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ABSTRACT

Objective:

The aim of this study was to evaluate the role of liver surgery as part of the treatment in high-grade metastatic gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC).

Background:

GEP-NECs are generally characterized by synchronous metastases, high aggressiveness and a dismal prognosis. Current international guidelines do not recommend resection of liver metastases in patients with metastatic GEP-NEC. However, the existing data are scarce.

Methods:

32 patients with a diagnosis of GEP-NEC (Ki-67 >20%) who had intended curative resection of liver metastases, were identified among 840 patients from two Nordic GEP-NEC registries. Tumor morphology (well vs poor differentiation) was reassessed. Overall survival (OS) and progression-free survival (PFS) was assessed by Kaplan-Meier analyses for the entire cohort and for subgroups.

Results:

Median OS after resection of liver metastases was 35.9 months (95%-CI: 20.6–51.3) with a five-year OS of 43%. The median PFS was 8.4 months (95%-CI: 3.9-13). Four patients (13%) were disease-free after five years. Two of 32 patients (6.3%) had well-differentiated morphology and 20 patients (63%) had Ki-67≥55%. A Ki-67<55% and receiving adjuvant chemotherapy were statistically significant factors of improved OS after liver resection.

Conclusion:

Our results show a long survival after liver surgery for many metastatic GEP-NEC patients, particularly for the group with a Ki-67 of 21-54%. Our results indicate that resection of liver metastases may be considered for selected GEP-NEC patients and that postoperative chemotherapy seems beneficial.

INTRODUCTION:

Gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) is broadly defined as a poorly differentiated neuroendocrine neoplasm (NEN) with Ki-67>20% or mitotic rate>20/10 high-power fields.[1] In contrast to well differentiated neuroendocrine tumors (NET) (WHO G1-G2), GEP-NECs (WHO G3) are highly aggressive with a propensity for early metastases and a dismal prognosis.[2-6] At the time of diagnosis 57-88% have distant disease with the liver as the main metastatic site.[2, 5-7] Patients with localized GEP-NECs have a median survival of 16 months, while in the metastatic setting median survival is only five months.[6] Current guidelines recommend platinum-based chemotherapy as first line treatment for patients with metastatic GEP-NECs.[8-10] Three large-scale series have reported a median survival of 11-13 months in chemotherapy-treated patients.[5, 7, 11] Long-term survival is rare, with a three-year survival of only 5-10%.[5, 11] Several prognostic factors have retrospectively been identified e.g. performance status, proliferation rate (Ki67 index above or below 55%), differentiation (well –vs poorly differentiated), location of the primary tumor, platelet count and lactate dehydrogenase values.[7, 11, 12]

Surgical resection of liver metastases is an established treatment option in colorectal adenocarcinomas with a five-year survival rate of 36-59%.[13-16] For other primary tumor locations and tumor types the benefit of liver surgery is still uncertain.[17, 18] Due to the highly aggressive behavior and high risk of metastatic disease, the benefit of surgery for GEP-NEC patients have been questioned. International guidelines currently recommend surgery only for NEN G1/G2 with resectable liver metastases and in selected cases as debulking surgery, while for GEP-NEC (WHO G3) surgery in the metastatic setting is not recommended.[10, 19, 20] These recommendations are supported by a recent neuroendocrine expert consensus statement.[21]

Published data on liver surgery for metastatic GEP-NECs are scarce. One study found no benefit when resecting the primary tumor in localized or metastatic colonic NEC.[5] Two recent studies on pancreatic NECs showed improved survival after curative resection in localized disease compared with patients not undergoing surgery.[22, 23] Two studies evaluating the role of surgical resection of liver metastases in NEN patients, found a median survival of 6-15 months for the fraction of patients with poorly differentiated NENs.[12, 24] Two case reports describe long-term survival in NEC patients after locoregional treatment of their liver metastases.[25] [26]

Thus the possible benefit of surgical treatment of liver metastases in GEP-NEC is unsettled. With the current study we aim to evaluate whether resection of liver metastases has a role in metastatic GEP-NEC management. For this purpose we used two large Nordic GEP-NEC registries with 840 patients to identify patients where liver surgery of metastatic disease had been performed. We present demographic data and overall and progression free survival for these patients.

