Palliative resection of primary site in advanced gastroenteropancreatic neuroendocrine tumors improves survivals

Derya Kıvrak Salim[1], Selami Bayram[1], İsmail Gömceli[2], Ayhan Hilmi Çekin[3], Mustafa Karaca[1], Murat Koçer[1], Mustafa Yıldız[1]

[1]Department of Medical Oncology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Gastroenterological Surgery, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[3]Department of Gastroenterology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey

Cite this article as: Kıvrak Salim D, Bayram S, Gömceli İ, et al. Palliative resection of primary site in advanced gastroenteropancreatic neuroendocrine tumors improves survivals. Turk J Gastroenterol 2019; 30(10): 910-6.

ABSTRACT

Background/Aims: Gastroenteropancreatic neuroendocrine tumors are rarely seen and have heterogeneous clinical outcomes. Mostly half of the patients had metastatic disease at presentation. Palliative resection of primary site in metastatic disease is still controversial. The aim of this study was to find out the influence of resection of primary tumor site on progression-free survival and overall survival in metastatic non-functioning gastroenteropancreatic neuroendocrine tumors. The secondary end point is to determine the prognostic factors influencing the survivals.

Materials and Methods: This study was conducted at a single medical oncology center, Antalya Education and Research Hospital. Patients who had non-functioning metastatic gastroenteropancreatic neuroendocrine tumors with primary site resected or unresected were compared retrospectively. Resection of metastases was excluded.

Results: Fifty-three patients were included in the study and 29 patients had primary tumor resection. The primary site resected group had favorable outcomes with the overall survival (median unreached) compared to the median overall survival of 30 months in the unresected group (p=0.001). Median progression-free survival was also better in the primary site resected group than the unresected group (60 months vs. 14 months, respectively) (p=0.013). In multivariate analysis, unresected primary site and high-grade tumors were found to be independent prognostic factors on low survivals (Hazard ratio (HR): 4.6; 95% CI: 1.21-17.47 and HR: 10.1; 95% CI: 1.15-88.84, respectively). Age (p=0.131), gender (p=0.051), chromogranin A level (p=0.104), Ki-67 index (p=0.550), tumor size (p=0.623), and primary tumor area (p=0.154) did not influence the overall survival.

Conclusion: Gastroenteropancreatic neuroendocrine tumors with primary site resected had improved survivals when compared to the unresected group.

Keywords: Primary tumor resection, survival, GEPNET

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors are rarely seen and have heterogeneous clinical outcomes. Mostly half of the patients had metastatic disease at presentation (1). Low-grade neuroendocrine tumors (NETs) are slow-growing tumors that may stay asymptomatic for a long time. With the effect of technological innovations in diagnosis, asymptomatic non-functioning NETs' incidence has been increased over the past years (2). Cytoreductive surgery is important in curative treatment but cytoreduction of unresectable liver metastases or extrahepatic disease is controversial (1,2). In European Neuroendocrine Tumor Society (ENETS) consensus guidelines update for non-functional pancreatic neuroendocrine tumors (pNET), conservative approach with observation versus surgical treatment is accepted as safe and feasible for asymptomatic ≤2 cm sporadic tumors (3). However, recent data showed extended surgical approach in pNET with pancreatic resection, and metastasectomies (i.e., hepatic, colon, and adrenal metastases) had similar survivals with tumors localized to the pancreas (4). North American Neuroendocrine Tumor Society (NANETS) consensus for small bowel NETs advises to remove primary tumor in asymptomatic patients with inoperable metastatic liver disease to interfere future symptoms and have survival advantage (5). There were no randomized controlled trials that had evaluated the role of primary tumor resection (PTR) in the setting of unresectable metastases (1). Survival information of NETs is derived mostly from epidemiological analysis of cancer registries. The Surveillance, Epidemiology, and End Results (SEER) Program registries, one of the largest epidemiological analysis, revealed that median survivals

Corresponding Author: **Derya Kıvrak Salim; deryakivrak@gmail.com**
Received: **March 9, 2019** Accepted: **April 18, 2019**

