The American Journal of Surgery 220 (2020) 284–289

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Radical intended surgery for highly selected stage IV neuroendocrine neoplasms G3

Elettra Merola [a, b, *], Massimo Falconi [c], Anja Rinke [d], Stefan Staettner [e], Felix Krendl [e], Stefano Partelli [c], Valentina Andreasi [c], Thomas M. Gress [d], Andreas Pascher [f, g], Ruza Arsenic [h], Claudio Doglioni [i], Daniel Kaemmerer [l], Bertram Wiedenmann [m], Marianne E. Pavel [a, m]

[a] Department of Medicine 1, Division of Endocrinology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
[b] Department of Gastroenterology, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy
[c] Pancreatic Surgery Unit, Vita-Salute University, San Raffaele Hospital IRCCS, Milan, Italy
[d] Department of Gastroenterology, Endocrinology, Metabolism and Infectiology, University Hospital Marburg and Philipps University, Marburg, Germany
[e] Department of Visceral, Transplant and Thoracic Surgery, Innsbruck Medical University, Innsbruck, Austria
[f] Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Münster, Münster, Germany
[g] Department of Surgery, Charité Universitätsmedizin, Berlin, Germany
[h] Department of Pathology, Charité Mitte, Charité Universitätsmedizin, Berlin, Germany
[i] Pathology Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy
[l] Department of General and Visceral Surgery, Zentralklinik Bad Berka, Bad Berka, Germany
[m] Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum and Campus Mitte, Charité Universitätsmedizin, Berlin, Germany

ARTICLE INFO

Article history:
Received 17 December 2019
Received in revised form
2 March 2020
Accepted 4 March 2020

Keywords:
Neuroendocrine neoplasms G3
Stage IV
Surgery
Overall survival
Recurrence

ABSTRACT

Background: Stage IV gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) G3 are the NENs with the worst prognosis. According to ENETS guidelines, platinum-based chemotherapy is the standard treatment for this population. Surgery is only considered in highly selected "resectable" NENs with usually lower Ki67. However, the role of surgery with curative intent has been poorly investigated.
Objective: To describe, in a retrospective series of stage IV GEP-NENs G3, overall survival (OS) and recurrence-free survival (RFS) rates after curatively intended surgery.
Methods: Multicenter analysis of stage IV GEP-NENs G3 receiving radical resection (R0/R1) from 2007 to 2017, with minimum post-surgical follow-up time of 3 months.
Results: Fifteen patients from 6 NEN referral centers, with median follow-up of 29 months (8-86), were included. Eight cases had a neuroendocrine carcinoma (NEC) and 7 a neuroendocrine tumor G3 (NET G3). Median OS after radical surgery was 59 months. All patients recurred, with a median RFS of 8 months.
Conclusions: Radical surgery might be considered for highly selected stage IV GEP-NENs G3. Larger series are needed to confirm these results.

Introduction

Neuroendocrine neoplasms (NENs) G3 encompass a heterogeneous population, with a prognosis depending on proliferation index (Ki67), stage and differentiation.[1,2,3,4,5,6] The World Health Organization (WHO) has recently established a novel classification (WHO 2019) distinguishing two subsets of gastro-entero-pancreatic NENs (GEP-NENs) G3: well-differentiated neuroendocrine tumors (NET G3) vs. poorly differentiated neuroendocrine carcinomas (NEC).[7] Among the NEC, cell morphology can further differentiate two subgroups: small cell and large cell NEC.

Among the GEP-NENs G3, patients presenting with distant metastases (stage IV disease) represent the group with the worst outcome.[8] Based on the assumed early systemic spread, chemotherapy adopting platinum-based regimens represents the standard of care for these patients according to the ENETS Guidelines.[8,9]

* Corresponding author. Department of Gastroenterology, Azienda Provinciale per i Servizi Sanitari (APSS) di Trento, Largo Medaglie D'Oro 9, 38122, Trento, Italy. Tel.: +390461 903954.
E-mail addresses: elettra.merola@gmail.com, elettra.merola@apss.tn.it (E. Merola).

https://doi.org/10.1016/j.amjsurg.2020.03.009
0002-9610/

Table 1
Main features at surgery and pathological characteristic of the patients.

