Ann Surg Oncol (2016) 23:1721–1728
DOI 10.1245/s10434-015-5013-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Surgical Treatment as a Principle for Patients with High-Grade Pancreatic Neuroendocrine Carcinoma: A Nordic Multicenter Comparative Study

Sven-Petter Haugvik, MD[1,2], Eva Tiensuu Janson, MD, PhD[3], Pia Österlund, MD, PhD[4], Seppo W. Langer, MD, PhD[5], Ragnhild Sørum Falk, PhD[6], Knut Jørgen Labori, MD, PhD[1], Lene Weber Vestermark, MD, PhD[7], Henning Grønbæk, MD, PhD[8], Ivar Prydz Gladhaug, MD, PhD[1,2], and Halfdan Sorbye, MD, PhD[9]

[1]Department of Hepato-Pancreato-Biliary Surgery, Rikshospitalet, Oslo University Hospital, Oslo, Norway; [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [3]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [4]Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; [5]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [6]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway; [7]Department of Oncology, Odense University Hospital, Odense C, Denmark; [8]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [9]Department of Oncology, Haukeland University Hospital, Bergen, Norway

ABSTRACT

Background. This study aimed to evaluate the role of surgery for patients with high-grade pancreatic neuroendocrine carcinoma (hgPNEC) in a large Nordic multicenter cohort study. Prior studies evaluating the role of surgery for patients with hgPNEC are limited, and the benefit of the surgery is uncertain.

Methods. Data from patients with a diagnosis of hgPNEC determined between 1998 and 2012 were retrospectively registered at 10 Nordic university hospitals. Kaplan–Meier curves were used to compare the overall survival of different treatment groups, and Cox-regression analysis was used to evaluate factors potentially influencing survival.

Results. The study registered 119 patients. The median survival period from the time of metastasis was 23 months for patients undergoing initial resection of localized non-metastatic disease and chemotherapy at the time of recurrence ($n = 14$), 29 months for patients undergoing resection of the primary tumor and resection/radiofrequency ablation of synchronous metastatic liver disease ($n = 12$), and 13 months for patients with synchronous metastatic disease given systemic chemotherapy alone ($n = 78$). The 3-year survival rate after surgery of the primary tumor and metastatic disease was 69 %. Resection of the primary tumor was an independent factor for improved survival after occurrence of metastatic disease.

Conclusions. Patients with resected localized non-metastatic hgPNEC and later metastatic disease seemed to benefit from initial resection of the primary tumor. Patients selected for resection of the primary tumor and synchronous liver metastases had a high 3-year survival rate. Selected patients with both localized hgPNEC and metastatic hgPNEC should be considered for radical surgical treatment.

High-grade gastroenteropancreatic neuroendocrine carcinomas (NECs) are rare but increasing in incidence,[1,2] accounting for 10 to 20 % of all malignant gastroenteropancreatic neuroendocrine neoplasms (NENs).[3] A NEC is defined as an NEN with a Ki67 proliferation index >20 %.[4,5] High-grade pancreatic neuroendocrine carcinomas (hgPNECs) are highly malignant neoplasms that typically invade adjacent structures or have metastasized at diagnosis.[6] The median survival time for patients with advanced hgPNEC varies from 11 to 21 months.[1,7,8]

The largest cohort of patients with advanced gastroenteropancreatic NECs to date was recently published.[1] In this Nordic multicenter study that included 305 patients, 71 had an hgPNEC, and 15 % ($n = 11$) of these patients had a resection of the primary tumor. In another recent report, the

First Received: 30 October 2015;
Published Online: 17 December 2015

S.-P. Haugvik, MD
e-mail: sphaugvik@yahoo.de; svhaug@ous-hf.no

outcomes of surgery for 310 patients with pancreatic NENs, including 24 patients with hgPNEC, were presented.[9] However, the role of surgery for hgPNEC was not assessed further in either of these studies.

Although surgical treatment of hgPNEC is controversial because most patients experience recurrent disease, reports discuss a beneficial effect of surgical treatment on survival.[10–14] These studies are either small case reports/series or larger series with lack of a well-defined comparative group.