DOI: **10.5152/tjg.2019.19168**

in metastatic setting varied according to tumor sites: 13 months for gastric NET, 24 months for pNETs, 56 months for small bowel/duodenum NETs, and 5 months for colon NETs (6). It was also found that survivals of metastatic disease improved from 18 months to 39 months with the use of somatostatin analog drugs. Advantages of the option of PTR in metastatic gastroenteropancreatic neuroendocrine tumors (GEPNETs) with unresectable metastases are still contradictive. Generally, resection is recommended in local regional disease and in the obstructive symptomatic disease. In advanced disease, long-acting somatostatin analogs are recommended for functional carcinoid tumors, newly diagnosed with intermediate and high-volume tumors and progressive disease. In NANETS, it is recommended that resection should be considered in resectable hepatic disease or if there is no extrahepatic disease (7). Recent studies showed that unresectable hepatic metastatic disease and extrahepatic advanced GEPNETs may also be candidates for primary surgical debulking and may have survival improvement (8-13). However, most of the studies are retrospective which may manipulate the reported results and cause selection bias. Randomized clinical data are still lacking due to rare cases and clinically heterogeneous presentation. Our study focuses on to determine the effect of PTR of advanced GEPNETs with unresectable metastases.

In this study, our aim was to compare survivals and prognostic factors in primary site resected and unresected advanced GEPNETs with unresectable metastases.

MATERIALS AND METHODS

Study design and patients

This retrospective study was conducted at a single medical oncology center in Turkey. The study protocol was approved by the University of Health Sciences Antalya Training and Research Hospital Ethics Committee (Decision date Oct 11, 2018, approval number: 19/3). Inclusion criteria were as follows: patients with histologically or cytologically confirmed grade 1 (G1) or grade 2 (G2) advanced GEPNETs with unresectable metastases, treated with PTR (group 1) or no resection (group 2). No prior systemic therapy or radiotherapy was allowed. All patients had long-acting somatostatin analogs. Brain metastases were not considered as exclusion criteria unless symptomatic. Grade 3 (G3) tumors and patients with resected metastases were excluded. Data of 53 patients treated between February 2007 and February 2018 were retrospectively collected. Due to the retrospective nature of this study, informed consent was not taken.

Assessment of response

Radiological response was assessed every 3 months or in the case of a clinical progression finding by using Response Evaluation Criteria in Solid Tumors (version 1.1). All patients underwent baseline computed tomography or positron emission tomography.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences, Statistics for Windows, Version 23.0 (IBM Corp.; Armonk, NY, USA). The normality assumptions were controlled by the Shapiro-Wilk test. Descriptive analyses were presented using median (min-max) or n (%), where appropriate. Categorical data were analyzed by Pearson chi-square or Fisher's exact test. The differences between two groups were evaluated with Student's t-test for normally distributed data or Mann-Whitney U test for non-normally distributed data. The Kaplan-Meier method and log-rank tests were used to determine survival differences for nominal variables. A multivariable Cox proportional hazards regression model was used to identify independent prognostic factors. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported. All prognostic factors that were significant on univariate analysis were analyzed in the multivariable model. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics

The baseline characteristics of 53 patients are outlined in Table 1. Twenty-nine patients underwent PTR. Age, gender, histopathological findings were similar in both groups. The median tumor size in all study population was 3.2 cm in diameter and was similar in both groups (p=0.295). Foregut and midgut NETs were more in number in group 1 whereas the number of patients with pancreatic NETs was similar in both groups. The median Ki-67 score of all study population was 3, and patients who did not undergo resection had higher median Ki-67 score than the unresected group (p=0.040). ECOG PS was better in group 1 (p=0.036). There was a female predominance in the resected group and male predominance in the unresected group. Liver and lung metastases were higher in group 2 (p=0.032 and p=0.049, respectively); on the other hand, lymph node metastases were more in group 1 (p=0.042). One patient with asymptomatic CNS metastases was treated in group 2. Chromogranin A (CgA) levels at presentation were not different in both groups (p=0.187) and the median level of all study population was 362.

