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Surgery of the primary tumour in 201 patients with high-grade gastroenteropancreatic neuroendocrine and mixed neuroendocrine-non neuroendocrine neoplasms

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Running head: Surgery in high-grade GEP NEN and MiNEN

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Abstract

Introduction: The benefit of surgery in high-grade gastroenteropancreatic neuroendocrine neoplasms (GEP NEN) and mixed neuroendocrine-non neuroendocrine neoplasms (MiNEN) is uncertain. The aim was to investigate outcomes after tumour surgery in patients with high-grade (Ki-67>20%) GEP NEN or MiNEN stage I-III or stage IV.

Methods: Analysis of data from patients treated in the period 2007-2015 at eight Nordic university hospitals. Overall survival (OS) and progression free survival (PFS)/disease free survival (DFS) were analysed by Kaplan-Meier estimates. Prognostic factors were evaluated using Cox regression.

Results: We included 201 surgically resected patients, 143 stage I-III and 58 stage IV with 68% having neuroendocrine carcinoma (NEC), 23% MiNEN, 5% NET G3 and 4% uncertain NEN G3. Primary tumours were located in colon/rectum (52%), esophagus/cardia (19%), pancreas (10%), stomach (7%), jejunum/ileum (5%), duodenum (4%), gallbladder (2%) and anal canal (1%). For patients with stage I-III, median DFS was 12 months (95% CI 5.5-18.5) and median OS was 32 months (95% CI 24.0-40.0). For patients with stage I-III and an R0 resection, median DFS was 21 months (95% CI 4.9-37.1) and median OS was 39 months (95% CI 25.0-53.0). For patients with stage IV, median PFS/DFS was 4 months (95% CI 1.9-6.1) and median OS was 11 months (95% CI 4.8-17.2). For patients with stage IV and an R0 resection, median DFS was 6 months (95% CI 0-16.4) and median OS was 32 months (95% CI 25.5-38.5). Performance status >1 and colorectal primary were associated with poor prognosis. There was no difference in survival between patients with high-grade GEP NEN and MiNEN.

Conclusion: Surgery of the primary tumour in patients with loco-regional high-grade GEP NEN or MiNEN led to good long-term results and should be considered if an R0 resection is deemed achievable. Highly selected patients with stage IV disease may also benefit from surgery.

Keywords: Gastroenteropancreatic neuroendocrine tumors, neuroendocrine carcinoma, surgery

Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP NEN) are classified according to the WHO 2019 classification based on Ki-67 proliferation index and differentiation. Well differentiated neuroendocrine tumours (NET) include NET G1 (Ki-67 < 3%), NET G2 (Ki-67 3-20%) and NET G3 (Ki-67>20%). Neuroendocrine carcinomas (NEC) are poorly differentiated with Ki-67>20% (1). The incidence of GEP NEC is 0.54 per 100,000 inhabitants and seems to be increasing (2, 3). The median survival of patients with NET G3 and NEC is 41-99 months and 8-13 months, respectively (4). Patients with NEC have metastatic disease at the time of diagnosis in 60-78% of cases (5, 6).

Surgery is often recommended for patients with localized high-grade GEP NEN (7), however, there is disagreement between guidelines, and surgery is not recommended for metastatic NEC. According to the North American Neuroendocrine Tumor Society (NANETS) guidelines from 2013 (8), surgical treatment of tumours with a TNM classification above T 1-2 and N0 is not recommended although it may be considered in patients with low comorbidity. In the updated NANETS guidelines from 2017, surgery is not recommended for small bowel NEC (9). Furthermore, according to the European Society for Medical Oncology (ESMO) 2012 guidelines and NANETS 2020 guidelines for pancreas NEN (10, 11), surgical treatment is not recommended for loco-regional pancreatic NEC. Lastly, surgery for stage III esophageal NEC is not recommended in a European Neuroendocrine Tumor Society (ENETS) 2019 publication (12).

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) represent about one third of all high-grade poorly differentiated GEP NEN and are a combination of a neuroendocrine neoplasm and a non-neuroendocrine neoplasm, typically an adenocarcinoma, each component representing a least 30% (1).

The aim of this study was to investigate outcome and prognostic factors in patients who underwent loco-regional surgical resection for high-grade (Ki-67>20%) GEP NEN or MiNEN, with or without resection of metastases.

Materials and Methods

This retrospective cohort study is a combined analysis of one prospective and two retrospective registries from eight Nordic specialized NET centres: The Nordic NEC database, in which data were retrospectively recorded, and the Nordic NEC prospective registry, in which data were prospectively recorded. In addition, clinical data from The Nordic Surgery in NEC database were included. The study is reported according to STROBE guidelines (13).

Included patients were diagnosed with GEP NET G3, GEP NEC or GEP MiNEN and had surgical treatment of the primary tumour with or without additional resection of metastases in the period 2007-2015 (retrospective database: 2007-2012; prospective database: 2013-2015). Last date of follow-up was November 2nd 2017.

Analysed outcomes were overall survival (OS) and disease-free survival (DFS) or progression free survival (PFS). Patients with stage I-III disease resected with curative intent and all patients with stage IV disease were investigated separately. DFS and PFS were measured from the time of surgery, whereas OS was measured from the time of diagnosis. DFS was used for patients with radical resections, whereas PFS was used for patients with non-radical resections. For analyses including both groups, the term PFS/DFS was used. Exposure variables included age, gender, performance status (PS), primary tumour site, tumour (NET G3, NEC or MINEN), cell type (large vs small cell), differentiation (well vs poor), Ki-67%, stage at operation (stage I-III only), metastatic sites (stage IV only), curative intent (stage IV only), resection margins (R0/R1/R2), bowel obstruction, debulking surgery (stage IV only), emergency operation, pre- or postoperative chemotherapy and time from diagnosis to surgery.

All specimens were evaluated by NEN-dedicated pathologists. Stage was defined according to ENETS consensus guidelines (14, 15). Regional lymph node metastases were deemed locally advanced disease (Stage IIIB). Metastatic sites were categorized as none, 1 or > 1 according to Goey et al. (16) including liver, distant lymph nodes, lungs, bones and other. Residual tumour was defined according to the AJCC Cancer Staging Manual 8th edition (17). Residual tumour was categorized into R0 (no residual tumour), R1 (microscopic residual tumour) and R2 (macroscopic residual tumour at the resection site). R2 was not used to classify known metastatic disease in other locations where resection was not attempted. Regarding patients with stage I-III disease, the residual tumour (R0, R1 or R2) represented resection margins of the primary tumour and regional lymph node metastases with the highest R-value being reported. Similarly, in patients with stage IV disease, the residual tumour (R0, R1 or R2) represented resection margins of the primary tumour,

regional lymph node metastases and distant metastases with the highest R-value being reported. Regarding differentiation, only well or poorly were considered, while specimens classified as intermediate differentiation (n=14) were deemed indeterminable. Eight of these cases were high-grade GEP NEN, where it was not possible to separate NEC from NET G3. Thus, they were termed uncertain NEN G3 as previously described (4). Chemotherapy was defined as chemotherapy administrated in relation to surgery (pre- or postoperative treatment). Curative intent was defined as the situation where the patient prior to surgery was considered to have an achievable curative R0 resection.