Features	All patients ($n = 15$)
Gender (male), *n*	9
Age [years; median (range)]	52 (26–78)
Tumor primary site	
Pancreas, *n*	9
Colorectal, *n*	2
Gastro-esophageal	1
Ileum, *n*	1
Appendix, *n*	2
Surgical procedures	
Pancreaticoduodenectomy + liver resection	2
Pancreaticoduodenectomy + liver resection + right hemicolectomy	1
Left-pancreatectomy + liver resection	4
Left-pancreatectomy + liver resection + adrenalectomy	1
Left-pancreatectomy + liver resection + partial gastrectomy	1
Abdominoperineal resection + liver resection	1
Right hemicolectomy + omental resection	2
Right hemicolectomy + liver resection + omental resection	1
Right hemicolectomy + histero-ovariectomy	1
Total gastrectomy + liver resection	1
Tumor primary size [mm; median (range)]	38 (20–125)
T	
T2, *n*	3
T3, *n*	9
T4, *n*	3
Lymph nodal metastases [15][a b]	
N0, *n*	7
N1, *n*	2
N2, *n*	6
R Status	
R0, *n*	11
R1, *n*	4
Ki67 [%; median (range)]	40 (25–80)
WHO 2019 [7]	
NET G3, *n*	7
NEC, *n*	6
MiNEN, *n*	2
Metastatic pattern at surgery	
Only liver, *n*	11
Liver + peritoneal infiltration, *n*	1
Peritoneal infiltration, *n*	2
Right ovary + uterus, *n*	1
Neoadjuvant chemotherapy, *n*	4

WHO: World Health Organization; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasm.
[a] The classification was applied also to non-pancreatic cases.
[b] N0: no lymph nodal metastases; N1: 1 to 3 positive lymph nodes; N2: at least 4 positive lymph nodes.

The role of radical intended surgery has been so far poorly investigated.[10,11,12,13,14,15]

The aim of this multicenter retrospective study is to investigate whether surgery might play a role in the management of highly selected patients with a stage IV GEP-NEN G3, describing their overall survival (OS) and recurrence-free survival (RFS) rates after radical intended surgery.

Material and methods

Patients newly diagnosed as sporadic GEP-NENs G3, with stage IV disease and receiving surgery with radical intent (R0-R1) in 6 NEN referral centers between 2007 and 2017 were included.

The exclusion criteria were: tumor primary site other than GEP, G1-G2 tumors, stage I-III disease, a non-radical surgery (R2 resection), a follow-up time shorter than 3 months for alive patients and/or lack of follow-up information, the presence of genetic syndromes (i.e., type I multiple endocrine neoplasia, von Hippel-Lindau syndrome).

All the patients signed an informed consent for treatment. The study was approved by the ENETS, whilst the ethical approval was waived due to the retrospective design of the study according to single centers regulation.

All patients were reclassified by expert pathologists in each center according to the definition established for the GEP-NENs G3 by the WHO 2019 classification.[7]

Post-surgical follow-up was based on clinical controls and conventional imaging every 3 months: computed tomography (CT) or magnetic resonance imaging (MRI). In a subgroup of patients functional imaging tests (Octreoscan®, ^{68}GaDOTA-PET/CT, or ^{18}FDG-PET/CT) were also performed.

OS was calculated as the time between surgery and death or last follow-up. RFS was defined as the interval between resection and disease recurrence or last follow-up.

The patient data were retrospectively retrieved from patient files in different centers and collected in an anonymized database. This included demographics (age, gender), tumor features (primary site and size, metastatic pattern, clinical syndrome), histological features (Ki67, differentiation, cell morphology, R status, lymph node metastases), use of neoadjuvant and/or adjuvant chemotherapy (if performed), survival data, disease recurrence and first line therapy after recurrence.

Table 2
Patients' presentation at surgery and clinical outcome.