PATIENTS AND METHODS:

Patients with gastroenteropancreatic neuroendocrine carcinoma (WHO G3) with surgical resection of liver metastases were identified from two Nordic NEC registries. One registry is a retrospective GEP-NEC database consisting of 485 patients diagnosed between 2000 and 2012. The second registry is a prospective GEP-NEC database of 355 patients, collected from January 2013 to September 2015. Twelve Nordic tertiary care institutions have submitted data. Informed consent is obtained from all patients included in the registries. The inclusion criteria for the present study were: Histopathological confirmed diagnosis of a high-grade neuroendocrine neoplasm (NEN) with Ki-67>20%, a gastroenteropancreatic primary or

an unknown primary with predominantly abdominal tumor burden, either synchronous or metachronous liver metastases, surgical treatment and/or RFA of metastatic disease in the liver with a curative intent. Tumor morphology was classified as small-cell or non-small cell. A central review to assess histological differentiation (well differentiated morphology vs poorly differentiated morphology) was performed by four dedicated neuroendocrine pathologists (LT, AP, JYS, BF). If the Ki-67 value was reported from both the primary tumor and metastases, the higher value was adopted. A cut-off value of 55% for Ki-67 was used when performing statistical analyses.[11] We chose to use progression free survival instead of disease free survival as some of our patients never became disease free. The patient who died within 30 days of surgery was excluded from the subgroup analysis comparing patients that did and did not receive adjuvant chemotherapy. This was in order to avoid potential bias as this patient died before chemotherapy could be given. Previously described prognostic markers in GEP-NEC patients were applied for subgroup analyses.[11, 12] Number of metastases is an important prognostic marker after hepatic surgery for metastatic colorectal cancer, and was therefore included in the analyses.[27, 28]

STATISTICAL ANALYSES:

OS was defined as the time from resection of liver metastases to last follow-up or death. PFS was defined as the time from resection of liver metastases until progression or recurrence of the disease. Descriptive methods were used to characterize the patient population. The survival was assessed by Kaplan-Meier analyses for the entire patient population and for subgroups. We compared the subgroups by logrank and Breslow tests. Since the proportional hazard assumption could not be approved we used the Breslow test as main criterion and abstained from fitting a Cox model. The general significance level was set to 0.05. All

computation was done using SPSS 22 (IBM Corp., Armonk, NY, 2013) and the graphics were produced by Matlab 7.10 (The MathWorks Inc., Natick, MA, 2010)

RESULTS:

Patient characteristics:

From the combined Nordic GEP-NEC registries of 840 patients, we identified 40 patients who had undergone liver surgery for metastatic disease. Eight patients were excluded as they did not meet the inclusion criteria: One patient was not operated on with a curative intent; two patients underwent surgery several years before they had a NEC diagnosis; one patient had a primary mixed adenoneuroendocrine carcinoma (MANEC) and an adenocarcinoma removed from the liver; two patients had a Ki-67≤20% after pathological re-evaluation; one patient had a large cell carcinoma with negative chromogranin A and synaptophysin and, after pathological re-evaluation, did not qualify as NEN. Among the remaining 32 patients, 29 had a known primary site and 27 of these had the primary tumor resected. One patient lacked information regarding surgical status of the primary tumor and one patient had a pancreatic primary not resected for unknown reasons. In 21 (66%) of the patients a NEC diagnosis was present before surgery. Distant lymph node involvement was reported for three patients, and these lymph nodes were removed simultaneously with the liver surgery in two of the patients. For the last patient relevant information is missing. The median interval from the primary NEC diagnosis to the diagnosis of liver metastases was 0 months (range 0-27 months). From the diagnosis of liver metastases to liver resection the median interval was 1.5 month (range 0-57 months). Table 1 describes the different procedures performed on the liver. The median diameter of the largest liver metastasis was

3.5cm (range 1-25cm). Median Ki-67 was 60% (range 25-100%) and 63% of the patients had Ki-67≥55%. Twenty three patients (70%) were amenable for the central pathological review. For three of the remaining patients the slides were evaluated by one of the present study pathologists, these three had Ki-67 values >80% and were all deemed poorly differentiated. In one patient, with a Ki-67 of 60%, the degree of differentiation could not be determined as the specimen was suboptimal. For the remaining five patients the histological slides could not be located. These had Ki-67 values of 30%, 37%, 45%, 70% and 95%. A complete list of patient characteristics is presented in Table 1.