OS and DFS/PFS were analysed as cumulative survival with 95% CI using Kaplan Meier estimates. For patients with curatively resected tumours with an R0 resection, DFS and OS were reported as five-year rates in addition to the median. For the remaining patients, DFS and OS were reported only as medians. Groups were compared with log-rank test. Univariate Cox regression model was used to evaluate association between included exposure variables and OS as well as PFS/DFS. Estimates were reported as hazard ratios (HR) with 95% confidence intervals (CI). To test the independent effect, significant variables were included in multivariate analyses. Proportional hazard assumption for exposure variables was investigated with log minus log plots with natural logarithm of follow-up time. Linear effect for continuous variables was evaluated by including the second order polynomial of the variables in the model. Dichotomous variables were compared by Fischer's exact test. Continuous variables are presented as median with range due to non-normal distribution. We used IBM SPSS statistic version 23 with statistical significance defined as p.

Results

We included 206 patients, of whom five were excluded because resection of the primary tumor was not performed (resection of metastases only). Thus, 201 patients were eligible for analysis (123 patients from the prospective database, 78 from the retrospective database). Patient characteristics are given in Table 1. A total of 26 postoperative complications occurred in 24 patients (11.9%). Nine patients (4.5%) had anastomotic leakage requiring reoperation and eight (4.0%) had anastomotic leakage treated conservatively. Three patients (1.5%) had bleeding requiring reoperation and six (3.0%) had bleeding managed conservatively. Two of these patients had both anastomotic leakage and bleeding. No patients died as a result of surgery measured at 30 days after the procedure. The median follow-up time from diagnosis regarding OS was 21 months (1-123) for

all patients, 23 months (1-122) for stage I-III and 11 months (1-121) for stage IV. The median follow-up time from diagnosis regarding PFS/DFS was eight months (0-123) for all patients, 11 months (0-123) for stage I-III and four months (0-103) for stage IV.

The majority of patients were diagnosed with NEC (68.2%), followed by MiNEN (23.4%), NET G3 (4.5%) and uncertain NEN G3 (3.9%). The median age was 68 years. The majority of patients were men (56.7%) and 44.7% had a performance status of 0. In 53.2% of cases the primary tumour was colorectal and 71.1% had no distant metastases. Tumours were mainly of large cell type (84.0%) and poorly differentiated with a Ki-67% ≥ 55% (77.6%). In 14 tumours (six MiNEN and eight NEN), differentiation was indeterminable. The most frequently reported stage was stage IIIB (46.3%) and most patients were operated with curative intent (81.1%). An R0 resection was achieved in 65.7% of patients.

Of the 154 patients with high-grade GEP NEN, 137 (89%) were NEC, nine (5.8%) were NET G3 and eight (5.2%) were uncertain NEN G3. In patients with NEC, 70.1% had large cell type and Ki-67% was ≥ 55% in 86.1% of cases (median 90 (21-100)). In patients with NET G3, Ki-67% was ≥ 55% in 11.1% of cases (median 30 (21-60)). In patients with uncertain NEN G3, all tumours were large cell type and Ki-67% was ≥ 55% in 37.5% of cases (median 40 (25-90)). Among the 47 patients with MiNEN, the neuroendocrine component was poorly differentiated in 35 (74.5 %), well in two, indeterminable in six and with missing data in four. Ki-67% was ≥ 55% in 72.3% (median 80 (25-100)), and large cell type in all cases. Tumour types and differentiation of MiNEN for the four largest primary tumour sites are shown in Table 2. There were no differences in OS or DFS/PFS between high-grade GEP NEN and MiNEN for the different primary sites.

Eighty-eight patients (44.4%) received perioperative chemotherapy; 19 neoadjuvant, 49 adjuvant and 20 both. The indication for chemotherapy was based on institutional practice. In the Nordic NET centres, preoperative treatment is normally used for downstaging, and postoperative adjuvant chemotherapy is considered after radically resected primary tumour with local lymph node metastasis. In general, platin/etoposide was preferred in NEC, and 5-fluorouracil-based therapy in MiNEN with adenocarcinomas - with modifications according to primary organ site.

All stages of disease

Median PFS/DFS for all included patients was 9 months (95% CI 6.4-11.6) from surgery and median OS was 26 months (95% CI 19.9-32.1) from diagnosis. Patients with stage I-III disease had longer median PFS/DFS (12 months (95% CI 5.2-18.8) vs 4 months (95% CI 1.9-6.1)) and OS (32

months (95%CI 24.0-40.0) vs 11 months (95%CI 4.8-17.2)) compared with stage IV (log-rank test, p<0.001, Figure 1a and 1b). PFS/DFS and OS decreased with increasing stage (log-rank test, p<0.001, Figure 1c and 1d).

Median PFS/DFS after R0 resection was 17 months (95% CI 9.1-25.0) and median OS was 36 months (95% CI 27.9-44.1). Patients with stage I-III had a longer DFS compared with PFS/DFS of stage IV patients (log-rank test, p=0.007, Figure 1e). However, OS was not significantly different between stage I-III and stage IV if an R0 resection had been obtained (log-rank test, p=0.465, Figure 1f).

The median PFS after R1 resection was 8 months (95% CI 3.7-12.3) and median OS was 22 months (95% CI 16.0-28.1), while for patients with R2 resection, median PFS was only 2 months (95% CI 0.3-3.7) and median OS 8 months (95% CI 6.8-9.2). These differences in PFS/DFS and OS were significant (R0 vs R1 vs R2, log-rank test, p<0.001, R0+R1 vs. R2, log-rank, p<0.001).

Patients with high-grade GEP NEN (n=154) had a median PFS/DFS of 7 months (95% CI 4.2-9.8) and a median OS of 26 months (95% CI 18.0-34.0). In patients with GEP MiNEN (n=47), the median PFS/DFS was 13 months (95% CI 5.4-20.6) and the median OS was 26 months (95% CI 17.8-34.2). There was no difference in PFS/DFS or OS between patients with high-grade GEP NEN and MiNEN, even when corrected for stage in cox-regression.