N	Tumor primary site	Metastatic pattern	Clinical presentation	Treatment	R	Histology	Ki67 (%)	Time to recurrence (months)	Site of recurrence	Follow-up (months)	Status at last follow-up
1	Appendix	Right ovary, uterus	Appendicitis	Surgery + adjuvant therapy	R0	MiNEN	25	45	Peritoneum	43	Alive
2	Ileum	Liver, peritoneum	Occasional finding	Surgery + adjuvant therapy	R1	NEC	70	8	Abdominal lymph nodes	18	Dead
3	Pancreas	Liver	Occasional finding	Neoadjuvant therapy + surgery	R0	NEC	75	7	Liver	8	Alive
4	Pancreas	Liver	Vomit	Surgery	R0	NET	40	6	Liver, abdominal lymph nodes	34	Alive
5	Rectum	Liver, abdominal lymph nodes	Rectal bleeding	Surgery	R0	NET	40	8	Liver, bones	86	Alive
6	Pancreas	Liver	Abdominal pain	Surgery	R0	NET	30	15	Liver	35	Alive
7	Pancreas	Liver	Acute pancreatitis	Surgery	R0	NEC	65	5	Liver	35	Alive
8	Pancreas	Liver	Occasional finding	Surgery	R0	NET	30	7	Liver, chest lymph nodes	32	Alive
9	Colon	Peritoneum	Rectal bleeding	Surgery + adjuvant therapy	R1	NEC	60	11	Liver, chest and abdominal lymph nodes	17	Alive
10	Cardias	Liver	Dysphagia	Neoadjuvant therapy + surgery	R0	MiNEN	80	1	Liver	13	Alive
11	Appendix	Peritoneum	Appendicitis	Surgery	R1	NET	40	16	Pleura	24	Dead
12	Pancreas	Liver	Occasional finding	Neoadjuvant therapy + surgery	R1	NET	30	23	Liver	59	Dead
13	Pancreas	Liver	Weight loss, vomit	Surgery + adjuvant therapy	R0	NEC	50	13	Liver	23	Alive
14	Pancreas	Liver	Occasional finding	Neoadjuvant therapy + surgery	R0	NEC	55	16	Chest lymph nodes	12	Alive
15	Pancreas	Liver	Symptomatic hypoglycemia	Surgery	R0	NET	30	4	Liver	29	Alive

NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor; MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasm.

Lymph nodal involvement was also categorized according to the absolute number of resected positive nodes: N0 when no lymph nodal metastases were found, N1 in case of 1–3 positive lymph nodes, N2 with at least 4 positive lymph nodes.[16] This classification was applied also to non-pancreatic neoplasms.

Disease recurrence was defined as the identification of at least one new lesion at imaging during follow-up.

The distribution of continuous variables was reported as the median and range. *P*-value was considered as statistically significant when lower than 0.05. A comparison between the subgroups was carried out using Fisher's exact test or the Chi-squared test for non-continuous variables, while the Mann-Whitney *U* test was adopted for continuous variables. Survival analysis was performed according to the Kaplan Meier method and comparisons among curves with the log-rank test.

Statistical analysis was performed using a dedicated software program (Medcalc 15.6.1, www.medcalc.be).

Table 3
Long-term outcome of the patients.

Features	All patients ($n = 15$)
Disease recurrence, *n*	15
Time to recurrence months; median (range)]	8 (1–45)
Metastatic pattern at recurrence time	
Only abdominal lymph nodes, *n*	2
Liver	11
Liver only, *n*	7
Liver +	4
chest lymph nodes, *n*	1
abdominal lymph nodes, *n*	1
abdominal lymph nodes + chest lymph nodes, *n*	1
bone lesions, *n*	1
Peritoneal implants, *n*	1
Pleura carcinosis, *n*	1
Observed death, *n*	3
Follow-up time [months; median (range)]	29 (8–68)

Results

Out of 88 GEP-NEN G3 patients screened, 63 were excluded due to a stage I-III disease and 10 because they had received a R2 resection. Fifteen cases fulfilled the inclusion criteria of the study and were analyzed. Main features are reported in Table 1 and Table 2. One insulinoma was observed in this series, all other cases were non-functioning neoplasms.

Metastatic pattern involved only the liver in 11/15 patients, peritoneal infiltration in 3/15 (associated to liver disease in 1 case), right ovary and uterus in 1/15.

Somatostatin receptors (SR) were investigated pre-surgery in 8 patients (2 by Octreoscan®, 4 by ^{68}GaDOTA-PET/CT, 2 by immunohistochemistry) and SR expression was observed in 6/8. The SR-positive neoplasms were 5/6 pancreatic and 5/6 NET G3.

In 7 patients ^{18}FDG-PET/CT was performed pre-surgery, with a positivity in 6/7. The negative case was affected by a rectal NET G3.