The current consensus guidelines of the European Neuroendocrine Tumor Society (ENETS) for the surgical treatment of hgPNEC refer to only two studies,[15,16] and state that "curative surgery should be attempted in localized disease" and that "debulking and surgery for liver metastases are not recommended".[17] The consensus guidelines of the North American Neuroendocrine Tumor Society (NANETS) state that "the benefit of surgery among patients who have completed a course of chemoradiation is uncertain," with no references to studies on pancreatic surgery.[18,19] Surgery is not even mentioned in the section on treatment for metastatic hgPNEC. Moreover, the European Society for Medical Oncology's (ESMO) guidelines state that "it is a general agreement not to operate on G3 pancreatic NEC." [20] This underscores the importance of defining the role of surgery for patients with hgPNEC.[11]

Because no clear evidence for the role of surgery used to treat hgPNEC exists, this study aimed to investigate the effect of surgery on the survival in patients with metastatic hgPNEC, and to identify potential prognostic factors for the survival in these patients. We investigated this in a retrospective study of data from a Nordic NEC registry.

METHODS

In this multicenter retrospective study, patients were identified from neuroendocrine registries, surgical records, chemotherapy registries, coding in hospital charts, and pathology coding at ten Nordic university hospitals. The 71 patients included in this study have been described previously in reports on another study with a different aim.[1]

The participating centers provided data as specified through standardized case report forms. An inclusion criterion was a histopathologically confirmed diagnosis of hgPNEC, defined as neuroendocrine tissue with a Ki67 value greater than 20 % in the primary tumor or metastasis pre- or intraoperatively, between August 1998 and October 2012. Histopathologic data were evaluated according to the World Health Organization (WHO) 2010 classification for NENs of the gastroenteropancreatic system[4] and the ENETS TNM classification.[21] In addition, resection status, tumor location, and tumor diameter were recorded.

Tumor morphology was based on pathology reports and classified into small cell or non-small cell morphology. Non-small cell morphology was defined as the presence of large-cell morphology or no mentioning of small-cell morphology in the pathology report. All Ki67 values reported for the subgroups that underwent surgery were from the primary tumor. For the patients not treated by surgery, the Ki67 values were not consistently from the primary tumor. The highest recorded value was used independently of organ. We chose to use a cutoff of 55 % for the Ki67 index because this cutoff value has previously been shown to distinguish two separate groups of gastroenteropancreatic NEC in terms of survival and response to chemotherapy.[1,22]

Performance status (PS) was defined according to the Eastern Cooperative Oncology Group (ECOG) definition [23] and registered at the time of the metastatic disease diagnosis. Reasons for exclusion from a surgical program included severe grade of comorbidity, preoperative findings of unresectable disease, and metastatic disease with aggressive tumor growth during the follow-up period.

Surgery of metastasis was defined as surgical resection, liver transplantation, and/or radiofrequency ablation (RFA) of liver metastases. The ethics committees in Norway, Sweden, Denmark, and Finland approved the study.

Follow-up time and overall survival were defined as the time from metastasis until death or last observation to minimize bias when the oncologic treatment of patients with synchronous metastatic disease was compared with the treatment of patients with metachronous metastatic disease. For the best supportive care (BSC) group, these parameters were defined from the time of diagnosis until death because these patients did not receive any active treatment. The survival times were censored at the end of the study (26 September 2013).

Statistical Analysis

Descriptive statistics are presented as frequencies, medians, ranges, and proportions. Overall survival was constructed using Kaplan–Meier curves with accompanying risk tables. Cox-proportional hazard models (uni- and multivariate) were fitted for evaluation of the effect of factors potentially influencing survival.

Due to the limited number of patients included in this study, we constructed a model with no more than six variables. After each of these variables had been subjected to an a priori evaluation to determine its clinical relevance, the following five variables, presumably independent, were included in the Cox-analysis: resection of primary tumor, courses of chemotherapy, Ki67, small cell morphology, and PS. The independence of the included variables was confirmed before performance of the Cox analysis. The assumption of proportional hazards was verified graphically and checked using tests of proportional hazard assumption. Cox-regression analysis was calculated based

on 3- and 5-year follow-up data. All p values lower than 0.05 were regarded as statistically significant. Data analysis was performed with the statistical software Stata (Version 13.1, StataCorp, College Station, Texas, USA).[24]

RESULTS

Patient Characteristics

The study enrolled 119 patients with a median age of 60 years (range 23–85 years). At the initial diagnosis, 85 % of the patients ($n = 101$) had metastatic disease. The main patient characteristics are presented in Table 1. The patients were divided into treatment groups as illustrated by the flowchart in Fig. 1.

