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ORIGINAL ARTICLE

Long-term outcome of surgical resection in patients with gastroenteropancreatic neuroendocrine neoplasia: results from a German nation-wide multi-centric registry

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Abstract

Background Neuroendocrine neoplasia (NEN) are rare and heterogenous tumours. Few data exist on the impact of surgical therapy.
Materials and methods This is a retrospective analysis of prospectively collected data of gastroenteropancreatic NEN in the German NET-Registry (1999–2012). It focuses on patients without distant metastases (limited disease, LD, stage I–IIIB).
Results Data of 2239 patients with NEN were recorded. Median age was 59 years, the gender ratio was 1:1.3 (f:m). A total of 986 patients (44%) had LD, and the 5-year survival rate (5 years) was 77% for all and 90% for patients with LD. A total of 1635 patients (73%) received a surgical therapy (1st to 6th line); the 5 and 10 ysr were 83/65% after and 59/35% without surgery for all patients ($p < .001$). The resection margins in the LD patients were 76%, 16%, and 3% for R0, R1 and R2, respectively. The 10 ysr was 84%, 59% and 42% for R0, R1 and R2 resections, respectively ($p = .021$ R0/R1, $p < .001$ R0/R2). The R0 resection rate was 75% for G1/G2 NET and 67% for G3 NEC.
Conclusion The rate of complete tumour resection (R0) in LD is independent of tumour grading, and R0 resection is the key determinant of long-term survival, as demonstrated by the 10 ysr. of 84%. All NEN patients with limited disease should be considered for operation, if possible, as the best 10-year survival is shown after an R0 resection.

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Introduction

Neuroendocrine neoplasia comprise a rare and heterogenous group of tumours. Recently published epidemiological data of large population-based cohorts and different nationwide tumour registries suggest an increasing incidence and improved clinical outcome for this disease over the last 15 years [1–5]. The incidence of neuroendocrine neoplasia (NEN) is low, with 4–6 cases/100,000 inhabitants per year. Due to an often indolent tumour biology, its prevalence is estimated at 18–20/100,000 inhabitants, and NENs are more prevalent than oesophageal, gastric, pancreatic or hepatobiliary malignancies [6–8]. In most registries, small bowel-, pancreatic- and NEN with unknown primary (CUP) are the most frequent entities among gastroenteropancreatic NEN. Lymph node metastases are seen in approximately 80% of patients, and distant metastases are observed in 50–64% of cases at the time of initial diagnosis. The liver is the most frequent site of distant metastases, followed by peritoneum, lung and bone [9]. The survival of patients decreases when lymph node metastases are present, and it decreases further when distant metastases are observed [10, 11]. Different classification systems to predict prognosis have been developed over the last decades, but they fail in clinical practice due to their complexity. The ENETS (European Neuroendocrine Tumor Society) classification and grading proposal, published in 2006 for foreguts and in 2007 for mid- and hindguts by Rindi et al., were implemented into the TNM classification in 2009 and into WHO 2010 classification systems to enable an easier handling of these rare and complex diseases [12–15]. The grading of NEN was insufficient by common histomorphological criteria [14, 15] and is currently based on the proliferation index Ki-67, which is proven to be of prognostic significance [16–18]. Surgical resection is currently the only curative treatment option for NEN. The main surgical principle in NEN patients is a radical resection of the primary tumour including locoregional lymph nodes and, if possible, the complete resection of metastases [19]. Although surgery is the cornerstone of curative treatment of NEN, only few outcome data are available, and they are mostly monocentric and retrospective [20–22], even less is known about the impact of surgery on long-term survival. The aim of this study was to analyze the long-term outcome of a surgical treated cohort of NEN with local and locoregional NEN (TNM stage $\leq$ IIIb) in a large, nationwide, multicentric cohort (German NET-Registry, 2000–2011).

Materials and methods

The German NET-Registry is a joint multicentric effort of 30 actively participating institutions caring for patients with NEN; it is organized by the German Society of Endocrinology (Deutsche Gesellschaft für Endokrinologie, DGE) and was founded in 2003; and the general mode of operation has previously been described [23]. Briefly, after registering at the NET - Registry, the participating institutions, which are either university, teaching, community hospitals or private chambers, obtain approval from the local ethics committee for participation in the NET-Registry. Prior to the documentation of patient data, signed informed consent is obtained from the NEN patients who are being considered for inclusion in the registry. The inclusion criteria, besides signed informed consent, require the presence of a histologically confirmed NEN and an age greater than 18 years at the time of inclusion into the NET-Registry. In this study, only NENs of gastroenteropancreatic (GEP) origin or of unknown primary tumour site (CUP) with intra-abdominal manifestation were analyzed for the results of oncological visceral surgery.

Data were repeatedly collected in the actively participating institutions from source documents by qualified study nurses who had obtained specific training and experience in the treatment of NEN and filled out a specifically designed questionnaire. For the period between 1999 and 2004, data were retrospectively documented; after 2004, they were prospectively documented. Documented data were transferred to an MS ACCESS database (Lohmann & Birkner Health Care Consulting, GmbH, Berlin, Germany) from which data were extracted and transferred to SPSS software (version 20.0, SPSS GmbH Munich, Germany) for further statistical evaluation and calculation.