Stage I-III disease

One-hundred and forty-three patients with stage I-III disease had a primary tumour resection, with a median follow-up of 23 (1-123) months from diagnosis. One patient had debulking surgery, leaving 142 patients resected with curative intent. Median DFS was 12 months (95% CI 5.5-18.5) and median OS was 32 months (95% CI 24.0-40.0).

In 112 patients where an R0 resection was obtained, five-year DFS was 33.8% (95% CI 22.6-45.3) and median DFS was 21 months (95% CI 4.9-37.1). Five-year and median OS were 42.1% (95% CI 30.3-53.5) and 39 months (95% CI 25.0-53.0), respectively. Tumour sites were upper GI tract (46.6%), colorectal (37.9%) and pancreas (15.5%). Of the 58 (51.8%) experiencing disease recurrence during follow-up, 51 (87.9%) patients had distant recurrence only, five (8.6%) had distant and local recurrence (one pancreatic, one rectal, one gastric cardia, two esophageal) and two (3.4%) had local recurrence only (colon). Regarding patients with R1 or R2 resections, median PFS was 8 months (95% CI 4.6-11.4) and median OS was 21 months (95% CI 17.6-24.4). Patients

with R1 or R2 resections had a shorter PFS/DFS (p=0.004, Figure 2a) and OS (p=0.012, Figure 2b) compared to patients with R0 resection. Lastly, there was no difference in PFS/DFS and OS between patients with NET G3, NEC Ki-67% < 55% and NEC Ki-67% ≥ 55%.

In univariate Cox regression analysis, poor PS, advanced stage, positive resection margins and time from diagnosis to surgery were significantly associated with a shorter PFS/DFS. Poor PS, advanced stage and positive resection margins were associated with shorter overall survival (Table 3). In the multivariate Cox regression analysis, only poor PS remained significantly associated with shorter OS (Table 4). Time from diagnosis to surgery was strongly correlated with receiving neoadjuvant therapy (p<0.001, Mann-Whitney and linear regression) and was not significant in multivariate Cox regression (corrected for stage).

Stage IV disease

Fifty-eight patients with stage IV disease underwent surgery with a median follow-up of 11 months (0-122). Median PFS/DFS was 4 months (95% CI 1.9-6.1) and median OS was 11 months (95% CI 4.8-17.2).

In the 18 patients with an R0 resection, median PFS/DFS was 6 months (95% CI 0-16.4) and median OS was 32 months (95% CI 25.5-38.5), respectively. R1 resection was obtained in two patients and R2 in 38. There was no significant difference in PFS/DFS with regard to resection margins. However, OS was shorter for patients with R1/R2 resections (R0 vs R1/R2, log-rank test, p=0.002, Figure 2c).

Thirty patients underwent resection of metastases in addition to the primary tumour of which 16 resections were curatively intended. In these patients, an R0 resection was obtained in 13 with a five-year DFS of 15.4% (95% CI 2.5-38.8), median DFS of 10 months (95% CI 1.8-18.2), five-year OS of 35.7% (95% CI 9.8-63.4) and median OS of 35 months (95% CI 17.1-52.9), respectively. R1 resection was obtained in one patient and R2 in two. There was no significant difference in DFS or OS with regard to resection margins.

Operation was non-curatively intended in 37 patients where the majority had macroscopic residual tumour at the resection site (R2 resections in 32, R1 in one and R0 in four). The indications for surgery among these patients were debulking (12 patients), release of obstruction (four patients), acute operation (one patient), operation for diagnostic purposes (two patients), release of obstruction and acute operation (eight patients) debulking, release of obstruction and acute operation (three patients), debulking and release of obstruction (six patients),

debulking and acute operation (one patient). OS was shorter in patients operated with non-curative intent (log-rank test, p=0.014). However, there was no significant difference in PFS/DFS between these groups.

In the univariate Cox regression analysis, a colorectal primary tumour location, a high Ki-67% and residual tumour were associated with significantly shorter PFS/DFS. Poor PS, a colorectal primary tumour location, residual tumour and bowel obstruction were associated with a significantly shorter OS, whereas curative intent as indication was associated with a favourable prognosis (Table 5). In the multivariate Cox regression analysis, poor PS and colorectal primary tumour location remained significantly associated with shorter OS (Table 6). However, of the 38 patients with R2 resections among stage IV patients, 28 (73.7%) had colorectal primary tumour. Among the subgroup of stage IV patients with R0 resections, colorectal primary tumour location was not significant in the multivariate cox regression for OS or PFS/DFS.

Discussion

In the present study, we showed that in patients with high-grade GEP NEN or MiNEN where an R0 resection was achieved, median PFS/DFS was 17 months (95% CI 9.1-25.0) and median OS was 36 months (95% CI 27.9-44.1). For patients with stage I-III and a curatively intended R0 resection, median DFS was 21 months (95% CI 4.9-37.1) and median OS was 39 months (95% CI 25.0-53.0). Our study shows that surgery of the primary tumour in patients with loco-regional high-grade GEP NEN or MiNEN has good long-term results. In addition, surgery of primary tumour and distant metastatic disease (stage IV) may be considered in suitable patients. We found a median DFS of 10 months (95% CI 1.8-18.2) and a median OS of 35 months (95% CI 17.1-52.9) in patients with curatively intended resections and R0 margins. PS and colorectal primary tumour (stage IV only) were the only factors associated with prognosis, while there was no influence by Ki-67%, tumour differentiation or perioperative chemotherapy. Moreover, there was no difference between high-grade GEP NEN and MiNEN in terms of prognosis.

In a retrospective study including 60 patients with stage I-III high-grade GEP NEN, a 2-year OS of 64.5% was found following radical surgery (R0/R1) (18). The study showed a significant difference in OS between patients with Ki-67% ≥55% and <55% and between NET G3 and NEC patients. This could not be reproduced in our results, which may be due to a small number of NET G3 in our material. Another study of 32 patients with stage IV high-grade GEP NEN (75%

poorly differentiated) confined to the liver showed a five-year OS of 43% after curatively intended liver surgery (19). In another study of 15 patients with stage IV high-grade GEP NEN with R0 or R1 resections, median DFS was 8 months and median OS was 59 months (20). The long survival may be explained by a high proportion of NET G3 (46.7%) in that study. In the Nordic NEC study (21), 305 patients with stage IV GEP NEC who received chemotherapy or best supportive care in the period 2000-2009 were retrospectively evaluated. Median overall survival for patients receiving chemotherapy was 11 months (95% CI 9.4–12.6).