Surgery

Of 28 patients (24 %) who underwent surgical treatment, 13 had a preoperative diagnosis of hgPNEC based on biopsy. For 14 patients, resection of the primary tumor in nonmetastatic disease (SURG1) was performed. All these patients experienced recurrent disease, as a local recurrence only ($n = 1$), as metastases only ($n = 12$), or both ($n = 1$). The median time to recurrence or metastasis in this group was 7 months (range 2–14 months) from the time of initial surgery. Resection of the primary tumor and metastatic liver disease was performed for 12 patients as single- or multiple-stage surgery (SURG2). Two patients underwent resection of only the primary tumor in metastatic disease due to liver metastases diagnosed intraoperatively (SURG3).

Of the 12 patients (SURG2) who underwent resection of metastatic disease, eight underwent liver resection (seven concomitant resections only and one later resection only) and four underwent RFA of liver metastasis (three concomitant resections only and one later RFA only). One patient underwent liver resection and later liver transplantation. One patient underwent concomitant adrenalectomy and nephrectomy and later liver resection, and one patient underwent concomitant resection of the liver, pleura, and pericardium.

Altogether, 26 patients underwent surgery with curative intent. For two of these patients, liver metastases were diagnosed intraoperatively. The one patient, who underwent palliative surgery, had a malignant insulinoma and underwent resection of the primary tumor and debulking of metastatic disease in the liver and retroperitoneum. The other patient underwent resection of the primary tumor and debulking of liver metastases while experiencing stable disease with administration of systemic chemotherapy. One patient died 13 days after surgery due to multiorgan failure after intraoperative bleeding from the hepatic artery and the superior mesenteric artery. The clinicopathologic characteristics of the 28 patients who underwent surgery are presented in Table 2.

Chemotherapy

All but one patient who underwent surgical treatment also received chemotherapy. Chemotherapy alone was administered to 82 patients (69 %). Of these 82 patients, 4 had nonmetastatic disease (CT1) and 78 had metastatic disease (CT2). Among all the patients who received chemotherapy, 54 received one to four courses and 52 received more than four courses. The following chemotherapy regimens were administered: cisplatin/etoposide ($n = 50$), carboplatin/etoposide ($n = 26$), carboplatin/etoposide/vincristine ($n = 11$), and a combination of cisplatin/etoposide and carboplatin/etoposide ($n = 2$). The remaining patients were initially treated with other regimens based on the assumption of pancreatic ductal adenocarcinoma. Patient data on the number of chemotherapy courses were missing for three patients.

Survival

Follow-up information was available for all the patients. The SURG1 group included two patients who experienced local recurrence after resection of the primary tumor before or at the same time as their diagnosis of liver metastasis. These two patients were excluded from the survival analysis. During the follow-up period, 92 patients (77 %) died of disease. The median follow-up period was 13 months (range 0–165 months).

The disease-free survival time was 7 months for the SURG1 group and 18 months for the SURG2 group. The median survival time after diagnosis of metastatic disease for all the patients who received surgical treatment, chemotherapy, or both was 15 months. The median survival time was longer in the surgical groups (SURG1–SURG3) (23 months) than in the nonsurgical groups (CT1–CT2) (13 months) (Table 1). The median survival time for the patients receiving BSC was 2 months, and all died during the follow-up period. The 3-year survival rates were 45 % for SURG1, 69 % for SURG2, and 17 % for CT2 (Fig. 2). The patients undergoing combined surgical treatment and chemotherapy had significantly better survival times than the patients receiving chemotherapy alone (SURG 1 and SURG 2 vs CT2: $p = 0.001$).

We also compared the effect of Ki67 on survival for the surgically resected patients but did not find any statistically significant difference between the patients with a Ki67 value lower than 55 % and those with a Ki67 value of 55 % or higher ($p = 0.92$). The multivariate Cox-regression analysis showed that resection of the primary tumor, more than four courses of chemotherapy, a Ki67 value

TABLE 1 Characteristics of 119 patients with high-grade pancreatic neuroendocrine carcinoma