Collected data included general epidemiologic information such as gender, age, date of initial diagnosis, last visit to the reporting institution and date and—if available—cause of death. Disease-specific information such as primary tumour localization, presence or absence of metastasis, date of detection of metastasis, localization of metastasis, presence or absence of functionality and hormone hypersecretion syndrome, and available histopathological classification criteria was also obtained. Finally, treatment-specific information on the treatment modalities and results with regard to overall outcome were also recorded. A R0 resection was defined as histologically proved tumour-free resection margin of more than or at least 1 mm. Overall survival was defined as the difference between the time of first tumour diagnosis to time of last visit or death of any cause. Further details can be obtained from previous publications [9, 23] and the website of the NET-Registry [www.net-register.org].

Statistical analysis

The statistical evaluation was performed using SPSS software, version 20.0 (SPSS GmbH Munich, Germany). All values are

given as the median ± standard deviation (SD). All metric values were tested for normal distribution using the Komolgorov-Smirnov test and were further analyzed by paired tests. Non-normally distributed metric variables and ordinally scaled variables were analyzed by the Wilcoxon-Mann-Whitney *U* test. For nominally scaled variables, we used χ^2 testing, Fisher's exact test, and Wilcoxon-Mann-Whitney *U* test. For nominally scaled variables in paired *t* tests in the presence of significance, log-rank testing was used. Univariate survival rates are given as cumulative estimation by Kaplan-Meier method and log-rank test with $p < .05$ as statistically significant.

Results

Description of the cohort

A total of 2239 patients with histologically confirmed GEP-NEN and an initial diagnosis between 1999 and 2012 were included in the analysis. The female-to-male ratio was 1051 to 1188 (1:1.3), the mean age at initial diagnosis was 56.7 years, and the median age was 59 years, ranging from 14 to 93 years. The median follow-up time was 27 months, ranging from 1 to 163 months. During the follow-up period, 372 (16.6%) deaths occurred. In 100 of 115 cases (86.9%) with a documented cause of death, the death was considered to be NEN-related (Table 1).

Data for disease stage were available in 2228 (99.5%) cases. Limited disease (LD, TNM stages I–IIIa), meaning absence of distant metastasis (M0), was recorded in 986 (44.3%) cases, and extensive disease (ED, TNM stage> IIIa), meaning distant metastases are present, was recorded in 1242 (55.7%) cases [14].

Grading data according to the WHO 2010 guidelines were available in 1266 (56.5%) patients: 498 (39.3%) were grade 1 NEN (NET-G1), 585 (46.2%) were grade 2 NEN, and 183 were grade 3 NEN [24].

The most common primary tumour localizations were the pancreas (757, 34.3%), small bowel (561, 25.4%), and carcinoma of unknown primary site (CUP, 322, 14.6%), followed by the stomach (163, 7.3%), rectum (108, 4.9%), and duodenum (104, 4.7%). Presentations of appendiceal (94, 4.3%), colonic (51, 2.3%), and oesophageal (16, 0.7%) NET were underrepresented in this cohort of patients from neuroendocrine referral centres (Fig. 1a). The distribution of the surgical cohort is shown in Fig. 1b. Characteristic hormone hypersecretion syndromes were documented in 500 (22.3%) of all 2239 cases with carcinoidsyndrome in 350 (70%), insulinoma syndrome in 70 (14%), Zollinger-Ellison syndrome in 45 (9%) cases, and other syndromes in 35 (7%) cases.

Therapy

In the nationwide registry, 1635 out of 2239 patients (73.0%) were operated on, and there were 1756 operations in total.

Depending on available information, surgery was 1st line therapy in 65% (1369/2109), 2nd line therapy in 31% (330/1083) and 3rd line in 17% (57 /569) of patients. In total surgery was documented up to 6st line therapy, which means surgery was done repeatedly or between and after other therapies like biotherapy, chemotherapy, or others. Non-surgical treatment in patients with remaining or recurring NEN included somatostatin analogue therapy (biotherapy) in 30% (667/2239), chemotherapy in 16% (364/2239), and PRRT in 15% (329/2239, Fig. 1c, d) of patients. The rate of surgery depending on tumour stage (extensive disease, ED, and limited disease, LD) is shown in Fig. 2.

The distribution of Ki-67-based grading was performed according to the ENETS proposal, which was adopted by the WHO 2010[citation] [25].

TNM-based staging was defined as limited (LD, TNM I–IIIa) or extensive disease (ED, TNM IIIb and IV) in patients with and without surgical therapy, as summarized in Fig. 3.

General outcome

The overall 5-year survival rate (5 ysr) was 77% for all patients ($n = 2217$) in the German NET-Registry, 59% for the non-surgical ($n = 502$) group, and 83% for the surgically treated group ($n = 1632$) ($p < .001$, Fig. 4).

The 5-year survival for all patients with LD ($n = 967$) was 77.3%, and the 10-year survival was 59%. The mean overall survival was 137 months, while a median overall survival was not calculated in the LD group (Fig. 5).