A NEC was identified in 6/15 cases, and all of them presented a large-cell histomorphology. The other cases included 7/15 NET G3 tumors and 2/15 mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) with a poorly differentiated neuroendocrine cancer morphology.

A neoadjuvant treatment was adopted in 4/15 patients, with a median of 6 cycles[3–7] per patient. Chemotherapy regimens were: FOLFIRINOX in 1 case, cisplatin/etoposide in 2, streptozotocin in 1. A partial response was achieved in 3/4 patients, a stable disease was obtained in 1/4.

Surgical procedures are summarized in Table 1. Only in one case the curatively intended resection was performed laparoscopically. A R0 resection was more frequently obtained in the absence of extra-hepatic disease (10/15 cases,67.0%) than in case of extra-liver disease (1 patient, 6.7%; $P = 0.01$).

Adjuvant therapy was adopted in 4 patients, with a median of 6

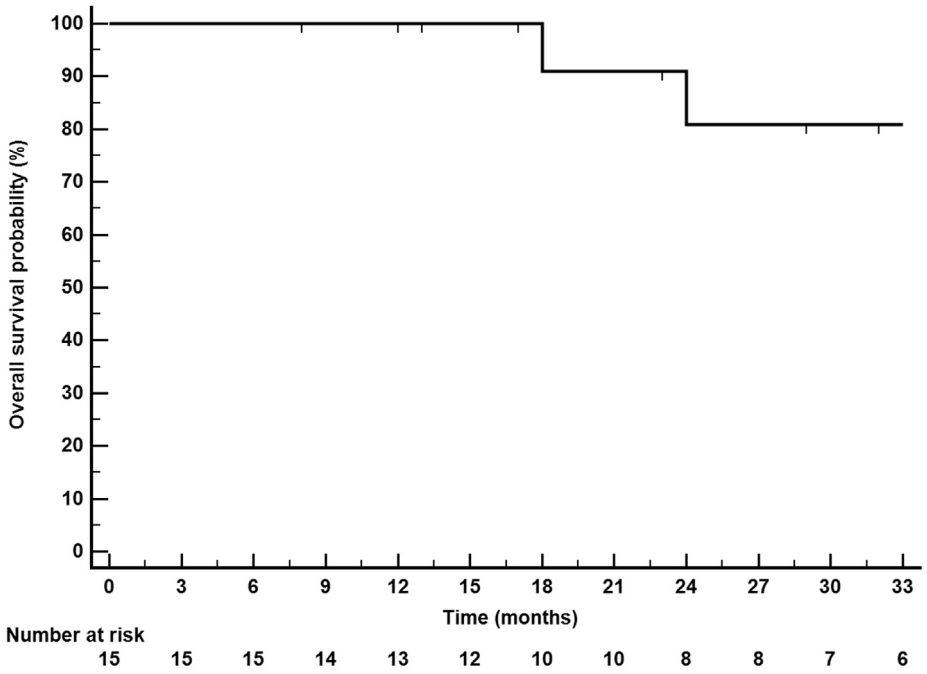

Fig. 1. Overall survival (OS) after radical surgery for the overall population.
The median OS was 59 months, and 2-yr OS rate was 80.8%.

chemotherapy cycles (range 4–6) per patient. Chemotherapy regimens included: FOLFIRI + cetuximab (MiNEN case) and cisplatinum/etoposide (3 cases). Patients were all affected by a NEC G3 neoplasm, and half of them had a R1 resection.

The median post-operative follow-up time was 29 months (range 8–86) (Table 2, Table 3). Three out of 15 patients had died at the last follow-up, 12 were alive but all of them with a disease recurrence. The 2-yr OS rate of the study population after first radical resection was 80.8%, with a "not reached" median OS (Fig. 1).

Disease recurrence was observed in all the patients with a median time to recurrence of 8 months (range: 1–45 months) and with a 2-yr RFS rate of 6.7% (Fig. 2). Metastatic pattern at recurrence is detailed in Table 2.

No statistically significant difference in survival was observed stratifying patients according to metastatic pattern at surgery, WHO 2019 classification (NET G3 vs NEC) or treatment.