Characteristic	All	Combined surgery and chemotherapy				Chemotherapy alone			BSC
Treatment (no. of patients)	119	SURG ($n = 28$)	SURG1 ($n = 14$)	SURG2 ($n = 12$)	SURG3 ($n = 2$)	CT ($n = 82$)	CT1 ($n = 4$)	CT2 ($n = 78$)	BSC ($n = 9$)
Median age: years (range)	60 (23–85)	52 (23–79)	59 (42–76)	46 (23–68)	51, 79	60 (25–84)	61 (55–65)	60 (25–84)	70 (60–85)
Male sex	75	20	9	9	2	50	4	46	5
PS (WHO)[a]									
0	35	8	4	4	0	27	2	25	0
1	56	14	7	6	1	40	0	40	2
≥2	24	3	1	1	1	15	2	13	6
Missing	4	3	2	1					1
Chemotherapy									
0 courses	10	1	0	0	1	0	0	0	9
1–4 courses	54	10	5	4	1	44	1	43	0
>4 courses	52	15	9	6	0	37	3	34	0
Missing	3	2		2		1		1	
Cell morphology									
Small cell	42	5	2	2	1	33	1	32	4
Non-small cell	76	22	12	9	1	49	3	46	5
Missing	1	1		1					
Elevated LDH									
>UNL-2x UNL	29	6	3	3	0	21	1	20	2
>2x UNL	23	3	1	1	1	18	1	17	2
Elevated platelets >400 × 10^9	24	5	2	3	0	15	0	15	4
Ki67 (%)									
<55	76	15	7	8	0	54	2	52	7
≥55	39	13	7	4	2	26	2	24	0
Missing	4					2		2	2
Median survival[b]: months (range)	15 (1–166)[c]	23 (2–166)	23 (3–52)	29 (6–166)	2 (2, 3)	13 (1–76)	14 (4–25)	13 (1–76)	2 (0–11)
3-Year survival rate (%)			45	69	0		NA	17	0

[a] At the time of metastatic disease diagnosis

[b] Median survival is calculated from different starting points: from the time of metastasis for the "combined surgery and chemotherapy" and "chemotherapy alone" groups, and from time of diagnosis for the BSC group

[c] Excluding BSC patients

SURG surgery, *SURG1* surgery of primary tumor in nonmetastatic disease, *SURG2* surgery of primary tumor and metastatic liver disease, *SURG3* surgery of primary tumor only in metastatic disease, *CT1* chemotherapy only in nonmetastatic disease, *CT2* chemotherapy only in metastatic disease, *BSC* best supportive care, *PS* performance status, *WHO* world health organization, *LDH* lactate dehydrogenase, *UNL* upper normal limit, *NA* not applicable

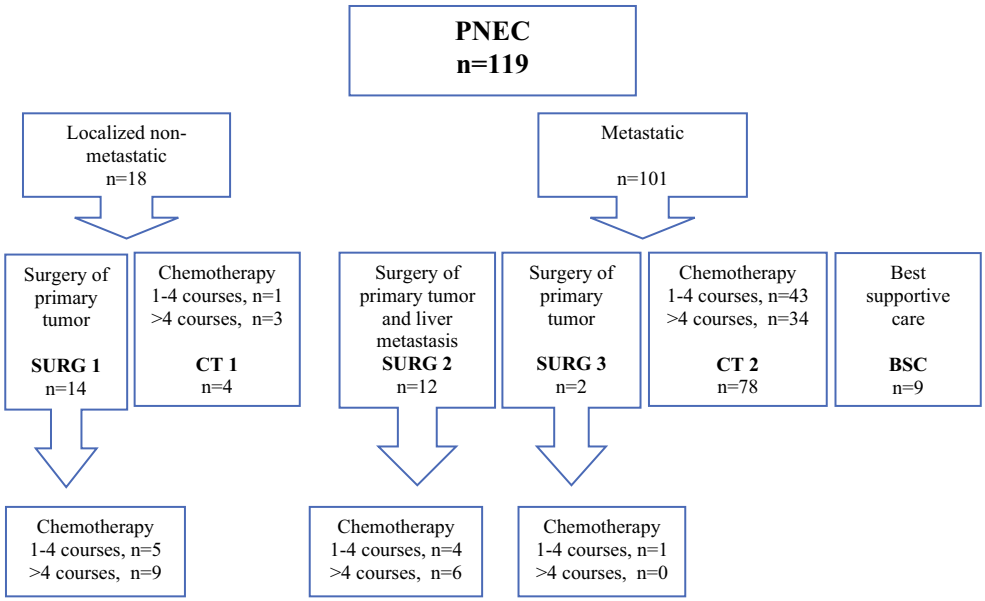

FIG. 1 Flowchart of the patients and treatment groups in the study. Patient data on the number of chemotherapy courses were missing for three patients