Results of surgery in limited disease

Resectional margin

In the surgically treated group, 840 out of 1632 (51.5%) patients had LD at their initial diagnosis, and this was confirmed in 808 (49.5%) patients at the time of surgery. A total of 32 (2%) patients developed extensive disease or were falsely stratified. Information on resection margins was available in 495 patients (58.8%). Of those, 376 patients (75.9%) had a complete resection with histologically confirmed tumour-free resection margins (R0 resection). These patients had a 5-year survival rate of 94% and a 10-year survival rate of 84%. In patients with microscopic positive tumour margins (R1 resection, $n = 78$, 15.7%) or macroscopic tumour persistence (R2 resection, $n = 14$, 2.8%), the survival rates were 88% and 85% after 5 years and 59% and 42% after 10 years, respectively

Table 1 Patient characteristics according to surgical and non-surgical therapy

		Total	Patients with surgery (%)	Patients without surgery (%)
Total	*n*	2239	1635 (76.2)	510 (23.8)
Primary tumour localization	*n* (*n* = 31: no information for primary)	2208	1633	499
	Oesophagus (*n*, %)	16 (0.7)	13 (0.8)	2 (0.4)
	Stomach (*n*, %)	163 (7.3)	128 (7.8)	31 (6.2)
	Pancreas (*n*, %)	757 (34.3)	545 (33.4)	182 (36.5)
	Duodenum (*n*, %)	104 (4.7)	75 (4.6)	19 (3.8)
	Appendix (*n*, %)	94 (4.3)	92 (5.6)	1 (0.2)
	Small intestine (*n*, %)	561 (25.4)	493 (30.1)	47 (9.4)
	Caecum (*n*, %)	32 (1.4)	29 (1.8)	3 (0.6)
	Colon (*n*, %)	51 (2.3)	40 (2.5)	7 (1.4)
	Rectum (*n*, %)	108 (4.9)	96 (5.9)	11 (2.2)
	Unknown primary (CUP) (*n*, %)	322 (14.6)	122 (7.5)	196 (39.3)
Age at ID	Median (years)	59	58	61
Sex	Female (*n*, %)	1051	772 (47.3)	240 (47.1)
	Male (*n*, %)	1188	863 (52.8)	270 (52.9)
ENETS grading	Total	1266	946	275
	G1 (*n*, %)	498 (39.0)	408 (43.1)	74 (26.9)
	G2 (*n*, %)	585 (46.2)	438 (46.3)	124 (45.1)
	G3 (*n*, %)	183 (14.5)	100 (10.6)	77 (28.0)
Disease stage at ID	Total	2262	1657	605
	LD (*n*, %)	986 (43.6)	840 (50.7)	146 (24.1)
	ED (*n*, %)	1276 (56.4)	817 (49.3)	459 (75.9)

($p = .021$ for R0 versus R1, $p < .001$ for R0 vs. R2, not significant for other groups, Figs. 4 and 5).

Grading and resection margin

Information on grading and resection margin was available in 422 out of 840 patients with an LD stage. Additionally, 398 patients (94%) presented with G1 and G2 tumours.

Data for resection margin were available in 84% (334/398) of these patients with G1 and G2 tumours. Specifically, 251 patients (75%) had an R0 resection, 56 (17%) had an R1 resection, and 13 (4%) had an R2 resection. In 14 (4%) of cases, the resection margin was documented as RX (unclear, Fig. 5). In patients with G3 NEC ($n = 24$), the resection margins were documented in 18 patients (75%), with 12 patients presenting with an R0 resection (67%), 4 patients with R1 (22%), and 2 with Rx (11%) (Fig. 6). There was a tendency for better survival in the R0-resected group: 5 ysr was 61% in this group vs. 50% in the R1 group, but this was not significant ($p = .176$ for R0 vs. R1, Fig. 6).

Discussion

Primary tumour distribution and rate of surgical therapy

The German NET-Registry is the first national platform comparing long-term outcomes after surgical and non-surgical therapies in patients with neuroendocrine neoplasia (NEN). This study was focused on patients with limited diseases and excluded patients with liver or other distant metastases. The data should be representative, as they have been contributed by centres of different sizes in Germany. However, they are not population-based. This aspect might result in some bias concerning the primary tumour distribution: appendiceal NEN, type I gastric NEN, and small rectal NEN are underrepresented when compared to population-based registries [26]. Small (< 2 cm) appendiceal NEN, without risk factors such as mesoappendiceal infiltration >3 mm or Ki-67 > 2%, is cured after an appendectomy and does not require any follow-up. Small incidental gastric NET, in the case of chronic-atrophic gastritis (type I), and small incidental rectal NEN, which can be removed endoscopically, are rarely referred to any NET centres (Fig. 6).

With this restriction, the distribution of primary tumours is comparable to other national registries [1–4]. The most