Table 1. Demographic data

	Primary Site Resected (n=29)	Primary Site Unresected (n=24)	p
Age, years, mean±SD	52±15.77	55.88±13.89	0.352
Sex, female/male n (%)	16 (55.2)/13 (44.8)	10 (41.7)/14 (58.3)	0.328
Primary Tumor Area, n (%)			
Unknown	0 (0)	3 (12.5)	NA
Foregut	10 (34.5)	4 (16.7)	
Midgut	5 (17.2)	1 (4.2)	
Pancreas	14 (48.3)	16 (66.7)	
ECOG PS, n (%)			
<2	29 (100)	20 (83.3)	0.036
≥2	0 (0)	4 (16.7)	
Histological Grade, n (%)			
G1	17 (58.6)	8 (33.3)	0.066
G2	12 (41.4)	16 (66.7)	
Ki-67, median (range)	%2 (1-10)	%3 (1-10)	0.040
Chromogranin A level, median (range)	293 (28-2045)	396.5 (65-20100)	0.187
Primary tumor size (cm) median (range)	3 (0.2-15)	3.5 (1-9.7)	0.295
Tumor necrosis, n (%)	7 (24.1)	7 (29.2)	0.679
Multicentricity, n (%)	6 (20.7)	3 (12.5)	0.487
LVI, n (%)	13 (44.8)	12 (50)	0.707
PNI, n (%)	6 (20.7)	4 (16.7)	0.999
Bone metastases, n (%)	7 (24.1)	4 (16.7)	0.735
Liver metastases, n (%)	12 (41.4)	17 (70.8)	0.032
Brain metastases, n (%)	0 (0)	1 (4.2)	0.453
Lung metastases, n (%)	5 (17.2)	10 (41.7)	0.049
LN metastases, n (%)	19 (65.5)	9 (37.5)	0.042

SD: standard deviation, PS: performance score, CgA: Chromogranin A, LVI: lymphovascular invasion, PNI: perineural invasion, LN: lymph node.

Efficacy

PTR arm experienced a progression-free survival benefit of 60 months (95% confidence interval [CI]=32.6-87.4), compared to 14 months (95% CI=4.8-23.2) for those in the unresected group (p=0.013; Figure 1). Five-year PFS was 30% in group 1 and 15.5% in group 2. The difference in overall survivals for the two groups was even more dramatic: median overall survival was not reached in patients who had PTR compared to 30 months (95% CI=0-69.6) for those in the unresected group (p=0.013; Figure 1). Five-year overall survival in the resection group was 90.5% versus 45.9% in the unresected group. In the subgroup analysis, regardless of resection, 5-year overall survivals were 33.3% in unknown primary NETs, 67.5% in foregut NETs, 68.5% in pNETS, and it was not reached in midgut NETs (p=0.154). Negative predictors of OS in univariate Cox analysis included male gender (p=0.012), G2 tumors (p=0.008), Ki-67 score >3% (p=0.011), and lack of PTR (p=0.004; Table 2). A multivariate Cox proportional hazards model was performed to define the factors independently influencing OS (Table 3). Gender and Ki-67 score were not found to be independently predictive of OS (p=0.051 and p=0.550, respectively). Patients who had not undergone PTR predicted worse survival compared with patients who underwent resection (HR: 4.6; 95% CI: 1.21-17.47). Increasing tumor grade was predictive of worsened survival (HR: 10.1; 95% CI: 1.15-88.84). CgA levels were dichotomized according to the median level for favorable CgA (≤362) and unfavorable CgA (>362) that did not influence the survival outcomes. Five-year overall survivals were 79.3% in the favorable group and 58.2% in the unfavorable group (p=0.093). Median PFS was 21 months (95% CI=0-47.1) in the favorable CgA group

Table 2. Univariate analysis of risk factors associated with survivals

	OS		PFS	
Variable	HR (95% CI)	p	HR (95% CI)	p
Gender				
Female	Reference	-	Reference	-
Male	13.71 (1.79-104.96)	0.012	7.9 (1.03-60.62)	0.047
Age				
≤65 years	Reference	-	Reference	-
>65 years	2.45 (0.77-7.85)	0.131	1.44 (0.44-4.73)	0.547
Size of Tumor				
≤3.2	Reference	-	Reference	-
>3.2	1.3 (0.45-3.77)	0.624	0.98 (0.34-2.84)	0.971
Tumor Grade				
G1	Reference	-	Reference	-
G2	16.1 (2.1-123.1)	0.008	5.79 (0.75-44.43)	0.091
PTR				
Yes	Reference	-	Reference	-
No	6.88 (1.88-25.18)	0.004	4.53 (1.23-16.72)	0.023
Ki-67				
≤%3	Reference	-	Reference	-
>%3	3.99 (1.38-11.55)	0.011	2.03 (0.68-6.06)	0.203
CgA Level				
≤362	Reference	-	Reference	-
>362	2.5 (0.83-7.56)	0.104	1.54 (0.51-4.65)	0.440
Primary Area				
Unknown	Reference	-	Reference	-
foregut	0.29 (0.05-1.79)	0.182	0.84 (0.14-5.2)	0.852
Midgut	0(0)	0.978	0(0)	0.989
Pancreas	0.4 (0.08-1.88)	0.244	1.31 (0.24-7)	0.756

PTR: Primary Tumor Resection.

and 14 months (95% CI=0-28) in the unfavorable CgA group (p=4.32). Age, primary NET area, metastatic area, Ki-67 score, grade, progression status, primary tumor size, and patho-morphological features are found to be not related to CgA levels (Table 4).