TABLE 2 Clinicopathologic characteristics of 28 patients with pancreatic neuroendocrine carcinoma who underwent surgical treatment

	SURG1	SURG2	SURG3
No. of patients	14	12	2
Primary location	12 Head, 1 tail, 1 whole organ	6 Head, 4 tail, 2 whole organ	2 Head
Synchronous metastasis location	NA	12 Liver, 1 gallbladder, 1 adrenal gland, 1 kidney, 1 thoracic lymph nodes	2 Liver
Curative intent of surgery	14 Yes	10 Yes, 2 no (1 with malignant insulinoma, 1 with stable disease on systemic chemotherapy)	2 Yes (both with intraoperative detection of liver metastasis)
Median tumor size: cm (range)	3.0 (0.8–8.0)	5.0 (1.5–17.0)	8.0 (5.0–11.0)
Staging (ENETS) T	1 T1, 3 T2, 9 T3, 1 T4	1 T1, 3 T2, 3 T3, 4 T4, 1 Tx	1 T3, 1 T4
Median Ki67: % (range)			
Primary	60 (20–90)	37 (5–100)	90 (80–100)
Metastasis	NA	50 (25–100)	NA
Surgery primary tumor	12 W, 1 DP, 1 TP	6 W, 4 DP, 2 T	2 W
Surgery metastasis	NA	8 Liver resections, 4 RFAs, 1 LTX, 1 adrenalectomy/nephrectomy, 1 pleurectomy/pericardectomy	NA

SURG1 surgery of primary tumor in nonmetastatic disease, *SURG2* surgery of primary tumor and metastatic liver disease, *SURG3* surgery of primary tumor only in metastatic disease, *NA* not applicable, *W* Whipple's procedure, *DP* distal pancreatectomy, *TP* total pancreatectomy, *RFA* radiofrequency ablation, *LTX* liver transplantation

lower than 55 %, and a PS of 0 were statistically significant independent factors for improved survival, with no difference between the 3- and 5-year follow-up data (Table 3).

DISCUSSION

This study investigated the effect of surgery on patients with hgPNEC and demonstrated that resection of the primary tumor was an independent prognostic factor of improved survival for patients with hgPNEC at different disease stages. This may suggest that resection of the primary tumor in localized hgPNEC should be considered, and additionally, that patients with resectable hgPNEC and resectable synchronous metastatic disease should be considered for surgery of both the primary tumor and the metastases. Surgical resection is an established treatment

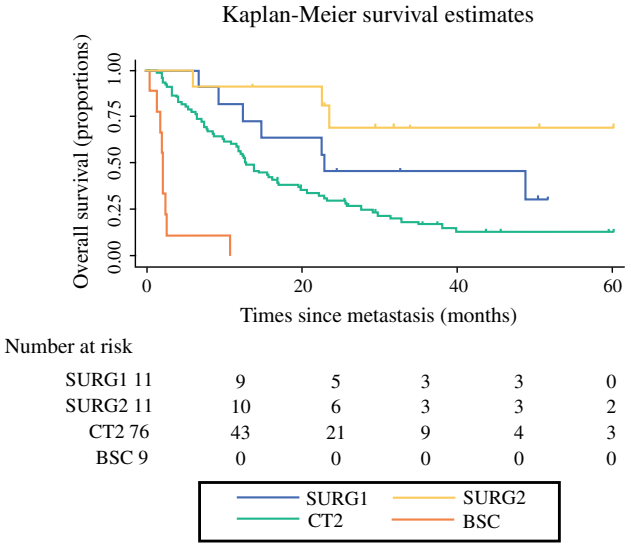

FIG. 2 Kaplan–Meier survival curves for patients with pancreatic neuroendocrine carcinoma according to treatment. SURG1, surgery of primary tumor in nonmetastatic disease; SURG2, surgery of primary tumor and metastatic liver disease; CT2, chemotherapy only for metastatic disease; BSC, best supportive care. Log-rank test: SURG2 vs CT2 after 3 years ($p < 0.01$)/5 years ($p < 0.01$); SURG1 vs CT2 after 3 years ($p = 0.08$)/5 years ($p = 0.09$). SURG1 and SURG 2 vs CT2 after 3 years ($p = 0.001$)/5 years ($p = 0.001$). Six patients were excluded from the survival analysis due to local recurrence after surgery (SURG1, $n = 2$) or unknown time of metastasis (SURG1, $n = 1$; SURG2, $n = 1$; CT2, $n = 2$)