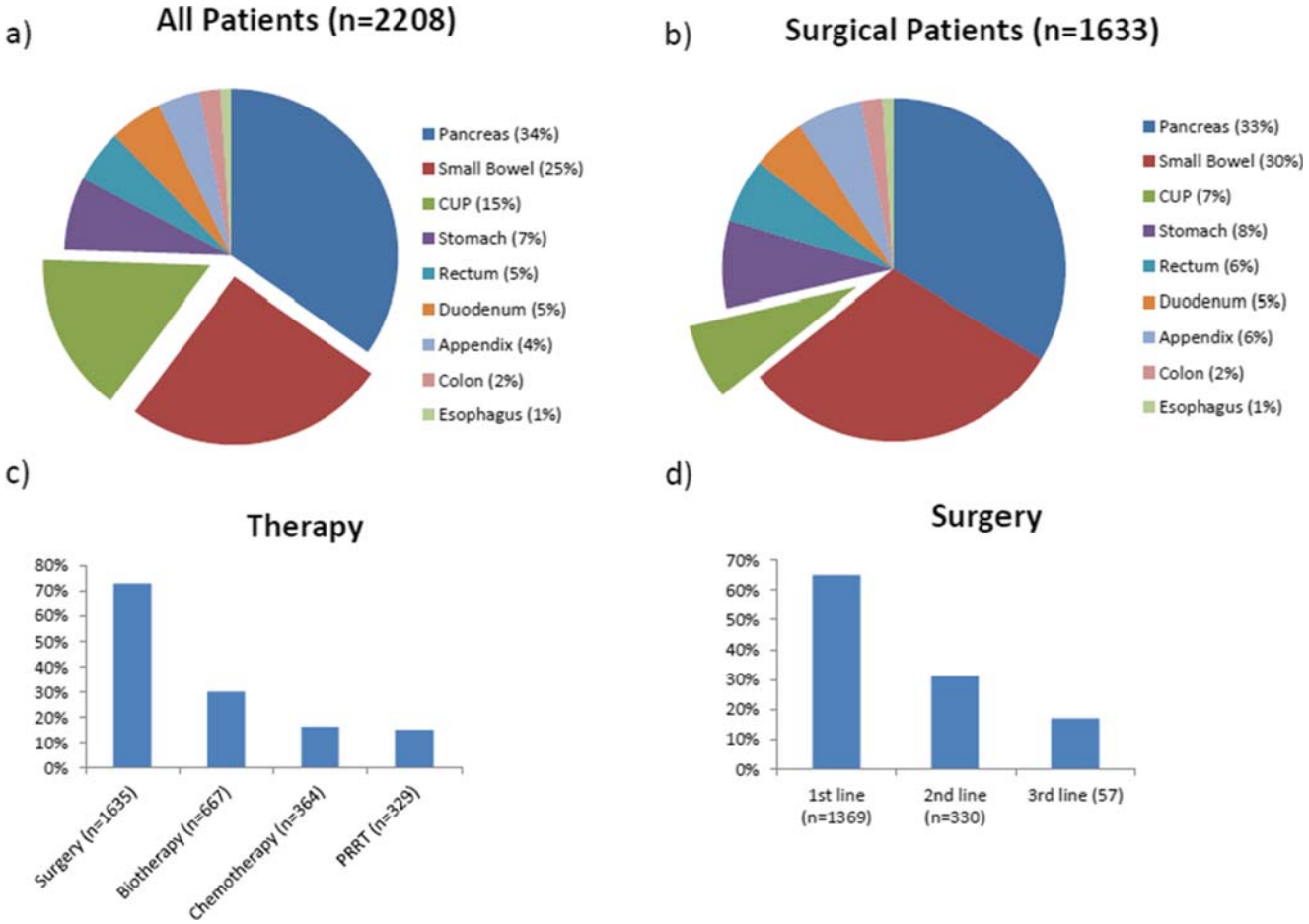

Fig. 1 **a**, **b** Distribution of primary tumours in the surgical and non-surgical groups. **c**, **d** Different therapies in the German NET-Registry and in surgery as multistep therapies

common primary localizations are the pancreas (34.3%) and the small intestine (SI, 25.4%), followed by the group of carcinomas of unknown primary tumours (CUP, 14.6%) and gastric NEN (7.3%, Fig. 1a, b).

At the initial diagnosis, a limited disease stage (ENETS stage I–IIIa), which includes locoregional lymph node metastases, was found in 43.6% of patients, and an extensive disease stage, including distant metastases, in 56.4% of patients. Surgical therapy was performed in 1635 of 2239 (73%) patients, and a total of 1756 operations were performed as a 1st to 6th line therapy (Fig. 1). The rate of surgical therapy is comparable to the findings of Sakin et al., with 70% of surgeries performed in a monocentric study of 85 NEN cases [25]. The authors described a curative surgery being used in

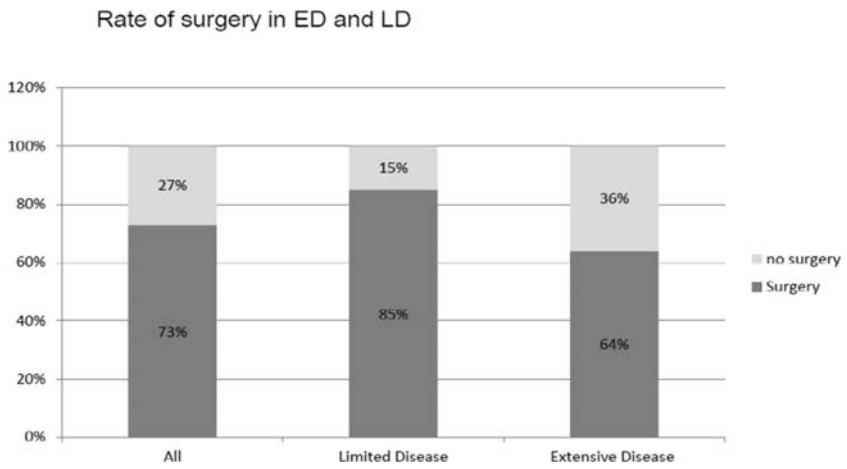

Fig. 2 Rate of surgical therapy in limited disease (LD, ENETS stage I–IIIa) and in extensive disease (ED, ENETS stage IIIB–IV)