Overall survival:

No patients were lost for follow-up. The median overall survival after liver surgery was 35.9 months (95% CI 20.6-51.3) (Figure 1a). Three-year survival after surgery was 47% and 5 year survival 43% (Table 2). For the 12 patients still alive at the time of the analysis, median follow-up was 46 months (range 23-184 months). Patients with a Ki-67of 21-54% had significantly longer survival than the group with a higher Ki-67 (61.6 vs. 21.2 months P=0.018) (Figure 1b). There was a trend towards longer survival for the group with a pancreatic primary, however these results did not reach statistical significance (40.6 vs. 21.2 months P=0.146) (Figure 1 c). There was a statistically significant longer survival for the group receiving adjuvant chemotherapy (66.8 vs. 29.9 months P=0.028) (Figure 1d). No significant difference was found when comparing the groups that did and did not receive neoadjuvant chemotherapy (>29.9 vs. 35.7 months P=0.142) (Table 2). Only two of the 26 patients with a known differentiation status had well differentiated tumor morphology, these two had an OS of 22.6 months (still alive) and 35.9 months (dead). Table 2 presents OS for the entire material and subgroups.

Recurrence and progression free survival:

Of the 32 patients, 28 had recurrence (five-year PFS: 13%) (Figure 2a). Three had local recurrence, 18 had hepatic recurrence, eight had lymph node recurrence, three had pulmonary recurrence, one had bone recurrence and five had recurrence in other localizations (ovary, cutaneous, peritoneum). Four of the patients had simultaneous recurrence in several locations. Twenty-three of the recurrences were treated with chemotherapy, five with surgery, two with best supportive care and five with other modalities (liver embolization, everolimus, interferon, somatostatin analog). The median progression free survival after liver surgery was 8.4 months (95% CI 3.9–13) (Figure 2a). In the group of patients with a Ki-67of 21-54% there was a trend towards longer PFS than in the group of patients with Ki67≥55% (11.3 vs. 5.0 months P=0.074) (Figure 2b). Having a pancreatic primary did not significantly affect PFS (40.6 vs. 21.2 months P=0.146) (Figure 2c). Receiving adjuvant chemotherapy significantly improved PFS (11.5 vs 5.0 months P=0.031) (Figure 2d). Table 2 presents PFS for the entire material and subgroups.

30-day morbidity and mortality:

Seven patients had complications within 30 days of surgery: wound infection treated with antibiotics, pancreatitis, small bowel obstruction requiring reoperation, pleural effusion requiring drainage, need for antibiotics and parenteral nutrition, postoperative thrombosis and abscess in the abdominal wall treated with antibiotics.

There were no fatalities due to surgery. One patient, with a resected small intestinal primary tumor, died within 30 days of liver surgery due to rapidly progressive disease with peritoneal carcinomatosis and liver recurrence.

Characteristics of long-term survivors without recurrence:

The four patients who were free from disease at the time of analysis had been followed for a median of 72.5 months (range: 60-184 months). Two had a primary pancreatic NEC, one had a colonic NEC and one had a rectal NEC. All had non-small cell morphology, three were poorly differentiated and one had an unknown tumor differentiation. The Ki-67 was 30%, 70%, 90% and 90%. The patients had few metastases (1-4) with a unilateral, synchronous presentation. The median size of the largest metastasis was 5.3cm (range 3-20 cm). All resections were R0. One patient received both neoadjuvant and adjuvant cisplatin/etoposide, one patient did not receive any chemotherapy and for the last two patients one received neoadjuvant and one received adjuvant cisplatin/etoposide.

DISCUSSION:

Liver surgery for metastatic GEP-NEC is currently not recommended in international guidelines. However the evidence for the recommendation is weak due to a paucity of data.