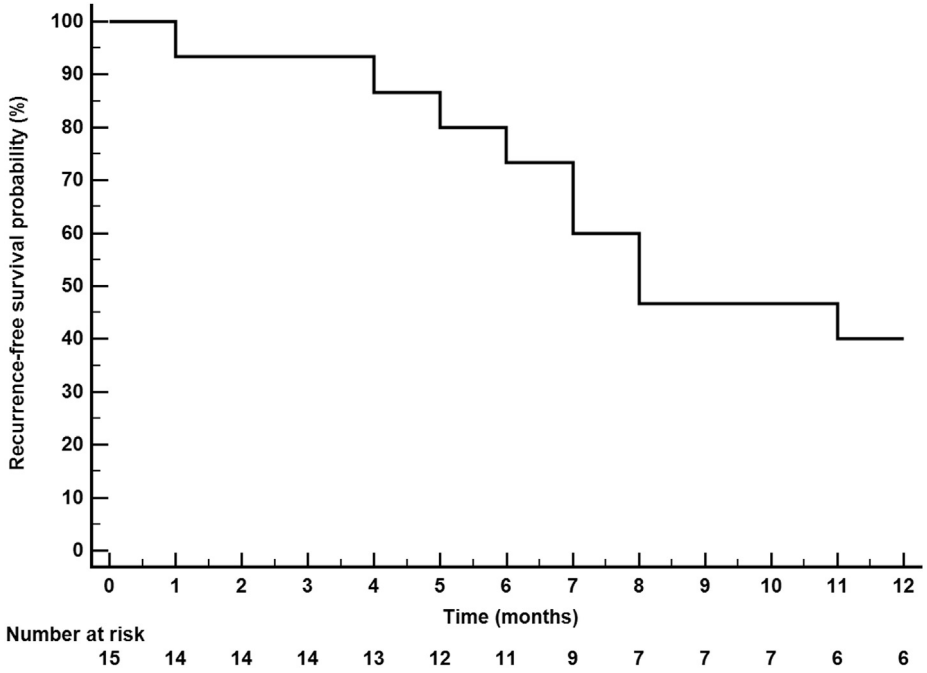

Fig. 2. Recurrence-free Survival (RFS) after radical surgery for the overall population.
The median RFS was 8 months, and 2-yr RFS rate 6.7%.

Table 4
Survival in stage IV GEP-NENs G3 treated with medical therapies: data from the literature.

First author	Patients, *n*	Treatment	Median OS, months
Sorbye[33],[a]	252	Chemotherapy	11.0
	53	BSC	1.0
Yamaguchi [16][a]	63	Chemotherapy	12.6
Iwasa [17][a]	21	Chemotherapy	6.0
Patta [18][a]	8	Chemotherapy	9.5
Okita [19]	8	Chemotherapy	10.4
Lu [20][a]	16	Chemotherapy	10.6
Okuma [21][a]	12	Chemotherapy	12.6
Rogowski [22][a]	32	Chemotherapy	4.6–22
Pellat [23][a]	61	Sunitinib	6.0
Panzuto [24]	15	Everolimus	28.0
Zhang [25]	69	PRRT	19.9
Carlsen [26][a]	149	PRRT	29.0
Collot [27]	11	Bevacizumab + chemotherapy	15.3

GEP-NENs: gastro-entero-pancreatic neuroendocrine neoplasms; OS: overall survival; BSC: best supportive care; PRRT: peptide receptor radionuclide therapy.
[a] Including also some patients with a locally advanced disease.

First-line approach after disease recurrence was characterized by a further radical intended surgery in one patient and TACE in another one. In 10 cases a systemic treatment was started: 9 patients received a chemotherapy and one NET G3 patient was treated with Peptide Receptor Radionuclide Therapy (PRRT). In 3 patients, best supportive care was applied.

Discussion

The present study shows that radically intended surgery can be considered as a possible therapeutic option for highly selected stage IV GEP-NENs G3. In our series, although all the patients experienced a disease recurrence after a median time of 8 months after resection, median OS was 59 months, with a mortality rate of 20.0% in a median 29-month-follow-up time.

A comparison of the observed survival between the current series and patients treated with chemotherapy alone in the same setting was not trustable, due to a different metastatic spread, clinical condition or other reasons not retrospectively identifiable. The same concern can be risen if the comparison with the literature were done, since reported data refer to patients treated with different regimens, with median OS ranging from only 4.6–29 months (Table 4)[1,17,18,19,20,21,21,22,23,24,25,26,27,28].