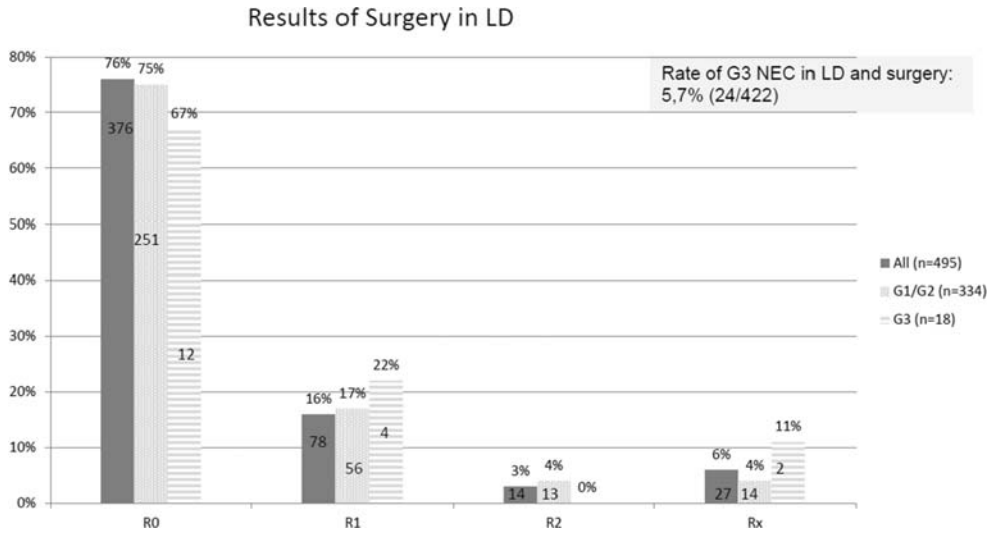

Fig. 3 Results of surgical therapy rate of resection margin in limited disease stage were available in 495 of 840 pts. with LD data for tumour grading in $n = 422$ with 398 (94.3%) G1 of G2 NET and 24 (5.7%) G3 NEC. Data for resection margin were available for 334 G1/G2 and 18 G3 NEC patients

64% of patients and a palliative surgery being used in 6% of patients. In our registry, we have no information about the intention of surgery.

In a Norwegian population-based study on NEN of all sites, the rate of the distant metastases of the rectum, stomach, small intestine, pancreas, and colon were 19.3, 26.6, 50.6, 52, and 60%, respectively. The rate of distant metastases for appendiceal NEN was only 5.3%.

Limited diseases and extensive diseases were seen in 57.9 and 42.1%, respectively, which is different from our findings, with 43.6 and 56.4% for LD and ED, respectively, in the German NET-Registry [27]. Herein, the comparability is weak because all of the primary sites and all of the NEN types, including epithelial and medullary types, are included.

Surgical therapy and survival

The difference in the survival rates between our patients who received or did not receive surgery is high; however, because the data were retrospectively added and due to the heterogeneity of the groups, a statistical comparison could not be performed. One hundred forty-six of 986 patients (15%) with limited disease and 36% (459/1276) of patients with ED did not receive any surgical therapy.

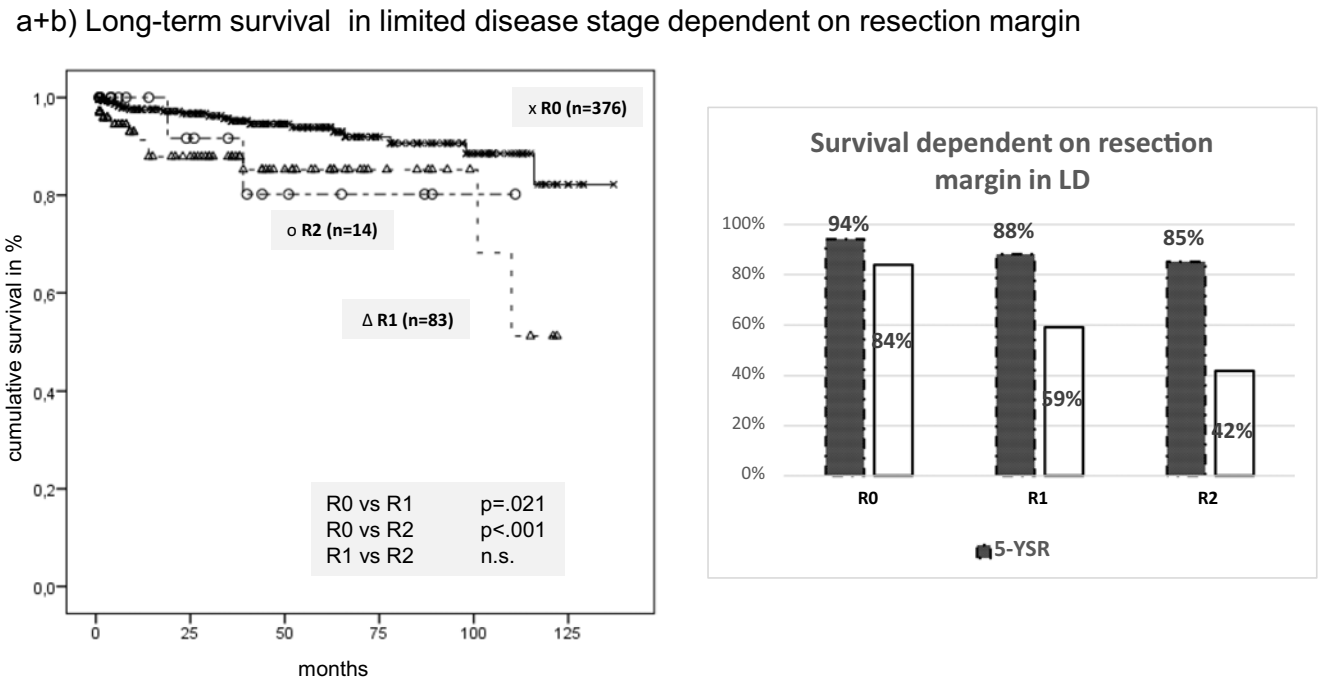

Fig. 4 **a**, **b** The benefit of complete tumour resection in limited disease is elucidated in long-term survival: a tumour-free resectional margin (R0) has crucial impact on long-term survival, resulting in excellent 10-year survival rates: 84% ($n = 376$), 59% ($n = 83$), and 42% ($n = 14$) for R0, R1, and R2-resection. p values are $p = .021$ for R0 versus R1 and $p < .001$ for R0 versus R2 resection, n.s. for R1 and R2