There is controversy in the literature concerning resection of pancreatic NEC which according to some guidelines is not recommended (10, 11). In a retrospective Nordic multicentre study of 119 patients with pancreatic NEC, surgical treatment, chemotherapy, combination treatment and best supportive care were evaluated in 18 patients with localized disease and in 101 patients with metastatic disease (22). Resection of the primary tumour was an independent prognostic factor for improved survival regardless of stage. In another study of 67 patients with pancreatic NET G3 (n=21) and NEC (n=46), survival was improved after resection of NET G3, regardless of the presence of metastases (23). However, in patients with NEC, survival was not significantly improved after surgical treatment, independent of metastases. In our study, we did not find any effect of the primary tumour location, except in stage IV colorectal tumours. Another study of 59 patients with pancreatic NEC stage III or stage IV, 23 patients (39%) underwent resection (8 stage IV and 15 stage III) (24). Among patients in whom an R0/R1 resection was obtained, median disease specific survival was improved compared with R2 or no resection (35 months vs 11 months). Our results showed a worse prognosis for patients with stage IV colorectal primary tumours. In a retrospective study of 126 patients with colorectal NEC, 67% had metastatic disease at the time of presentation. Of patients with non-metastatic disease, 71% had surgery performed. Three-year OS was 5 and 18% for metastatic and non-metastatic disease, respectively (25). In an analysis of the National Cancer Database in USA 2004–2015, 1208 patients with colorectal NEC (62.5% colon, 37.5% rectum) were evaluated (26). In patients with colonic tumours, 78.6% underwent resection whereas only 32.8% of patients with rectal tumours were resected. Patients undergoing surgery had a median survival of 10.5 months (95% CI 9.4–11.6) compared with 6.9 months (95% CI 6.2–7.6) for patients not undergoing surgery ($p<0.001$). Patients with no lymph node metastases and R0 resections had improved survival. Thus, despite the worse prognosis, surgery may still be beneficial in colorectal NEC if an R0 resection can be obtained. In a study of 49 patients who underwent surgery for esophageal or gastric MiNEN. One-, three- and five-year OS

rates were 71%, 50% and 35% and 62%, 50% and 39% for esophageal and gastric MiNEN, respectively (27). However, another study with 53 esophageal NEC or MiNEN found better prognosis for MiNEN (28). In the present study, we found no difference in prognosis between esophageal NEC and MiNEN.

The results of the present study may impact future clinical guidelines to recommend surgery in a wider patient population, even for selected patients with stage IV disease, when an R0 resection is deemed probable. Roughly half of our patient population had a colorectal primary tumour. Among stage IV patients, the association between a colorectal primary tumour location and prognosis seems to be influenced by a high R2 resection rate among colorectal primaries. However, among R0 resections there was no effect of tumour site on prognosis. This suggests that a colorectal primary location may be a contraindication for resection if an R0 resection is not deemed feasible. Due to a small number of patients, we are not able to give specific recommendations for the remaining primary tumour locations.

This study is the largest of its kind to date and the first partly prospective study with sufficient follow-up and substantial information on important variables. Apart from primary tumours in colon/rectum and esophagus/cardia, the remaining locations had small numbers of patients which reduces our ability to evaluate the outcome of these patients separately. In addition, patients in the present study undergoing surgery represent a selected population with better performance and less comorbidity compared with the average patient. Moreover, due to limitations in the collected data, we could not evaluate the impact of external radiation therapy in a relevant manner and this variable was therefore not included in the analyses. Furthermore, we did not find any effect of pre- or postoperative chemotherapy. However, data was limited by a lack of information regarding the intention of the treatment and whether concomitant radiation therapy was given. Lastly, time from diagnosis to surgery was strongly correlated with receiving neoadjuvant therapy. Thus, increased time from diagnosis to surgery may represent patients with advanced tumours receiving neoadjuvant therapy. Indeed, time from diagnosis to surgery was not significant in multivariate analysis when corrected for stage.

In conclusion, we found that surgical treatment resulted in good long-term results and should be considered in selected patients with loco-regional high-grade GEP NEN and MiNEN if an R0 resection is considered achievable. Even selected patients with stage IV disease may benefit from radical surgery. The results of the present study may have an impact on future clinical guidelines concerning the recommendation of surgical treatment in this patient group.

Statement of Ethics

The study was approved by the Danish Data Protection Agency (30-30-0605) and Danish Patient Safety Authority (31-1521-453). Due to the retrospective design of the study, no written informed consent was required from patients.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of Interest Statement

UK and AS: research grants from Novartis and Ipsen, honorary from Novartis and Ipsen and advisory board Ipsen and Novartis – all outside the present work. AS: medical consultant for Spago Nanomedical AB, Sweden. ET: Merck & Co., Pfizer inc., Ipsen and Novartis funded the participation in international conferences. BF: advisory board Novartis. HS: research grants from Novartis, Amgen and Ipsen, Advisory board for Novartis, Pfizer, Keocyt, AstraZeneca and Hutchinson, Honoraria from Novartis, BMS, Roche, Amgen, Ipsen, Merck, Shire, Celgene and Bayer. GOH: research support of honoraria from Ipsen, Amgen, BMS, MSD, Roche and Bayer. SL: Research grant from Abbvie. Advisory board Roche. Honoraria from Ipsen. Spouse ass. director in Genmab.

Author contributions

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Table 1: Patient characteristics