Since GEP-NEC is an aggressive disease with a median survival of 11 months and 3-year survival of less than 10% after palliative chemotherapy, it is important to explore alternative methods that could improve survival.[11] We present data from our retro- and prospective NEC registries comprising 840 patients with 32 having had intended curative surgery for liver metastases. The 32 patients with liver surgery presented with good performance status and most had liver surgery close to the time of diagnosis, reflecting probably a low tumor burden. The median OS of 35.9 months and 5-year survival of 43% is surprisingly high and in contrast to results from previous studies. Saxene et al found a median

OS of 15 months for their eleven patients with high grade NEC.[26] However, their inclusion criteria and methods differ from ours in several aspects. The high grade NEC patients represented only a small fraction of their material (11/74) and the surgery was not exclusively performed with a curative intent, but in 35% also with a debulking purpose. Furthermore, patient characteristics regarding tumor load, tumor grade (Ki-67-level), tumor differentiation and primary site were not specified for the high-grade group in Saxene's study. Cho et al did a similar study on metastatic NEN patients including seven high-grade cases.[12] These patients survived for a median of 6 months, but again relevant patient characteristics are not described.

Our long-term results are almost similar to results after liver surgery for metastatic colorectal cancer (mCRC), where median OS is 43-70 months and 5 year survival is 36-59%.[13-16] However, our PFS results (median 8.4 months and 5-year PFS 13 %) seem to be inferior compared to mCRC results with median PFS of 20-23 months and 5-year PFS of 24-35%.

Recent studies have demonstrated a new subgroup of neuroendocrine neoplasms with predominate pancreatic primaries and a high proliferation rate (Ki 67>20%), which place them into the G3 category, but with histologically well-differentiated morphology, thus coined as NET G3.[29, 30] However the distinction between NET G3 and NEC may be difficult to establish on routine pathologic assessment.[31, 32] Survival for the NET-G3 subgroup appears to be significantly longer than for patients with poorly differentiated high-grade tumors.[33] To ascertain that our material did not exclusively consist of well-differentiated cases, four experienced neuroendocrine pathologists reexamined available tumor slides. Only two of twenty-six patients had verified morphological well-differentiated tumors, and this can therefore not explain the long survival in our patients. In addition, given the higher incidence of NET G3 in pancreatic primaries we compared pancreatic primaries with the non-pancreatic primaries. This did not reveal a significance difference in overall survival and progression

free survival in this small sample size. Higher proliferation rate in GEP-NEC is associated with significantly worse OS.[11, 34, 35] In the Nordic NEC study, median OS was 14 months and 10 months for chemotherapy-treated patients with Ki67: 21-55% and Ki67≥55% respectively.[11] When we stratified our patients according to Ki-67 level, the group with Ki-67: 21-54% had the longest PFS and OS. However, also patients with a higher Ki-67 seemed to benefit from resection of liver metastases, with a median OS of 21.2 months and a 5-year survival of 31%. Our results seem to indicate a benefit from receiving adjuvant chemotherapy, whereas the value of neoadjuvant chemotherapy is more uncertain. Neoadjuvant chemotherapy may be considered in order to identify the rapidly progressive group who will not benefit from surgery. The possible benefit of surgery must be weighed against the risk of postoperative complications and of rapid postoperative disease progression. In our material there were no fatalities due to surgery, however the postoperative complication rate was reported to be 22%. Of special interest are the four patients without disease recurrence after a median time of follow-up of 72 months. These patients seem to have been cured of their disease.

Our study has some strengths and limitations. All patients are recruited from high-volume NEN centers reporting data to a central Nordic NEC database. Therefore the patients are well characterized with clinical and histopathological evaluation and with follow-up evaluated by NEN experts. However, a limitation is the retrospective design with a risk of confounding factors. The patients receiving liver surgery are most likely highly selected with good performance status, low comorbidity, no progression during preoperative chemotherapy and limited disease. The criteria for liver surgery depended on the local expertise and were thus not consistent throughout this cohort.

In conclusion, liver surgery in GEP-NEC patients with metastatic disease limited to the liver and with a curative intent may be considered as a possible part of the treatment plan

for selected patients, especially if the Ki-67 is in the range 21-54%. Although few in numbers, our results indicate a long survival for many patients and in some 10% likely cure after liver surgery for metastatic GEP-NEC. Adjuvant chemotherapy seems to improve survival. Further prospective studies would be necessary to define clinical and pathologic criteria for this modality in patients with high grade GEP-NEN.