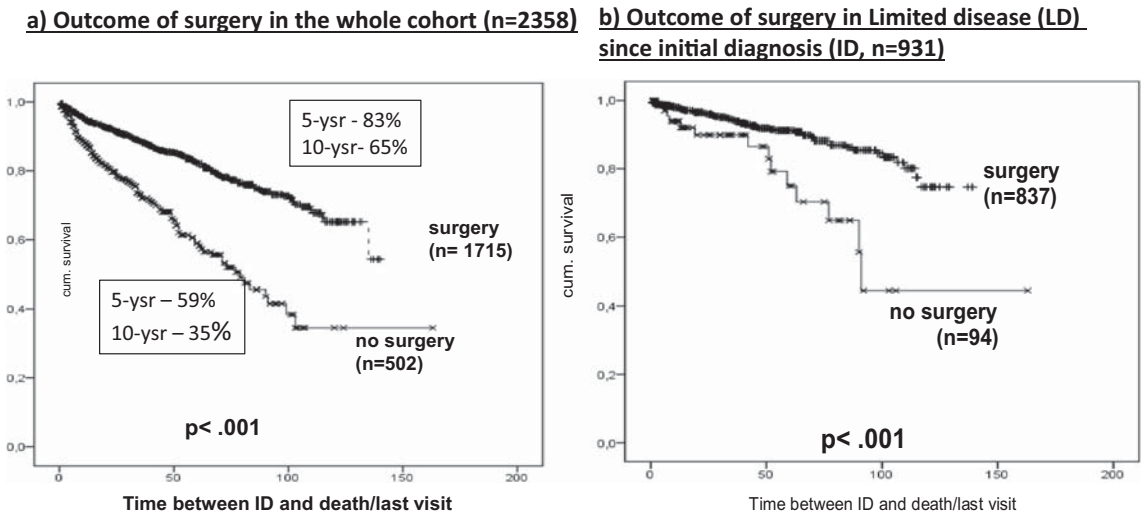

Fig. 5 Surgery dependent survival in limited disease

Gender and age were comparable in both groups, but tumour stage and tumour grade were different (see Table 1). LD stage was present in only 51% of the surgical group and in 24% of the non-surgical group. The distributions of the ENETS grading were 43, 46, and 11% in the surgical group for G1, G2, and G3, respectively, and 27, 45, and 28% in the non-surgical group for G1, G2, and G3, respectively. No information was available for the general health status and local operability, as well as if any surgical procedure was discussed.

Data for survival after surgery in the registries are rare. In a review of the period ranging from 2000 to 2013, Jilesen et al. found a 5 ysr for a limited disease of pancreatic NEN between 85 and 93%, which is comparable to our finding of a 5 ysr of 92% for NEN with limited diseases [28]. No data for resection margins were available. Hill et al. found an improved median survival of 114 months in localized, regional, and metastatic pancreatic NEN after complete tumour resections, compared to 35 months if surgery was recommended but not performed ($n = 310/115$, HR 0.48, national study). No data for resection margins were available in the retrospective study, and the reason for not performing surgery is not known. Furthermore, both groups displayed heterogeneity in tumour stage and age [29]. Prospective randomized controlled trials will be necessary to answer this question in a satisfactory way.

The overall 5-year survival rate (ysr) was 77%, and the 10 ysr was 59%, for all patients ($n = 2217$) in the German NET-Registry. These findings are comparable to or slightly better than other registries, with the restriction that many registries include NEN of all sites. In the Spanish database, the 5 ysr is 83 and 78% for small bowel and pancreatic NEN, respectively. In the SEER and Norwegian databases, the 5 ysr is 50% for all NEN types, 74% for rectal and appendiceal NEN, 59% for small bowel NEN, 45% for stomach NEN, 41% for colon NEN, and 43% for pancreas NEN [1, 27]. Hallet et al. found a 5 ysr of 61% and a 10 ysr of 46.5% in a population-based retrospective study in Canada ($n = 5619$) and 38% of metastases at the initial diagnosis, including lung and other NEN [6].

Cetinkaya et al. analyzed a population-based registry of Norway in the time period from 1993 to 2015 and found

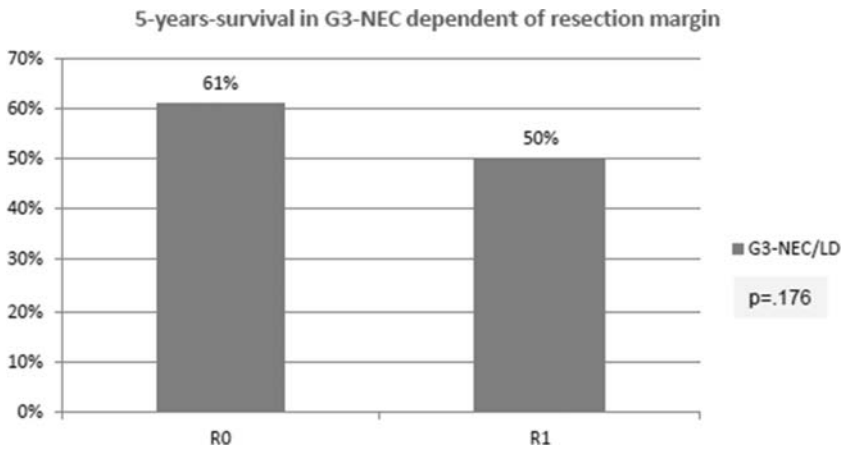

Fig. 6 A total of 24 G3 NEC patients with limited disease were registered; resection margin was available for 18 patients. R0 in12/18 pts. (67%), R1 in 4/18 (22%), and Rx in 2/18 (11%). There was a tendency seen to better survival in R0 vs R1 resected patients; *p* value was not significant

