7 patients)	57.1	42.9	42.9

Fig. 7 Kaplan–Meier curve presenting the overall survival after different resection procedures.(Log-Rank test: $p = 0.102$)

In 60/76 patients (78.9 %) who underwent surgery of the primary NEN, a selective or systematic lymphadenectomy was performed. The Kaplan–Meier curve (Fig. 8) reveals that

systematic lymphadenectomy was associated with improved prognosis (median survival 241 months) compared to selective lymph node resection (median survival 77 months). In 16 patients the lymphadenectomy was performed after an incomplete primary operation. In most of those patients, the diagnosis was made during an emergency situation.

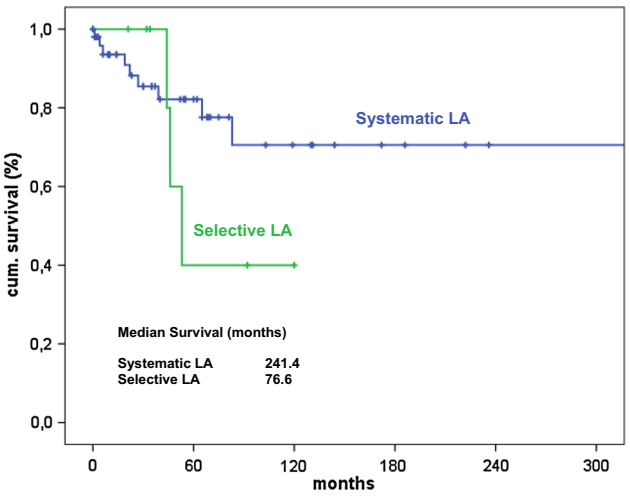
In 58 patients (69.9 %), distant metastasis were present at time of diagnosis. Frequently the detection of the liver metastasis during a routine abdominal ultrasound leads to the diagnosis of a NEN in the jejunum/ileum. The decision to resect the liver metastasis was made if according to the preoperative imaging the metastasis could be removed completely or at least a R1 resection could be carried out. In addition, a severe carcinoid syndrome, which could not be controlled by the treatment with somatostatin analogs indicated hepatic surgery. In those cases, surgery was performed if a resection of more than 90 % of the liver metastases was achievable. In addition, in some patients with bilobar unresectable liver metastases a resection of small peripheral metastases was carried out for diagnostic reasons.

Of 58 patients with liver metastases, 37 were subjected to various forms of liver resection. 31 patients underwent liver resection once, while in 6 patients secondary liver resection were performed. Of those 37 resections, 24 (64.9 %) were combined with the resection of the primary tumor in case of synchronous hepatic metastasis. In the other 13 (35.1 %) patients, resections of metachronous metastasis were performed. Resection procedures included hemihepatectomy in 5 patients, with one-staged hemihepatectomy. 16 patients underwent solitary atypical resection and 7 patients several atypical liver resections. Segmentectomies or larger wedge resections were carried out in another 7 patients. One patient underwent a laparoscopic liver resection of a small peripheral metastasis, and in one case an intraoperative radio frequency ablation (RFA) was performed.

Major postoperative complications were bile leakage ($n = 4$) and intra-abdominal bleeding that required surgical re-intervention ($n = 2$). There was no case of postoperative severe liver insufficiency and no postoperative mortality.

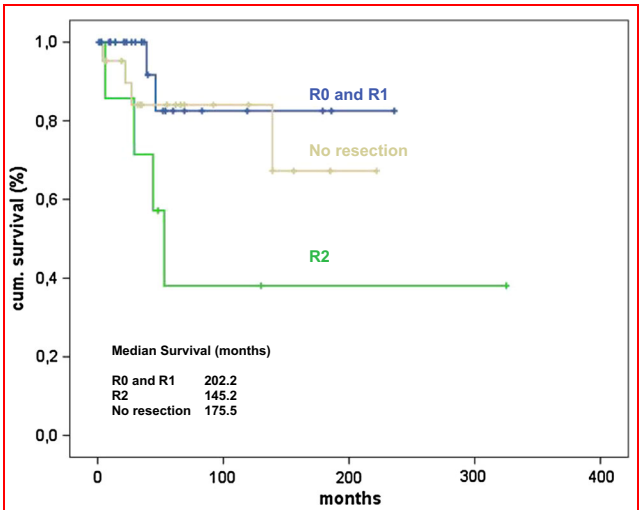
In 21 of the 58 patients with liver metastasis, a postoperative R0 situation could be achieved, in 9 patients a R1 situation was determined. As other studies showed, those groups have a very similar prognosis [11]. For further analysis, we combined R0/R1-resections into one group.