		Stage at operation					
		Stage I-III (n=143, 71.1%)		Stage IV (n=58, 28.9%)		Total (n=201)	
Age, median (range)		69 (27-91)		64 (34-84)		68 (27-91)	
Sex, n (%)	Male	82	57.3%	32	55.2%	114	56.7%
	Female	61	42.7%	26	44.8%	87	43.3%
Performance status, n (%)	0	71	49.7%	18	32.1%	89	44.7%
	1-2	69	48.3%	36	64.3%	105	52.8%
	3-4	3	2.1%	2	3.6%	5	2.5%
Location of primary tumour, n (%)	Esophagus	16	11.2%	0	0.0%	16	8.0%
	Gastric cardia	21	14.7%	2	3.4%	23	11.4%
	Stomach	8	5.6%	5	8.6%	13	6.5%
	Pancreas	15	10.5%	6	10.3%	21	10.4%
	Duodenum	7	4.9%	0	0.0%	7	3.5%
	Jejunum/ileum	3	2.1%	7	12.1%	10	5.0%
	Colon	47	32.9%	32	55.2%	79	39.3%
	Rectum	23	16.1%	5	8.6%	28	13.9%
	Gallbladder	2	1.4%	1	1.7%	3	1.5%
	Anal canal	1	0.7%	0	0.0%	1	0.5%
Metastatic sites*, n (%)	None	143	100.0%	0	0.0%	143	71.1%
	One site	0	0.0%	37	63.8%	37	18.4%
	> One site	0	0.0%	21	36.2%	21	10.4%
NEC/MINEN/NET G3, n (%)	NEC	90	62.9%	47	81.0%	137	68.2%
	MINEN	41	28.7%	6	10.3%	47	23.4%
	NET G3	6	4.2%	3	5.2%	9	4.5%
	Uncertain NEN G3	6	4.2%	2	3.4%	8	4.0%
Cell type, n (%)	small cell carcinoma	13	11.2%	8	16.0%	21	16.0%
	large cell carcinoma	103	88.8%	42	84.0%	145	84.0%
Differentiation, n (%)	Poorly	112	84.8%	49	90.7%	161	86.6%
	Well	8	6.1%	3	5.6%	11	5.9%
	Indeterminable	12	9.1%	2	3.7%	14	7.5%
Ki-67%, n (%)	<55	31	21.7%	14	24.1%	45	22.4%
	≥55	112	78.3%	44	75.9%	156	77.6%
Stage at operation, n (%)	I	5	3.5%	0	0.0%	5	2.5%
	IIA	16	11.2%	0	0.0%	16	8.0%
	IIB	27	18.9%	0	0.0%	27	13.4%
	IIIA	1	0.7%	0	0.0%	1	0.5%
	IIIB	93	65.0%	0	0.0%	93	46.3%
	IV	0	0.0%	58	100.0%	58	28.9%

	< IV	1	0.7%	0	0.0%	1	0.5%
Resection margins**, n (%)	R0	112	80.0%	18	31.0%	130	65.7%
	R1	26	18.6%	2	3.4%	28	14.1%
	R2	2	1.4%	38	65.5%	40	20.2%
Curative intent, n (%)	Yes	142	99.3%	21	36.2%	163	81.1%
	No	1	0.7%	37	63.8%	38	18.9%
Debulking, n (%)	Yes	1	0.7%	22	37.9%	23	11.5%
	No	141	99.3%	36	62.1%	177	88.5%
Bowel obstruction, n (%)	Yes	18	12.7%	23	40.4%	41	20.6%
	No	124	87.3%	34	59.6%	158	79.4%
Emergency surgery, n (%)	Yes	7	4.9%	14	24.6%	21	10.6%
	No	135	95.1%	43	75.4%	178	89.4%
Perioperative chemotherapy, n (%)	Yes	75	46.8%	13	22.8%	88	44.4%
	No	66	53.2%	44	77.2%	110	55.6%
Time from diagnosis to surgery (months), median (range)		0 (0-7)		0 (0-25)		0 (0-25)	

* metastatic sites: liver, distant lymph nodes, lung, bone, other

** for patients with stage I-III disease margins regarded the highest R-stage for primary tumor or regional lymph nodes metastases, for patients with stage IV disease margins regarded the highest R-stage for primary or resected metastases (excluding regional lymph nodes)

Table 2: Tumour types and differentiation of MiNEN for the four largest primary tumour sites

	Colorectal (n=107)	Gastric cardia (n=23)	Pancreas (n=21)	Esophagus (n=16)
Tumour type	82 NEC (76.6%) 22 MiNEN (20.6%) 3 NET G3 (2.8%)	16 NEC (69.6%) 7 MiNEN (30.4%)	14 NEC (66.7%) 5 MiNEN (23.8%) 2 NET G3 (9.5%)	8 NEC (50%) 8 MiNEN (50%)
Differentiation of MiNEN	17 poorly (77.3%) 1 well (4.5%) 2 indeterminable (9.1%) 2 data missing (9.1%)	6 poorly (85.7%) 1 indeterminable (14.3%)	1 poorly (20%) 1 well (20%) 2 indeterminable (40%) 1 data missing (20%)	6 poorly (75%) 1 indeterminable (12.5%) 1 data missing (12.5%)

Table 3: Univariate Cox regression for patients with Stage I-III disease resected with curative intent (n=142)

	Overall survival		Progression/disease free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (0.99-1.03)	0.300	1.00 (0.98-1.02)	0.789
Gender (female)	0.73 (0.46-1.17)	0.194	0.70 (0.45-1.08)	0.107
Performance status	2.12 (1.57-2.86)	**<0.001**	1.49 (1.15-1.95)	**0.003**
Primary tumour location	1.23 (0.78-1.63)	0.527	1.15 (0.82-1.62)	0.414
Colorectal primary tumour	0.74 (0.47-1-18)	0.203	0.67 (0.44-1.03)	0.065
High-grade GEP NEN vs MINEN	1.10 (0.68-1.79)	0.697	0.85 (0.54-1.35)	0.488
Cell type (large cell vs small)	1.57 (0.67-3.64)	0.296	0.87 (0.43-1.75)	0.691
Differentiation (well vs poor)	0.77 (0.28-2.12)	0.613	0.70 (0.26-1.93)	0.496
Ki-67%	1.00 (0.99-1.01)	0.667	1.00 (0.99-1.01)	0.895
Stage at operation	1.19 (1.00-1.42)	**0.048**	1.25 (1.05-1.48)	**0.011**
Resection margins	1.91 (1.17-3-10)	**0.009**	1.86 (1.19-2.90)	**0.007**
Bowel obstruction	1.19 (0.62-2.25)	0.603	1.33 (0.75-2.36)	0.329
Emergency surgery	2.50 (1.00-6.28)	0.051	1.31 (0.53-3.25)	0.559
Perioperative chemotherapy	0.96 (0.61-1.52)	0.852	0.90 (0.59-1.37)	0.624
Time from diagnosis to surgery	1.08 (0.94-1.25)	0.295	1.18 (1.03-1.34)	**0.019**

HR: hazard ratio. 95% CI: 95% confidence intervals. Progression/disease free survival was measured from the time of surgery, whereas OS was measured from the time of diagnosis.

Table 4: Multivariate Cox regression for patients with Stage I-III disease resected with curative intent (n=142)

	Overall survival		Progression/disease free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Performance status (≥1 vs 0)	2.18 (1.31-3.63)	**0.003**	1.43 (0.90-2.27)	0.133
Stage at operation (III vs I-II)	1.34 (0.77-2.34)	0.298	1.63 (0.97-2.75)	0.067
Resection margins primary tumour + regional lymph nodes (R1/R2 vs R0)	1.48 (0.86-2.54)	0.156	1.66 (1.00-2.78)	0.052
Time from diagnosis to surgery	-	-	1.15 (1.00-1.33)	0.054

HR: hazard ratio. 95% CI: 95% confidence intervals. Progression/disease free survival was measured from the time of surgery, whereas OS was measured from the time of diagnosis.