17,128 NEN incidences of all sites, including NEC and small cell NEC. They described a 5 ysr of 64.8% for low/intermediate aggressive tumours and 8.4% for aggressive tumours. Tumour classification was not performed according to the ENETS, and comparability was not attained, due to unrestricted tumour sites. The use of surgical therapy was not analysed, but there was an interesting increase in survival observed over time [27].

In our study, the 5 ysr for the non-surgical ($n = 502$) group was 59%, and the 5 ysr for the surgically treated group was 83% ($n = 1632$, $p < .001$). The 5 and 10 ysr in LD were 83 and 65% with surgery, respectively, and 59 and 35% in LD without surgery, respectively ($p < .001$). The mean overall survival was 137 months, whereas the median overall survival was not obtained in LD (Fig. 4). There are no other registry data analysing the survival rates according to surgical outcomes.

Resection rate and survival

Our data suggest a survival advantage for surgically resected patients with limited NEN disease (LD, stage I–IIIb). In this collective group, 52% of the surgically treated group (839/1632) had a limited disease at initial diagnosis, and 48% had a limited disease at the time of surgery. The reason for the delay of surgery with subsequent tumour progression from the initial diagnosis to the time of surgery is not able to be extracted from our database and may reflect the situation of healthcare status, e.g. time to referrals to a centre.

A macroscopic complete tumour resection was achieved in 92% of patients (454/495, R0 and R1), of which 78 cases (16%) showed a microscopic incomplete tumour resection (R1), and in 14 cases (3%), the resection was macroscopically incomplete.

The LD survival rates were 94, 88, and 85% after 5 years for R0, R1, and R2 resections, respectively (Fig. 6b), and the LD survival rates were 84, 59, and 42% after 10 years for R0, R1, and R2 resections, respectively. Thus, complete tumour resection (R0) is a superior method, compared to a microscopic incomplete resection (R1, $p = .021$), and superior to a macroscopic incomplete tumour resection (R2, $p < .001$). No significance could be observed between R1 and R2 resections. Surprisingly, the survival disadvantages for R1 and R2 resections were not evident after 5 years but were evident after a long-term follow-up of 10 years, as is described in Fig. 6. The missing significance level between the R1 and R2 resections may be explained by the small group that was analysed, with 78 patients receiving R1 resections and 14 patients receiving R2 resections.

The comparison of our results with other surgical studies is difficult, as most studies focus on resection rates of liver metastases and rarely focus on resections of primary tumours without distant metastases.

Surgery in G3-NEC

There are little data concerning the outcomes of surgery in G3-NEC with limited disease, as only 4% (18/421 in LD) of patients who received surgical therapy were classified as G3. However, these results show a possible benefit of R0 resection in these patients (5 ysr of 61% vs. 50% in R1, n.s.). Similar findings were observed by Shafqat et al. [30]. In this retrospective study of the SEER database from 2000 to 2011, 1367 patients were identified with colorectal neuroendocrine carcinoma. Patients with localized and non-small cell NEC had better survival rates with surgery (median survival of 21 months versus 6 months, respectively, $p < .0001$). Notably, the prognoses in resected NEC were worse, with an increasing number of lymph node metastases reported. However, no differences in median survival were observed after surgery in small cell NEC (18 months versus 14 months, respectively) ($p = .95$). The overall 5 ysr in this distinct cohort was 16.3% for all of the patients and 57.4, 56.4, 26.3, and 3% for stages I, II, III, and IV NEC, respectively.

Limitation of this study

The limitations of this study include the retrospective inclusion and the heterogenous quality of the data, leading to small subgroups. The low rate of complete information of the performed surgical procedures, the resection margins, and the details of immunohistochemistry weaken the validity of this study. Furthermore, only univariate analysis was performed to prove the impact of surgical therapy in a heterogenous population. In future analysis of the German Net-Registry, multivariate analyses should be performed.

Conclusion

In patients with limited NEN disease (I–IIIB), complete surgical tumour resection (R0) is indicated, independent of tumour grade. A histological tumour-free margin (R0) leads to excellent long-term survival after 10 years that is not seen in R1- or R2-resected patients. Multimodal approaches and neoadjuvant procedures should be further evaluated in these patients, but additional studies are needed to evaluate the role of such a therapy in locally advanced NEN.