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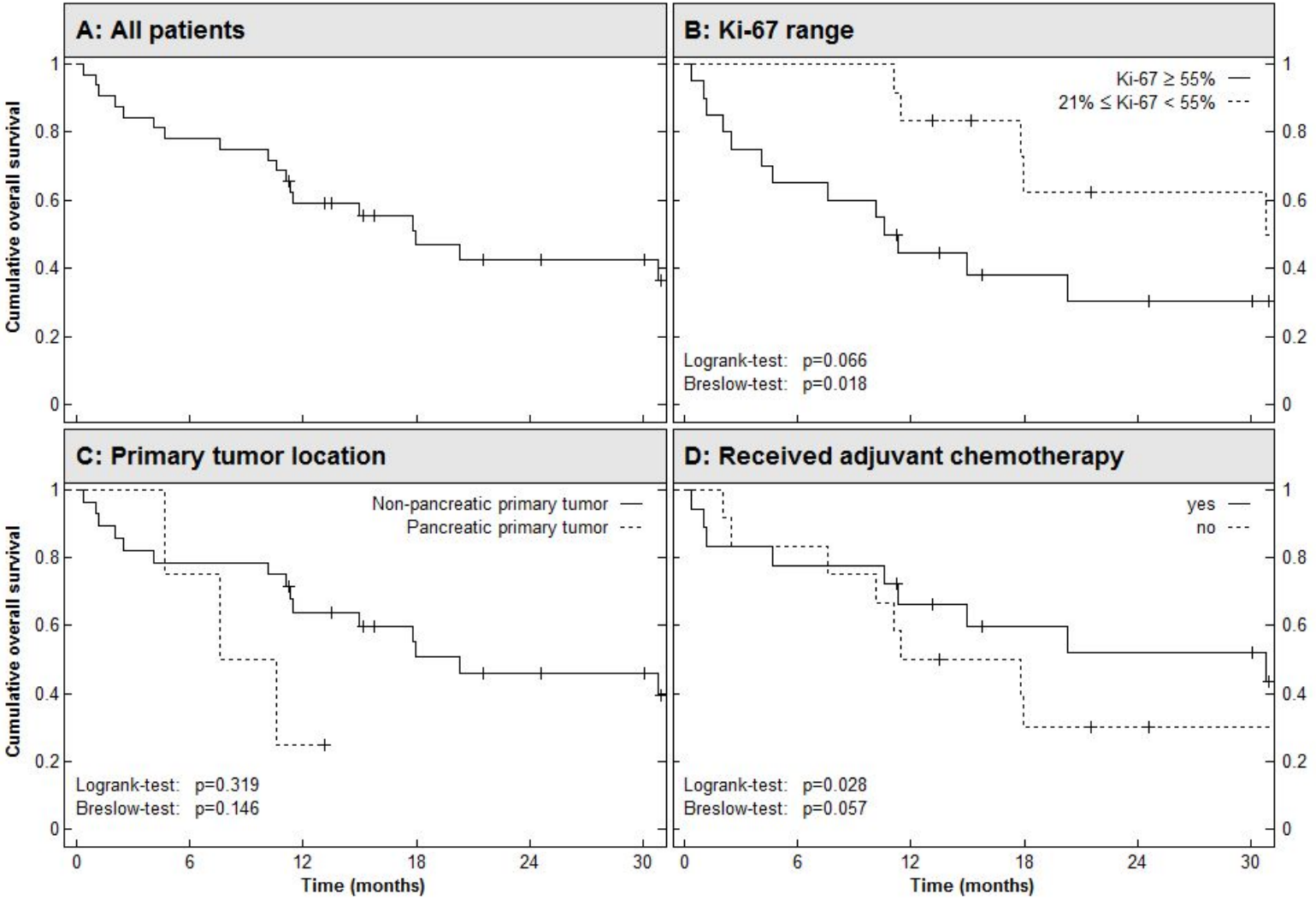
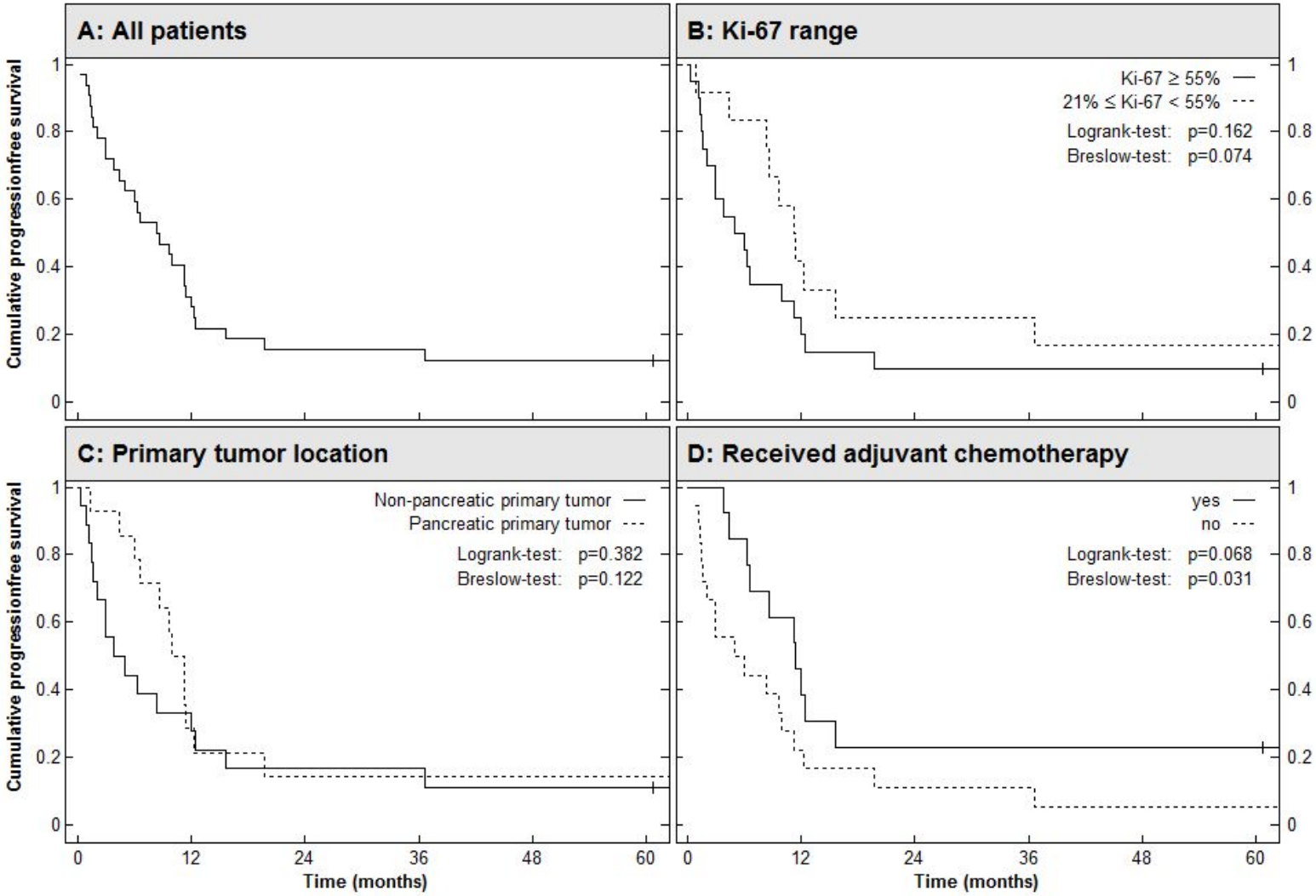

A: All patients
B: Ki-67 range
Ki-67 ≥ 55%
21% ≤ Ki-67 < 55%
Logrank-test: p=0.066
Breslow-test: p=0.018
C: Primary tumor location
Non-pancreatic primary tumor
Pancreatic primary tumor
Logrank-test: p=0.319
Breslow-test: p=0.146
D: Received adjuvant chemotherapy
yes
no
Logrank-test: p=0.028
Breslow-test: p=0.057
Cumulative overall survival
Time (months)
0
0.2
0.4
0.6
0.8
1
6
12
18
24
30


A: All patients
B: Ki-67 range
Ki-67 ≥ 55%
21% ≤ Ki-67 < 55%
Logrank-test: p=0.162
Breslow-test: p=0.074
C: Primary tumor location
Non-pancreatic primary tumor
Pancreatic primary tumor
Logrank-test: p=0.382
Breslow-test: p=0.122
D: Received adjuvant chemotherapy
yes
no
Logrank-test: p=0.068
Breslow-test: p=0.031
Cumulative progressionfree survival
Time (months)
0
0.2
0.4
0.6
0.8
1
12
24
36
48
60