DISCUSSION

Recent retrospective studies recommending PTR in advanced GEPNETs with unresectable metastases are mostly single center series or analysis of medical records of cancer registries. There is a debate on whether the PTR in these patients may improve the survivals. There are no comparative randomized trials on the role of PTR of GEPNETs with unresectable metastases. Current guidelines NANETS and ENETS recommend surgery with curative intent when applicable, independent from liver or lymph node metastases. In advanced disease with unresectable metastases, guidelines refer patients to clinical trials or recommend surgery in the era of symptom control of functioning NETs or symptom control of tumor burden (7,14). UKINET guidelines for non-resectable disease recommend somatostatin analogs, biotherapy (octreotide and interferon), targeted radionuclide therapy, locoregional ablative and (chemo) embolization and chemotherapy (15). In addition, PTR in midgut NETs reduced symptoms and improved survival, even though inoperable mesenteric lymph node and liver metastases are present (16). Sev-

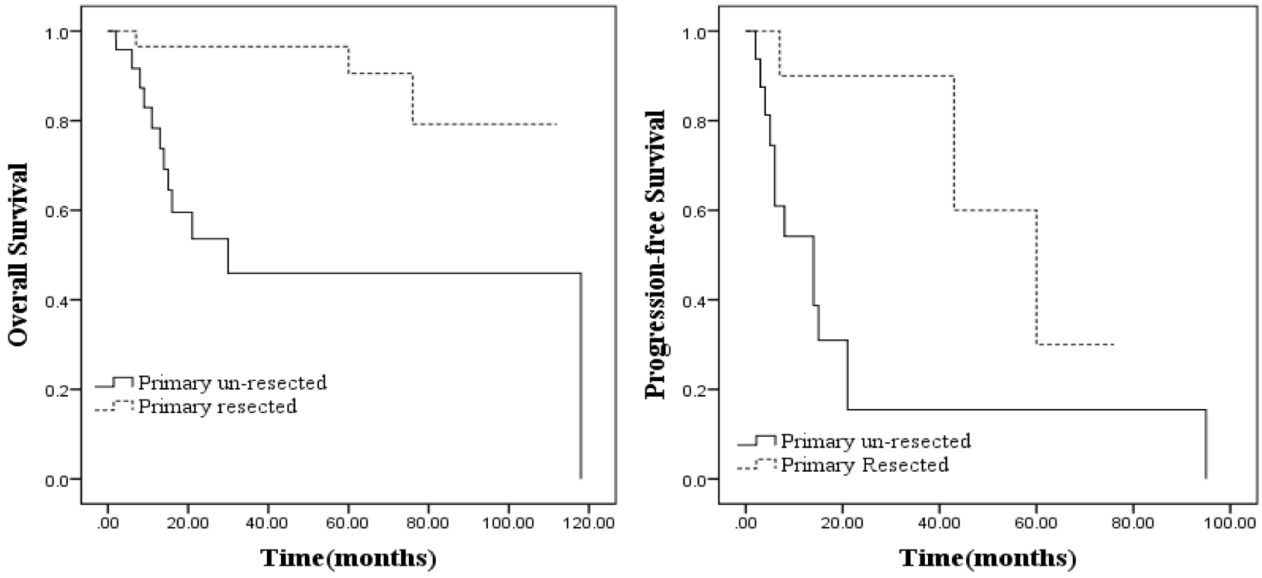

Figure 1. OS and PFS.