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Compliance with ethical standards

Conflict of interest Author Rinke, Anja received honoraria from Ipsen Pharma and Novartis Pharma. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. National ethical approval was given by the ethic committee of the Charite, University Hospital, approval no. EA1/279/13.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez del Prado M, Alonso Orduña V, Sevilla-García I, Villabona-Artero C, Beguiristain-Gómez A, Llanos-Muñoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jiménez-Fonseca P, Teulé A, Sastre-Valera J, Benavent-Viñuelas M, Monleon A, Salazar R (2010) 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):1794–1803
2. Lombard-Bohas C, Mitry E, O'Toole D et al (2009) Thirteen-month registration of patients with gastroenteropancreatic endocrine tumours in France. Neuroendocrinology 89(2):217–222. https://doi.org/10.1159/000151562
3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 26:3063–3072
4. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG (2001) Epidemiology and survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2391 patients. Ann Oncol 12(9):1295–1300
5. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ (2008) Changing incidence of pancreatic neoplasms. A 16-year review of nationwide tumor registry. Pancreas 37:134–138
6. Hallet J, Law C, Cukier M, Saskin R, Liu N, Singh S (2015) Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer 121:589–597
7. Öberg K (2015) Neuroendocrine gastro-enteropancreatic tumors-from eminence based to evidence-based medicine – a Scandinavian view. Scand J Gastroenterol 50(6):727–739. https://doi.org/10.3109/00365521.2015.1033001
8. Hallet J, Law CHL, Karanicolas PJ, Saskin R, Liu N, Singh S (2015) Rural-urban disparities in incidence and outcomes of neuroendocrine tumors: a population-based analysis of 6271 cases. Cancer 121:2214–2221
9. Begum N, Maasberg S, Plöckinger U, Anlauf M, Rinke A, Pöpperl G, Lehnert H, Izbicki JR, Krausch M, Vashist YK, Raffel A, Bürk CG, Hoffmann J, Goretzki P, Pape UF, Weitere Vertreter des deutschen NET-Registers (2012) Neuroendocrine tumours of the GI tract–data from the German NET registry. Zentralbl Chir 139(3):276–283. https://doi.org/10.1055/s-0032-1315199
10. Klith G, Couvelard A, Perren A et al (2009) ENETS consensus guidelines for the standards of care in neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology 90:162–166
11. Boninsegna L, Panzuto F, Partelli S (2012) Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. Eur J Cancer 48:1608–1615
12. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol A, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B, all other Frascati Consensus Conference participants, European Neuroendocrine Tumor Society (ENETS) (2006) TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 449(4):395–401
13. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol A, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B (2007) TNM staging of midgut and hindgut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 451(4):757–762
14. Sobin LH, Gospodarowicz MK, Wittekind C (eds) (2009) TNM classification of malignant tumours, Seventh edn. Wiley-Blackwell, Oxford
15. Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) (2010) WHO classification of tumours of the digestive system, Fourth edn. International Agency for Research on Cancer (IARC), Lyon
16. Pape UF, Pascher A, Arsenic R, Ezziddin S, Jann H, Pavel ME, Wiedenmann B (2011) Gastrointestinal neuroendocrine neoplasias: novel individualized therapeutic strategies. Dtsch Med Wochenschr 136(36):1801–1806. https://doi.org/10.1055/s-0031-1286106
17. Rindi G, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, Capella C, Caplin M, Couvelard A, Doglioni C, Delle Fave G, Fischer L, Fusai G, de Herder WW, Jann H, Komminoth P, de Krijger RR, la Rosa S, Luong TV, Pape U, Perren A, Ruszniewski P, Scarpa A, Schmitt A, Solcia E, Wiedenmann B (2012) TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst 104(10):764–777. https://doi.org/10.1093/jnci/djs208
18. Jann H, Roll S, Couvelard A et al (2011) Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer 117(15):3332–3341. https://doi.org/10.1002/cncr.25855
19. Steinmüller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, Lopes JM, Perren A, Nikou G, Yao J, Delle Fave GF, O'Toole D, Frascati Consensus Conference participants (2008) Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 87(1):47–62
20. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE (2009) Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 96(2):175–184. https://doi.org/10.1002/bjs.6468
21. Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, Jensen RT (2006) Surgery increases survival in patients with gastrinoma. Ann Surg 244(3):410–419
22. Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V, Tamburrino D, Keck T, Caplin ME, Bartsch D, Thirlwell C, Fusai G, Falconi M (2015) Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. Neuroendocrinology 102:68–76
23. Ploeckinger U, Kloeppel G, Wiedenmann B, Lohmann R, representatives of 21 German NET Centers (2009) The German NET-

registry: an audit on the diagnosis and therapy of neuroendocrine tumors. Neuroendocrinology 90:349–363
24. Rindi G, Arnold R, Bosman FT et al (2010) Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) WHO classification of tumors of the digestive system. Lyon, IARC
25. Sakin A, Tambas M, Secmeler S et al Factors affecting survival in neuroendocrine tumors: a 15-year single center experience. Asian Pac J Cancer Prev 19(12):3597–3603
26. Niederle MB, Hackl M, Kaserer K, Niederle B (2010) Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 17: 909–918
27. Boyar Cetinkaya R, Aagnes B, Myklebust TÅ, Thiis-Evensen E (2018) Survival in neuroendocrine neoplasms: a report from a large Norwegian population-based study. Int J Cancer 142(6):1139–1147. https://doi.org/10.1002/ijc.31137 PMid:29082524
28. Jilesen APJ, van Eijck CHJ, in't Hof KH et al (2016) Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrein tumor: a systematic review. World J Surg 40:729–748
29. Hill JS, McPhee JT, McDade TP et al (2009) Pancreatic neuroendocrine tumors-the impact of surgical resection on survival. Cancer: 741–751
30. Shafqat H, Ali S, Salhab M et al Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population ation population lation h and colon, surgery is seen as the

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