Figure 9 depicts the Kaplan–Meyer curves comparing the overall survival following R0/R1 resection with R2 debulking of irresectable liver metastasis. R0/R1 resection was associated with 5- and 10-year survival rates of 88.5 and 88.5 %. Much poorer survival rates were observed following R2 resection with 69.1 and 57.0 % after 5 and 10 years.



	3 year survival	5 year survival	10 year survival
systematic LA (52 patients)	85.4	82.2	70.5
selective LA (8 patients)	100.0	40.0	40.0

Fig. 8 Survival depending on realization and technique of the lymphadenectomy. Two groups of patients were compared. In the first with systematic lymphadenectomy, ≥6 lymph nodes were resected. In the second group with selective lymphadenectomy, <6 lymph nodes were mentioned in the pathological report. (Log-Rank test: $p = 0.347$)



	3 year survival	5 year survival	10 year survival
R0 / R1 (30 patients)	100.0	82.5	82.5
R2 (7 patients)	71.4	38.1	38.1
No resection (21 patients)	84.0	84.0	84.0

Fig. 9 Kaplan–Meier survival curve of patients with R0/1, R2, or no resection of their liver metastasis. (Log-Rank test: $p = 0.573$)

Potentially prognostic factors such as ENETS stage, lymph node status, distant metastases, grade, functional activity, tumor diameter, different types of lymphadenectomy, and gender were included in a Cox multivariate regression analysis. Tumor grade ($p = 0.040$, Log-Rank test) and lymphadenectomy ($p = 0.003$, Log-Rank test) were identified as independent prognostic factors, while the size of the primary tumor, tumor stage ($p < 0.001$, Log-Rank test), functional activity, and gender were not independent significant factors in multivariate analysis of our patient cohort.

Discussion

NEN of the small intestine are frequently diagnosed by the detection of liver metastasis (40 %) or during an emergency laparotomy when the primary tumor causes complications like bowel obstruction (40 %) [12]. Corresponding to these reports in the presented retrospective analysis, 45.8 % were diagnosed after surgery and in 48.2 % hepatic metastasis lead to the identification of the NEN.

In these different clinical settings, determination of the indication, timing, and extent of surgical interventions remains difficult. The limited and predominantly retrospective evidence available provokes an ongoing controversial discussion between clinician supporting a very conservative approach in the absence of significant symptoms and on the contrary an aggressive approach aiming at the complete or almost complete resection of all detected tumor foci in order to prevent future complications.

Due to the high rate of hepatic and lymph node metastasis present at time of diagnosis (85.5 %), the number of patients in an early tumor stage (ENETS) was very low in our patient cohort (3 patients in stage I, 9 patients in stage II). Death of one of the patients in stage I was not caused by the tumor, and two patients of stage I had a NET G2. In the group of patients with stage II, three patients died, two of them not associated to their malignant disease. In these 9 patients we noticed 5 G1, 2 G2, and 2 G3 NEN. Therefore, we could not demonstrate the ENETS staging system as a relevant prognostic factor. Congruously, there was no significant influence of the WHO tumor stage on the survival time in our patient cohort. In contrast, Norlen et al. [6] demonstrated in a cohort of 603 patients that the WHO staging (according to Rindi et al. [3]) is associated with the prognosis of the patients. However, only three patients of the 603 (0.5 %) were defined stage I and 15 patients (2.5 %) stage II. The survival differences therefore were related to the course of a very small group of patients in stage I and II. While other studies with even lager patient cohorts have demonstrated that the ENETS classification system is closely associated with the prognosis of NEN of the small intestine [13], prediction of the prognosis of the main number of patients in stage III and IV has to include additional factors.

75.9 % of the primary tumors were ≤3 cm. Even small NEN were associated with frequent lymph node and distant metastasis which may explain the lacking impact of the size of the primary tumor on patient survival (Fig. 4). Similarly, we observed no influence of the functional activity on the overall survival of the patients. A classic carcinoid syndrome occurred with a rate of 32.5 %, which corresponds to statements of other authors [2, 14, 15].

The Ki-67 index and therefore the ENETS Grading were identified as independent predictor of patient survival (Log-Rank: $p < 0.001$). In agreement with published results from other groups [6, 11], patients with grade 1 or a Ki-67 index ≤2 had better prognosis and a 5-year overall survival of 92.9 % compared to the patients with grade 2 (84.5 %) and those with grade 3 (30.7 %). The factor remained significant in our multivariate analysis.