Table 5: Univariate Cox regression for patients with Stage IV disease (n=58)

	Overall survival		Progression/disease free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (0.99-1.04)	0.358	1.01 (0.99-1.03)	0.404
Gender (female)	1.23 (0.70-2.18)	0.472	0.90 (0.53-1.55)	0.714
Performance status	2.37 (1.20-4.66)	**0.013**	1.24 (0.87-1.76)	0.246
Primary tumour location	0.66 (0.40-1.08)	0.099	0.66 (0.41-1.08)	0.096
Colorectal primary tumour	2.63 (1.42-4.90)	**0.002**	1.91 (1.07-3.42)	**0.029**
Metastatic sites (0,1,>1)	1.40 (0.77-2.53)	0.271	1.13 (0.65-1.99)	0.661
High-grade GEP NEN vs MINEN	1.91 (0.74-4.98)	0.183	1.44 (0.61-3.39)	0.409
Cell type (large cell vs small)	0.69 (0.31-1.57)	0.379	0.88 (0.41-1.90)	0.741
Differentiation (well vs poor)	0.16 (0.02-1.16)	0.069	0.34 (0.08-1.39)	0.132
Ki-67%	1.01 (1.00-1.02)	0.147	1.01 (1.00-1.02)	**0.034**
Resection margins	1.79 (1.27-2.52)	**0.001**	1.40 (1.02-1.91)	**0.035**
Curative intent	0.47 (0.26-0.88)	**0.018**	0.71 (0.40-1.24)	0.229
Debulking	1.10 (0.61-1.98)	0.764	0.83 (0.47-1.44)	0.496
Bowel obstruction	2.32 (1.29-4.19)	**0.005**	1.49 (0.86-2.60)	0.156
Emergency surgery	0.95 (0.49-1.88)	0.890	0.94 (0.50-1.77)	0.855
Perioperative chemotherapy	0.50 (0.24-1.04)	0.062	0.52 (0.26-1.02)	0.055
Time from diagnosis to surgery	0.92 (0.83-1.02)	0.116	0.99 (0.92-1.06)	0.736

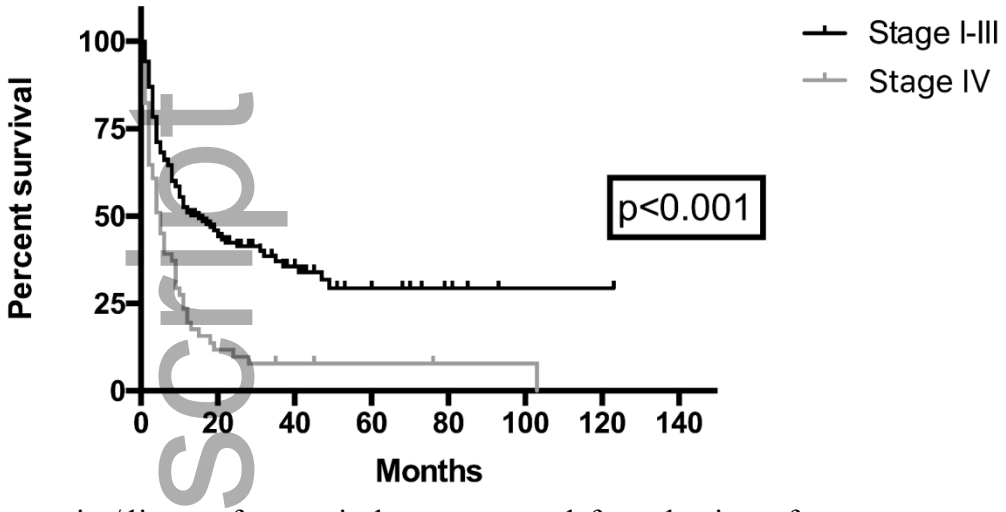
HR: hazard ratio. 95% CI: 95% confidence intervals. Progression/disease free survival was measured from the time of surgery, whereas OS was measured from the time of diagnosis.

Table 6: Multivariate Cox regression for patients with Stage IV disease (n=58)

	Overall survival	
	HR (95% CI)	p-value
Performance status (≥1 vs 0)	4.60 (2.02-10.5)	**<0.001**
Colorectal primary tumour	4.50 (2.03-10.0)	**<0.001**
Resection margins primary tumour + metastases (R1/R2 vs R0)	1.44 (0.60-3.46)	0.418
Curative intent	0.49 (0.20-1.22)	0.128
Bowel obstruction	1.02 (0.49-2.12)	0.966
	Progression/disease free survival	
	HR (95% CI)	p-value
Colorectal primary tumour	1.42 (0.69-2.95)	0.345
Ki-67%	1.01 (0.99-1.02)	0.247
Resection margins primary tumour + metastases (R1/R2 vs R0)	1.70 (0.93-3.11)	0.087

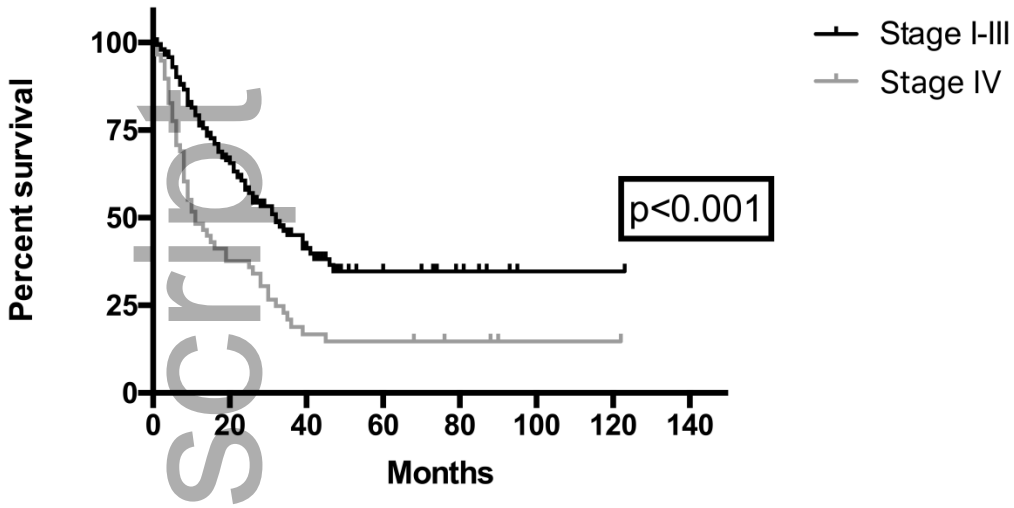
HR: hazard ratio. 95% CI: 95% confidence intervals. Progression/disease free survival was measured from the time of surgery, whereas OS was measured from the time of diagnosis.