Data on surgery in stage IV NENs G3 are unfortunately scarce since standard therapy in advanced NENs G3 is platinum-based chemotherapy, and an early therapy onset is crucial. This also applies to small cell NECs of lower stages. The few previous papers investigating the role of surgery for stage IV GEP-NENs G3 analyzed mixed patient populations, with different disease stages (stage I-III and stage IV), different grading (G1-G2 and G3), and a short post-surgical follow-up. Moreover, different therapeutic options were also included.[10,13,12,11,15,14]

Fischer et al.[10] showed in a series of 24 PanNENs G3 a median OS of 14 months for the stage IV cases resected with curative intent. Yoshida et al.[14] reported instead a more optimistic outcome for this subset of patients ($n = 10$): not reaching median OS for PanNETs G3 vs. a 9.1-month-rate for PanNECs.

Performing a sub-analysis of our patient population, median OS was 59 months when only pancreatic cases were included (9/15 patients). However, a statistically significant different OS according to tumor differentiation[29] could not be reached in the present study, due to the small number of included patients. One of the most crucial factors might be that our cohort did not include patients with small cell NEC, but only patients with large cell NEC and NET G3, characterized by a more favorable prognosis.

Although the results are encouraging, supporting the hypothesis that highly selected cases might benefit from a resection with radical intent, the small population of the present study limits the possibility to describe the optimal subgroup benefitting from radical resection. Molecular definition of subsets of NEN G3 might help to identify most suitable candidates for surgery in the future.

The same limitation, together with other biases of the study (the retrospective design, the inclusion of different primary tumor sites, the heterogeneity of histopathology and the long period for enrollment) might explain the reason why no benefit from (neo) adjuvant therapy in comparison to only radically intended resection was observed.

Current evidence about the indication for adjuvant treatments in NENs is still so far limited.[30,31,32] Only within a prospective trial comparing patients receiving curatively-intended surgery alone vs. patients also receiving (neo)adjuvant therapies the potential role of (neo) adjuvant therapies might be properly investigated, but due to the low number of observed patients this logical step will remain almost impossible.

Conclusions

Radical intended surgery may be considered for very highly selected stage IV GEP-NENs G3, with a large cell NEC or a NET G3 histopathology. Larger studies are needed to confirm these results, and to explore the role of (neo) adjuvant therapy in this setting of patients.

Funding

The study was supported by the European Neuroendocrine Tumor Society (ENETS) “Excellence Academy Fellowship Grant” (2017).

Declaration of competing interest

Authors have no conflicts of interest do declare.

Acknowledgement

The study was endorsed by an unrestricted support among the “Ipsen Scientific Exchange Program” (2016–2018); Valentina Andreasi PhD scholarship is supported by the Gioja Bianca Costanza Fund.