method for pancreatic ductal adenocarcinoma[25] as well as for low- and intermediate-grade pancreatic neuroendocrine tumors,[9] but the role of surgery in the treatment of hgPNEC is uncertain due to the lack of data from large comparative cohorts of patients with hgPNEC.

Surgery for metastatic disease in patients with hgPNEC is not recommended in the current ENETS and NANETS guidelines.[17–19] However, the current study demonstrated that surgery of localized nonmetastatic disease combined with chemotherapy improved survival despite recurrent disease after a median time of 7 months postoperatively compared with chemotherapy alone. The early manifestation of metastatic disease in 13 of 14 patients with localized disease at the time of initial surgery may indicate that these patients likely had occult metastases at the time of resection. Accordingly, it remains to be established whether chemotherapy also should be given in a neoadjuvant setting. Interestingly, the subgroup of patients who underwent surgery of the primary tumor and synchronous metastatic disease had the longest median survival (29 months).

Our results, especially the 3-year survival rate of 69 % for patients with resection of all metastatic disease (SURG2), question the very rigid guideline recommendations.[17–19] Our data showed a surprisingly good survival among patients with synchronous disease who underwent resection. We were not able to identify any bias or obvious explanations for the favorable survival of this group of patients. However, recent data have shown considerable heterogeneity within the G3 NEC group,[5] probably much more than for patients with other gastrointestinal malignancies, and this might explain why they seem to behave differently as a group. Based on the results of our study, we suggest that hgPNEC patients should be considered on an individual basis for surgery combined with chemotherapy if all tumor tissue can potentially be resected.

Another important finding was that resection of the primary tumor seemed to result in better survival from the date of metastatic disease for the patients with metachronous metastatic disease than for the patients with synchronous metastatic disease who did not undergo resection of the primary tumor. One obvious explanation for this may be that having metachronous metastatic disease is prognostically better than having synchronous disease. However, comparison of the independent prognostic factors found in the Nordic NEC study[1] (PS, lactate dehydrogenase levels, and platelets) showed no major differences in these patient characteristics. The Ki67 index was more often lower than 55 % for the patients with synchronous disease (68 %) than for the patients with metachronous disease (50 %), which may underscore the importance of surgical treatment regardless of the Ki67 value. This is supported by another important finding in our study, which showed similar survival for the surgically resected patients with a Ki67 lower than 55 % and those with a Ki67 of 55 % or higher. This indicates that patients with hgPNEC should be considered for surgery, even those whose Ki67 values are high.

A recent study that included only poorly differentiated colorectal NEC did not demonstrate any benefit from resection of the primary tumor.[26] However, primary colonic NEC has a worse prognosis than hgPNEC.[27] Our observation of 23 months survival after surgical resection is better than the 12 months survival observed in a cohort of 44 patients with poorly differentiated hgPNEC reported by Basturk et al.[8] Tumor location, surgical procedure, tumor size, and T stage were comparable between these studies. However, the study by Basturk et al. [8] included only poorly differentiated hgPNEC, whereas our study included all hgPNEC cases with a Ki67 higher than 20 % without differentiation of grading. The optimal histologic classification of NEN G3 (Ki67 > 20 %) remains controversial,[5] and well-differentiated tumors have been found among tumors with a Ki67 higher than 20 %.[28] Patients with well-differentiated hgPNEC seem to have a longer survival than patients with poorly differentiated hgPNEC,[29,30] which may bias comparison between these studies.