Figure 1a: Disease/progression free survival of Stage I-III and Stage IV patients



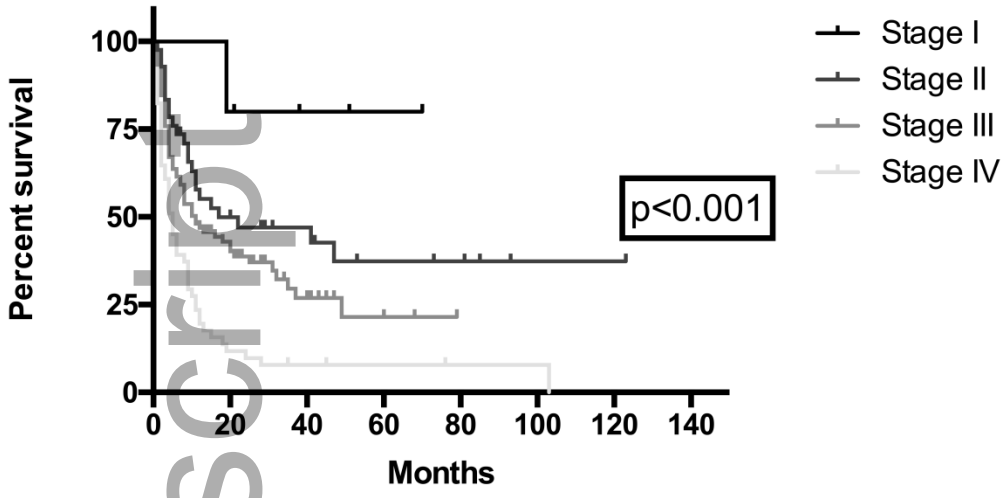
Progression/disease free survival was measured from the time of surgery.

Figure 1b: Overall survival of Stage I-III and Stage IV patients



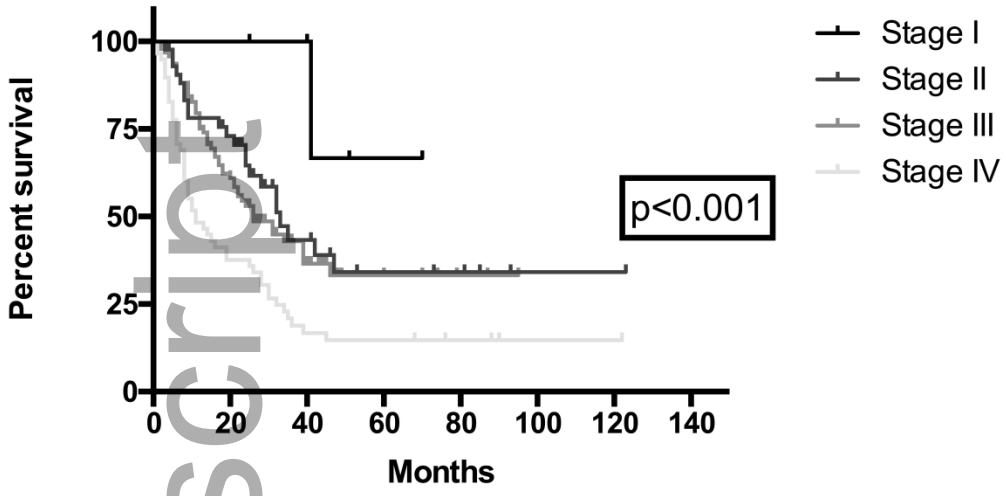
OS was measured from the time of diagnosis

Figure 1c: Disease/progression free survival in Stage I-IV patients



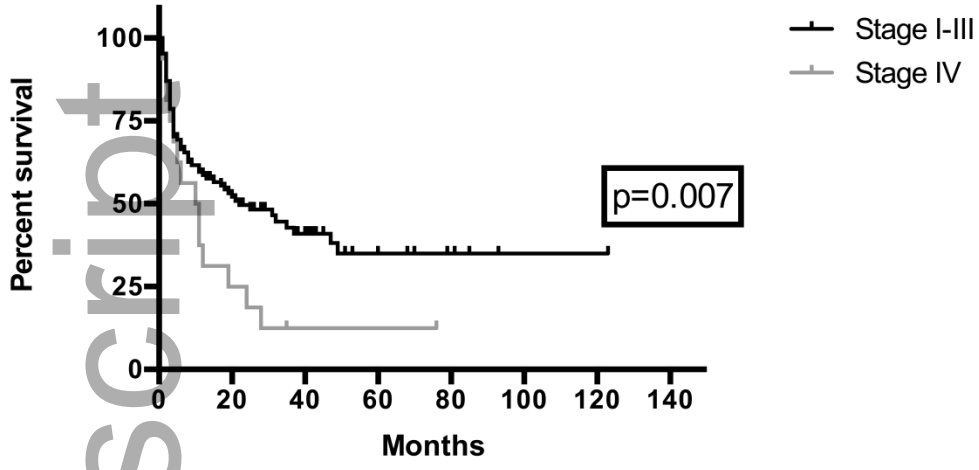
Progression/disease free survival was measured from the time of surgery.

Figure 1d: Overall survival in Stage I-IV patients



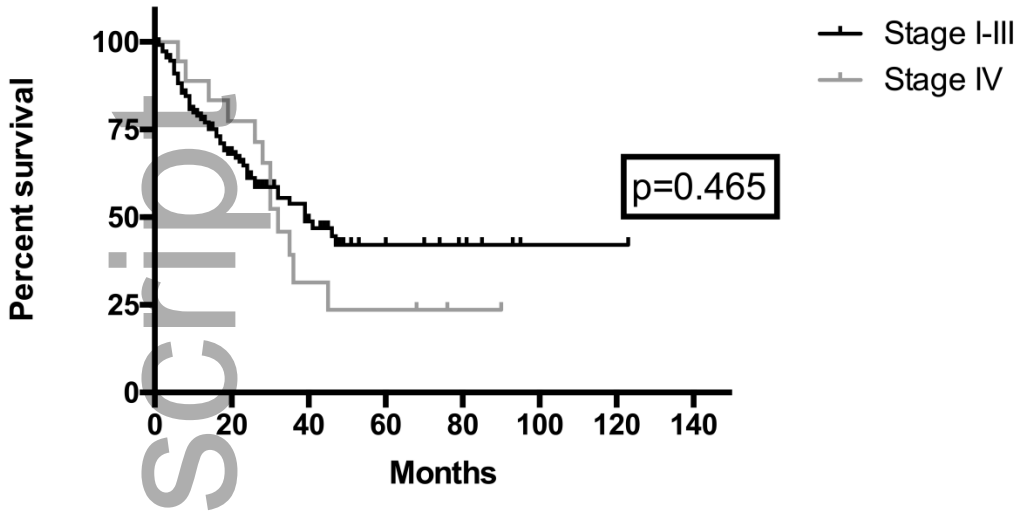
OS was measured from the time of diagnosis.