Table 3. Multivariate analysis of factors associated with OS

	HR	95%CI	p
Gender			
Female	Reference	-	-
Male	7.96	0.99-63.71	0.051
Tumor Grade			
G1	Reference	-	-
G2	10.1	1.15-88.84	0.037
PTR			
Yes	Reference	-	-
No	4.6	1.21-17.47	0.025
Ki-67			
≤%3	Reference	-	-
>%3	0.69	0.21-2.31	0.550

PTR: Primary Tumor Resection.

eral small-scale studies have offered either in favor or not in favor of PTR for survival advantage in advanced NETs with unresectable metastases (Table 5). Bertani et al. (8) had found out PTR was independently associated with better survival outcome; thereafter, they also reported improved PFS and OS with PTR in response to peptide receptor radionuclide therapy (17). In contrast with our results, Strosberg et al. (12) reported no survival improvement with prophylactic resection of primary tumor. Lewis et al. (1) supported PTR in 854 gastrointestinal neuroendocrine tumor (GI-NET) patients who had survival advantage independent of liver treatment and tumor grade. A population-based study, which included 442 stage IV pNET patients, resulted in favor of PTR in propensity score-matched survival analysis (11). Keutgen et al. (9) reported another population-based study in which 882 non-functioning pNET patients were identified from the SEER database. They found out PTR practice, younger age, well or moderately differentiated tumor grade were associated with longer survival. The present study underlays that the increased grade is an independent bad prognostic factor. Givi et al. (13) advocated PTR with a median survival difference of nearly a decade (159 months for resected patients vs. 47 months for the unresected group). These marked differences were not related to age, gender, biotherapy or performance status, or primary tumor area (foregut, hindgut, or midgut NETs). The present study sought to determine the potential impact of PTR on GEPNETs' survival outcomes and prognostic factors associated with survivals. The results indicate that patients, who had primary tumor resected in spite of unresectable metastases (liver or extrahepatic metastases), had longer-term survivals. Our survival results corroborate the findings of recent retrospective studies favoring PTR for survival advantage in advanced NETs (8,9,11,13,17,18). Furthermore, age, gender, size, primary tumor area, CgA levels at presentation, and Ki-67 index were not found to be independent prognostic factors.

Table 4. CgA levels and demographic features

	CgA≤362 (n:25)	CgA>362 (n:24)	p
Age, n (%)			
≤65	21 (84)	19 (79.2)	0.725
>65	4 (16)	5 (20.8)	
Primary NET Area, n (%)			
unknown	1 (4)	2 (8.3)	NA
foregut	5 (20)	8 (33.3)	
Midgut	4 (16)	1 (4.2)	
Pancreas	15 (60)	13 (54.2)	
Metastatic Area, n (%)			
Liver metastases	12 (48)	17 (70.8)	0.104
Bone metastases	8 (32)	3 (12.5)	0.102
Lung metastases	6 (24)	9 (37.5)	0.305
Cranial metastases	0 (0)	1 (4.2)	0.490
Lymph node metastases	14 (56)	10 (41.7)	0.316
Ki-67 Group, n (%)			
≤3	18 (72)	15 (62.5)	0.478
>3	7 (28)	9 (37.5)	
Grade, n (%)			
G1	10 (40)	12 (50)	0.482
G2	15 (60)	12 (50)	
Progression, n (%)			
Yes	15 (60)	8 (33.3)	0.062
No	10 (40)	16 (66.7)	
Tumor Size, n (%)			
≤3.2	13 (52)	10 (41.7)	0.469
>3.2	12 (48)	14 (58.3)	
Patho-morphologic Features, n (%)			
Multicentric disease	2 (8)	6 (25)	0.108
Vascular invasion	13 (52)	9 (37.5)	0.308
Perineural invasion	5 (20)	4 (16.7)	0.999
Punctate necrosis	6 (24)	7 (29.2)	0.682

Table 5. Comparison of OS in recent studies

Study, Year All Retrospective	Patient No.	PTR	mOS (mo) or 5-year OS (%)	p
Bertani et al. (8) 2013	43	Yes (12)	%82	0.027
pNET		No (31)	%50	
Bertani et al. (17) 2016	94	Yes (63)	112 mo	0.011
pNET		No (30)	65 mo	
Keutgen et al. (9) 2016	882	Yes (303)	65 mo	<0.0001
pNET (G1, G2, G3)		No (579)	10 mo	
Lewis et al. (1) 2018	854	Yes (392)	38 mo	<0.001
GEPNET		No (462)	10 mo	
Hüttner et al. (11) 2015	442	Yes (75)	%47.6	<0.001
pNET		No (367)	%21	
Citterio et al. (18) 2016	139	Yes (93)	138 mo	<0.001
GEPNET(G1, G2)		No (46)	37 mo	
Lin et al. (19) 2017	63	Yes (35)	72 mo	0.010
pNET		No (28)	32 mo	
Givi et al. (13) 2006	104	Yes (60)	159 mo	<0.001
Midgut NET		No (24)	47 mo	
Strosberg et al. (12) 2009	146	Yes (100)	110 mo	0.32
Midgut NET		No (46)	88 mo	
Kıvrak et al. 2018	53	Yes (29)	NA/ %90.5	0.001
GEPNET		No (24)	30 mo/ %45.9	

PTR: Primary Tumor Resection.