Some retrospective studies [6] have demonstrated that curative as well as palliative resection of the primary tumor may improve the prognosis and the quality of life of patients. Due to the fact that mesenteric lymph node metastases are almost invariably present, many authors hypothesize that an effective clearance of the regional lymph nodes is essential in order to prevent complications like bowel obstruction, ischemia, or venous congestion [2, 14–16]. In agreement with this hypothesis, we observed that more radical (systematic) lymphadenectomy was associated with an improved 5-year survival rate (82.2 %) compared to less radical lymph node dissection (40.0 %). 7 (77.7 %) of the selective lymphadenectomies were carried out during an emergency laparotomy, and in 8 cases a stage IV NEN was diagnosed. In the former cases, the NEN often was diagnosed after surgery in the pathologic report.

In order to evaluate the impact of lymphadenectomy, we used the certainly arbitrary surrogate of >6 resected lymph nodes to define a systematic lymphadenectomy. Landry et al. recently used the almost similar number of >7 lymph nodes to discriminate more radical procedures [17], however, both numbers lack sufficient evidence and have to be interpreted with caution.

Regarding the performed surgical procedures we noticed that patients who underwent a right hemi-colectomy also showed a very good prognosis (10 year survival rate of 81.9 %). This may be related to the fact that extended lymphadenectomy is carried out more easily during a right hemi-colectomy compared to a segmental resection of the small intestine on the left side of the ileocolic artery [14].

The presented results led us to the proposal that an aggressive approach including radical lymph node dissection seems to prevent complications and therefore

improves patient survival. This hypothesis is further supported by the results of a recent analysis of the SEER register. This retrospective review of 1364 patients demonstrates that regional mesenteric lymphadenectomy in conjunction with resection of the primary tumor is associated with improved survival of patients with small bowel neuroendocrine tumors. In absence of clearly defined surgical margins for a systematic lymph node dissection, we recommend that the lymphadenectomy has to be adapted to the localization of the primary tumor. A primary tumor site in the terminal ileum requires dissection of the lymph nodes on the right side of the ileocolic artery which usually requires a right hemi-colectomy. In case of a primary tumor site located in the lower ileum up to the distal jejunum, a cone-shaped resection of the mesentery of the small bowel with extension of the lymphadenectomy into adjacent segments with preservation of vascularization should be performed [14].

Besides the mesenteric lymph node metastasis, a number of patients (69.9 %) presented with hepatic metastasis at time of diagnosis. Ahmed et al. [11] demonstrated in his study that patients benefit from hepatic tumor resection with respect to survival and symptom palliation. In our patient cohort, we observed that patients who underwent an R0 or R1 resection of their hepatic metastasis had a better 5-year survival rate (88.5 %) than patients who underwent R2 resection or no liver resection (69.1 %). Even if the result was not significant in the Log-Rank test ($p = 0.136$), due to the small number of patients included and acknowledging the selection bias with more advanced disease in the group with R2 resection or no resection, respectively, it confirms that if an R0 or R1 resection seems possible a resection of the hepatic metastasis should be performed.

Finally, we think that adjuvant biotherapy represents an important part of the treatment strategy, which is used to slow down tumor progression and reduce clinical symptoms. Mostly patients with low Ki-67 index showed a long-term stable disease under treatment with somatostatin analogs and/or interferon, even if there is no verified evidence for survival benefit from the use of biotherapy in the literature.

This single-center retrospective study has certain inherent limitations. Foremost, the sample size of our study does not offer sufficient power to delineate survival differences between certain parameters. In addition, it is a retrospective analysis that includes a significant selection bias with regard to type of resection. We have investigated new and known prognostic factors on their influence of the prognosis for patients with NEN of the small intestine. The Ki-67 Index (Grading) was confirmed as the most important prognostic factor. Other factors like stage and tumor size were not identified as predictors of the overall survival, which may relate to the overall high frequency of lymph node and distant metastasis even in small tumors. With regard to the surgical treatment strategy, we noticed that the realization of a systematic lymphadenectomy prevents complications and improves patients' survival. Patients who are suitable for a R0 or R1 liver resection should be offered this therapy since it improves patient's survival and supports quality of life by reducing carcinoid symptoms. These surgical procedures can be performed with low morbidity and mortality. However, the potential benefits of the surgical intervention have to be compared with possible alternative treatment option. The treatment strategies should be discussed by an interdisciplinary team of clinicians treating patients with neuroendocrine tumors in order to develop a comprehensive oncologic concept.

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Compliance with ethical standards

Conflicts of interest No potential conflicts of interest to be announced.

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