Figure 1e: Disease free survival of Stage I-III and Stage IV patients with R0 resection



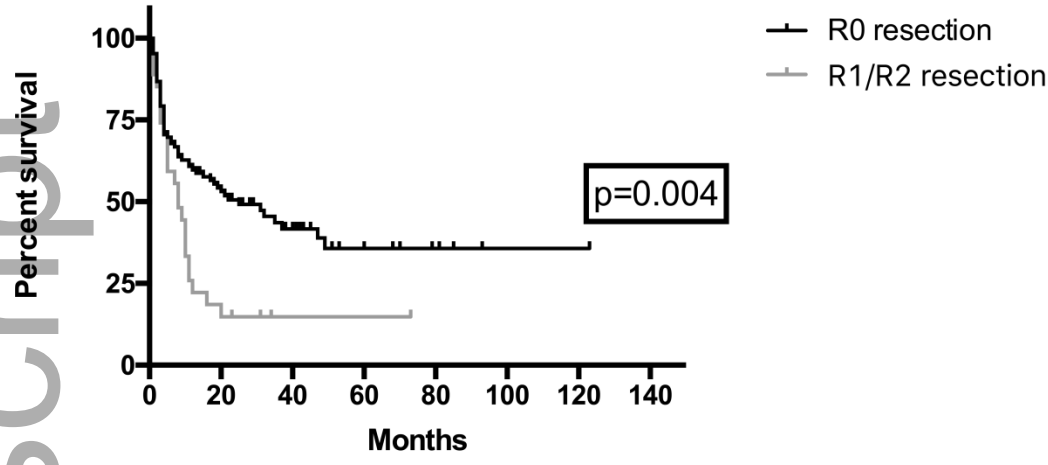
Progression/disease free survival was measured from the time of surgery.

Figure 1f: Overall survival of Stage I-III and Stage IV patients with R0 resection



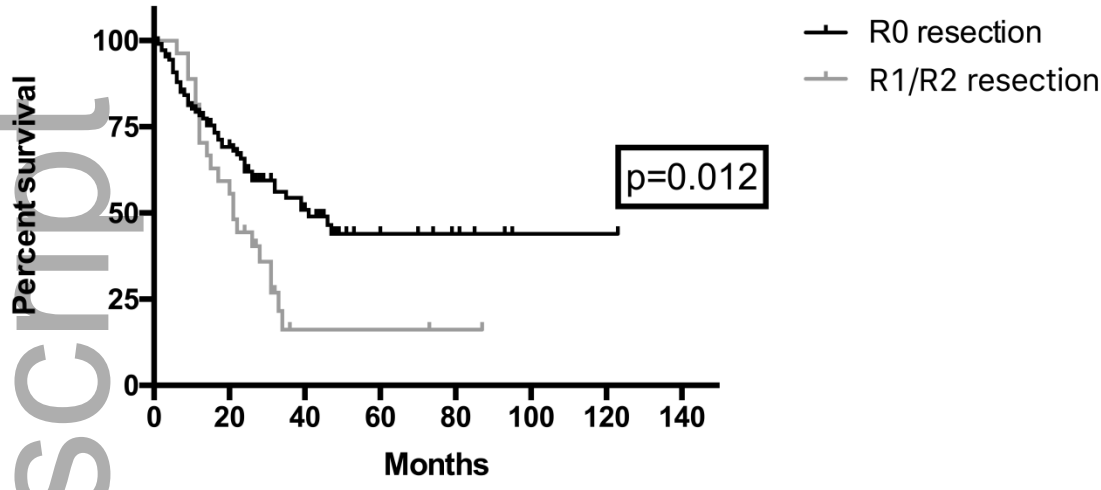
OS was measured from the time of diagnosis.

Figure 2a: Disease/progression free survival of patients with R0 or R1/R2 resection and stage I-III disease



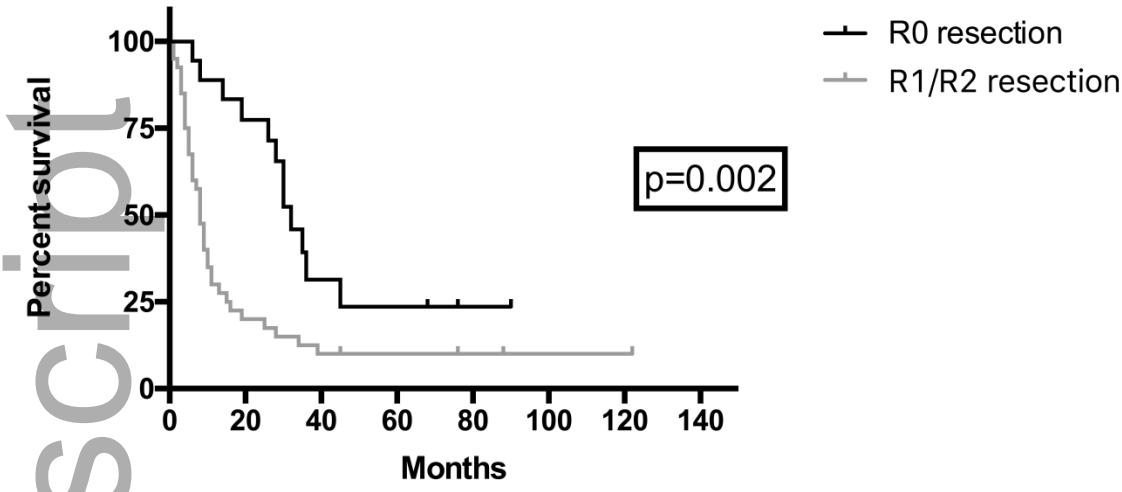
Progression/disease free survival was measured from the time of surgery.

Figure 2b: Overall survival of patients with R0 or R1/R2 resection and stage I-III disease



OS was measured from the time of diagnosis.

Figure 2c: Overall survival of patients with R0 or R1/R2 resection and stage IV disease



OS was measured from the time of diagnosis.