Small and large cell morphology has previously been evaluated as a prognostic factor for patients with gastroenteropancreatic NECs. Results have been divergent,

TABLE 3 Cox-regression analysis of risk factors for overall survival of 99 patients who underwent oncologic treatment for pancreatic neuroendocrine carcinoma

Risk factor	Adjusted HR up to 3 years follow-up (95 % CI)	*p* value	Adjusted HR up to 5 years follow-up (95 % CI)	*p* value
Resection of primary tumor (no vs yes)	2.80 (1.37–5.71)	<0.01	2.75 (1.38–5.49)	<0.01
Systemic chemotherapy (≤4 vs >4 courses)	3.11 (1.85–5.23)	<0.001	2.86 (1.72–4.76)	<0.001
Ki67 (≥55 % vs <55 %)	2.15 (1.30–3.56)	<0.01	2.05 (1.24–3.38)	<0.01
Morphology (non–small cell vs small cell morphology)	1.49 (0.89–2.49)	0.13	1.46 (0.88–2.41)	0.14
PS (PS 1 vs PS 0)	1.86 (1.04–3.32)	0.04	1.95 (1.11–3.45)	0.02
PS (PS ≥ 2 vs PS 0)	7.52 (3.41–16.58)	<0.001	7.78 (3.54–17.07)	<0.001

The study excluded best supportive care (BSC) patients ($n = 9$), patients with unknown time of metastasis ($n = 4$), patients with >5-year follow-up ($n = 5$), and patients with local recurrence after resection of primary tumor ($n = 2$)

HR hazard ratio, *CI* confidence interval, *PS* performance status

with improved survival related to large cell morphology reported by some[27] and no difference in survival reported by others.[1,8,26] In our study, small cell morphology was not a statistically significant prognostic factor. Thus, the clinical relevance of this morphologic classification remains uncertain for hgPNEC patients. Patients with poor PS received BSC without chemotherapy, which was related to a poor oncologic outcome, with a median survival time of only 2 months, similar to other reports.[10]

Patients with metastatic hgPNEC are traditionally treated with palliative chemotherapy.[17,18] In our study, all but one patient who underwent surgical treatment were given adjuvant chemotherapy. Recent NANETS guidelines recommend adjuvant platinum-based chemotherapy after radical surgery, although there are no studies to support such a recommendation.[18] The same is the case for the duration of chemotherapy. The multivariate analysis showed that more than four courses of administered adjuvant chemotherapy is a significant factor of improved survival compared with one to four courses. Our study may suggest that more than four courses are better than one to four courses as postoperative chemotherapy, although there will be a bias concerning which patients are given or can receive more than four courses.

A clear limitation of our study was the small sample size, especially for the patients who underwent surgical treatment. A further limitation of the study was its retrospective design, with the risk of unintended bias. The dates of diagnosis and treatment early in the cohort versus late in the cohort were not tested for influence on the results, and we did not take into account that patients may have different comorbidities, thus resulting in a nonregistered selection bias. Because the data were acquired from several institutions in different countries, there may have been a selection bias associated with divergent diagnostic and treatment strategies among the participating institutions. In addition, because the patients included in this study had their diagnoses determined during a period of 14 years, the diagnostic procedures likely developed over time.

Another weakness of our study was the lack of a centralized pathologic reevaluation of the tissues from the enrolled patients. The lack of Ki67 values from both primary tumor and metastatic tissue was another limitation of the study. For seven patients, all of whom underwent surgery, Ki67 was determined from both the primary and metastatic tissue. Metastatic tissue generally had a higher Ki67 than primary tumor tissue, consistent with other reports.[31,32] However, in the studied cohort, the mean Ki67 value for those who did not undergo surgery was 48 ± 26 %, whereas the mean Ki67 value of the metastatic tissue from the surgically treated patients was 47 ± 26 %. Based on these data, the two groups seemed comparable in terms of tumor biology defined by Ki67. Other limitations of the study included absence of data on the total hepatic tumor burden for patients with liver metastases as well as heterogeneity of the chemotherapy regimens administered.

The data from this study indicate that surgical treatment combined with chemotherapy may improve the survival of patients with metastatic hgPNEC compared with chemotherapy alone. Resection of the primary tumor is an independent prognostic factor of improved survival for patients with metastatic hgPNEC and should therefore always be considered. Furthermore, patients with resectable hgPNEC and resectable synchronous metastatic disease should be considered for surgery of both the primary tumor and the metastases. Our study suggests the notion of surgery as a principle for the treatment of patients with hgPNEC.

ACKNOWLEDGMENT The study was initiated by the Nordic Neuroendocrine Tumor Group. We thank Randi Eikeland (Clinical Cancer Research Office, Haukeland University Hospital, Bergen, Norway) for assisting with data management. The study was supported by grants from the Nordic Cancer Union and Eckbo Foundations. Halfdan Sorbye received funding from the Norwegian Cancer Society; Eva Tiensuu Janson received a research grant from

the Swedish Cancer Society; and Henning Grønbæk received a clinical research grant from the Novo Nordisk Foundation.

DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24:152–60.
2. Cho MY, Kim JM, Sohn JH, et al. Current trends of the incidence and pathological diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Korea 2000–2009: multicenter Study. *Cancer Res Treat.* 2012;44:157–65.
3. Lepage C, Bouvier AM, Faivre J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. *Eur J Endocrinol.* 2013;168:R77–83.
4. Bosman FT, Carneiro F, Hruban RH. WHO Classification of Tumours of the Digestive System. Lyon: International Agency for Research on Cancer (IARC), 2010.
5. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer.* 2014;120:2814–23.
6. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol.* 2011;29:2372–7.
7. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol.* 2011;29:3044–9.
8. Basturk O, Tang L, Hruban RH, et al. Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. *Am J Surg Pathol.* 2014;38:437–47.
9. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg.* 2014;101:1405–12.
10. Kinoshita K, Minami T, Ohmori Y, Kanayama S, Yoshikawa K, Tsujimura T. Curative resection of a small cell carcinoma of the pancreas: report of a case of long survival without chemotherapy. *J Gastroenterol Hepatol.* 2004;19:1087–91.
11. Winter JM, Narang AK, Mansfield AS, et al. Resectable pancreatic small cell carcinoma. *Rare Tumors.* 2011;3:e5.
12. Berkel S, Hummel F, Gaa J, et al. Poorly differentiated small cell carcinoma of the pancreas: a case report and review of the literature. *Pancreatology.* 2004;4:521–6.
13. Sorbye H, Westre B, Horn A. Curative surgery after neoadjuvant chemotherapy in metastatic poorly differentiated neuroendocrine carcinoma. *Eur J Surg Oncol.* 2007;33:1209–10.
14. Groeschl RT, Christians KK, Turaga KK, Gamblin TC. Management of primary hepatopancreatobiliary small cell carcinoma. *J Surg Oncol.* 2013;107:692–5.
15. Kolby L, Nilsson O, Ahlman H. Gastroduodenal endocrine tumours. *Scand J Surg.* 2004;93:317–23.
16. Akerstrom G. Management of carcinoid tumors of the stomach, duodenum, and pancreas. *World J Surg.* 1996;20:173–82.
17. Nilsson O, Van CE, Delle FG, et al. Poorly differentiated carcinomas of the foregut (gastric, duodenal, and pancreatic). *Neuroendocrinology.* 2006;84:212–5.
18. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas.* 2010;39:799–800.
19. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013;42:557–77.
20. Oberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012;23(Suppl 7):vii124–30.
21. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449:395–401.
22. Hadoux J, Malka D, Planchard D, et al. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer.* 2015;22:289–98.
23. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–55.
24. StataCorp. Stata Statistical Software: Release 13. College Station: StataCorp LP, 2013.
25. Winter JM, Brennan MF, Tang LH, et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol.* 2012;19:169–75.
26. Smith JD, Reidy DL, Goodman KA, Shia J, Nash GM. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol.* 2014;21:2956–62.
27. Korse CM, Taal BG, van Velthuysen ML, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. *Eur J Cancer.* 2013;49:1975–83.
28. Yang Z, Tang LH, Klimstra DS. Gastroenteropancreatic neuroendocrine neoplasms: historical context and current issues. *Semin Diagn Pathol.* 2013;30:186–96.
29. Velayoudom-Cephise FL, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer.* 2013;20:649–57.
30. Basturk O, Yang Z, Tang LH. Increased (>20%) KI67 proliferation index in morphologically well-differentiated pancreatic neuroendocrine tumors (pannets) correlates with decreased overall survival. *Lab Invest.* 2013;93(Suppl 1):4234.
31. Shi C, Gonzalez RS, Zhao Z, et al. Liver metastases of small intestine neuroendocrine tumors: Ki-67 heterogeneity and World Health Organization grade discordance with primary tumors. *Am J Clin Pathol.* 2015;143:398–404.
32. Zen Y, Heaton N. Elevated Ki-67 labeling index in "synchronous liver metastases" of well-differentiated enteropancreatic neuroendocrine tumor. *Pathol Int.* 2013;63:532–8.