There are limitations of this study. The unresected group had more lung and liver metastases in addition to higher levels of Ki-67 score. The retrospective nature of this study may cause potential selective bias due to the absence of randomized matching. Secondly, there is no information on tumor burden, concomitant or afterward treatments (biotherapy, targeted therapy-tyrosine kinase use, radionuclide treatment, or locoregional ablative treatments). Because patients who underwent PTR were younger and had better ECOG performance scores, those may have influenced the decision of PTR.

We report that PTR nearly doubled 5-year PFS and OS versus the unresected group. In conclusion, our results suggest that there are survival benefits to resect primary tumor in advanced GEPNETs with unresectable metastases. Nevertheless, for the confirmation of the value of PTR in this group, randomized prospective studies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of University of Health Sciences Antalya Training and Research Hospital (Decision Date: October 11, 2018; Approval Number: 19/3).

Informed Consent: Due to the retrospective nature of this study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.K.S.; Design - D.K.S.; Supervision - D.K.S., M.Y.; Resources - M.K.; Materials - İ.G., A.H.Ç.,

M.K.; Data Collection and/or Processing - D.K.S.; Analysis and/or Interpretation - D.K.S.; Literature Search - D.K.S., S.B.; Writing Manuscript - D.K.S.; Critical Review - A.H.Ç., İ.G., M.K., D.K.S.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Lewis A, Raoof M, Ituarte PHG, et al. Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival with or without Liver Treatment. Ann Surg 2018 May 9. doi: 10.1097/SLA.0000000000002809. [Epub ahead of print] [CrossRef]

2. Chan DL, Dixon M, Law CHL, et al. Outcomes of Cytoreductive Surgery for Metastatic Low-Grade Neuroendocrine Tumors in the Setting of Extrahepatic Metastases. Ann Surg Oncol 2018; 25: 1768-74. [CrossRef]

3. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology 2016; 103: 153-71. [CrossRef]

4. Birnbaum DJ, Turrini O, Vigano L, et al. Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study. Ann Surg Oncol 2015; 22: 1000-7. [CrossRef]

5. Howe JR, Cardona K, Fraker DL, et al. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. Pancreas 2017; 46: 715-731. [CrossRef]

6. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-72. [CrossRef]

7. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013; 42: 557-77. [CrossRef]

8. Bertani E, Fazio N, Botteri E, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. Surgery 2014; 155: 607-14. [CrossRef]

9. Keutgen XM, Nilubol N, Glanville J, et al. Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. Surgery 2016; 159: 311-8. [CrossRef]

10. Nguyen SQ, Angel LP, Divino CM, Schluender S, Warner RR. Surgery in malignant pancreatic neuroendocrine tumors. J Surg Oncol 2007; 96: 397-403. [CrossRef]

11. Hüttner FJ, Schneider L, Tarantino I et al. Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis. Langenbecks Arch Surg 2015; 400: 715-23. [CrossRef]

12. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. Neuroendocrinology 2009; 89: 471-6. [CrossRef]

13. Givi B, Pommier SJ, Thompson AK, Diggs BS, Pommier RF. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. Surgery 2006; 140: 891-7. [CrossRef]

14. Pavel M, O'Toole D, Costa F, et al. Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016; 103: 172-85. [CrossRef]

15. Ramage JK, Ahmed A, Ardill J, et al. UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61: 6-32. [CrossRef]

16. Hellman P, Lundström T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002; 26: 991-7. [CrossRef]

17. Bertani E, Fazio N, Radice D, et al. Resection of the Primary Tumor Followed by Peptide Receptor Radionuclide Therapy as Upfront Strategy for the Treatment of G1-G2 Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases. Ann Surg Oncol 2016; 23(Suppl 5): 981-9. [CrossRef]

18. Citterio D, Pusceddu S, Facciorusso A, et al. Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. Eur J Surg Oncol 2017; 43: 380-7. [CrossRef]

19. Lin C, Dai H, Hong X, et al. The prognostic impact of primary tumor resection in pancreatic neuroendocrine tumors with synchronous multifocal liver metastases. Pancreatology 2018; pii: S1424-3903(18)30081-4. [CrossRef]