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 Jan;24(1):152–160. PubMed PMID: 22967994.
2. Velayoudom-Cephise FL, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Canc*. 2013 Oct;20(5):649–657. PubMed PMID: 23845449.
3. Heetfeld M, Chougnet CN, Olsen IH, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Canc*. 2015 Aug;22(4):657–664. PubMed PMID: 26113608.
4. Basturk O, Yang Z, Tang LH, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015 May;39(5):683–690. PubMed PMID: 25723112. Pubmed Central PMCID: PMC4398606.
5. Tang LH, Untch BR, Reidy DL, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Canc Res*. 2016 Feb 15;22(4):1011–1017. PubMed PMID: 26482044. Pubmed Central PMCID: PMC4988130.
6. Crippa S, Partelli S, Bassi C, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. *Surgery*. 2016 Mar;159(3):862–871. PubMed PMID: 26602841.
7. *WHO Classification of Tumors Editorial Board: Digestive System Tumors*. fifth ed. 2019.
8. Garcia-Carbonero R, Rinke A, Valle JW, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms. Systemic therapy 2: chemotherapy. *Neuroendocrinology*. 2017;105(3):281–294. PubMed PMID: 28380493.
9. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology*. 2016;103(2):186–194. PubMed PMID: 26731334.
10. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg*. 2014 Oct;101(11):1405–1412. PubMed PMID: 25132004.
11. Yang M, Ke NW, Zeng L, et al. Survival analyses for patients with surgically resected pancreatic neuroendocrine tumors by World Health organization 2010 grading classifications and American joint committee on cancer 2010 staging systems. *Medicine (Baltim)*. 2015 Dec;94(48), e2156. PubMed PMID: 26632896. Pubmed Central PMCID: PMC4674199.
12. Shen C, Chen H, Chen H, et al. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. *BMC Gastroenterol*. 2016 Sep 9;16:111. PubMed PMID: 27613657. Pubmed Central PMCID: PMC5016962.
13. Partelli S, Inama M, Rinke A, et al. Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. *Neuroendocrinology*. 2015;102(1-2):68–76. PubMed PMID: 26043944.
14. Yoshida T, Hijioka S, Hosoda W, et al. Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. *Ann Surg Oncol*. 2019 Mar 12;26(5):1385–1393. PubMed PMID: 30863939.
15. Yang M, Zhang Y, Zeng L, et al. Survivals of patients with surgically treated and High-grade pancreatic neuroendocrine carcinomas: a comparative study between two American Joint Committee on Cancer 8th tumor-node-metastasis staging systems. *Eur J Surg Oncol*. 2019 Jan 11;45(6):1054–1060. PubMed PMID: 30661921.
16. Partelli S, Javed AA, Andreasi V, et al. The number of positive nodes accurately predicts recurrence after pancreaticoduodenectomy for nonfunctioning neuroendocrine neoplasms. *Eur J Surg Oncol*. 2018 Jun;44(6):778–783. PubMed PMID: 29610023.
17. Yamaguchi T, Machida N, Morizane C, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Canc Sci*. 2014 Sep;105(9):1176–1181. PubMed PMID: 24975505. Pubmed Central PMCID: PMC4462387.
18. Iwasa S, Morizane C, Okusaka T, et al. Cisplatin and etoposide as first-line chemotherapy for poorly differentiated neuroendocrine carcinoma of the hepatobiliary tract and pancreas. *Jpn J Clin Oncol*. 2010 Apr;40(4):313–318. PubMed PMID: 20047862.
19. Patta A, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. *Anticancer Res*. 2011 Mar;31(3):975–978. PubMed PMID: 21498724.
20. Okita NT, Kato K, Takahari D, et al. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. *Gastric Cancer*. 2011 Jun;14(2):161–165. PubMed PMID: 21327441.
21. Lu ZH, Li J, Lu M, et al. Feasibility and efficacy of combined cisplatin plus irinotecan chemotherapy for gastroenteropancreatic neuroendocrine carcinomas. *Med Oncol*. 2013;30(3):664. PubMed PMID: 23864251.
22. Okuma HS, Iwasa S, Shoji H, et al. Irinotecan plus cisplatin in patients with extensive-disease poorly differentiated neuroendocrine carcinoma of the esophagus. *Anticancer Res*. 2014 Sep;34(9):5037–5041. PubMed PMID: 25202088.
23. Rogowski W, Wachula E, Gorzelak A, et al. Capecitabine and temozolomide combination for treatment of high-grade well-differentiated neuroendocrine tumour and poorly-differentiated neuroendocrine carcinoma. *Retrosp. Anal Endokrynol Pol*. 2019 Mar 7;70(4):313–317. PubMed PMID: 30843182.
24. Pellat A, Dreyer C, Couffignal C, et al. Clinical and biomarker evaluations of sunitinib in patients with grade 3 digestive neuroendocrine neoplasms. *Neuroendocrinology*. 2018;107(1):24–31. PubMed PMID: 29518779.
25. Panzuto F, Rinzivillo M, Spada F, et al. Everolimus in pancreatic neuroendocrine carcinomas G3. *Pancreas*. 2017 Mar;46(3):302–305. PubMed PMID: 28099254.
26. Zhang J, Kulkarni HR, Singh A, et al. Peptide receptor radionuclide therapy in grade 3 neuroendocrine neoplasms: safety and survival analysis in 69 patients. *J Nucl Med*. 2019 Mar;60(3):377–385. PubMed PMID: 30115686.
27. Carlsen EA, Fazio N, Granberg D, et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. *Endocr Relat Canc*. 2019 Feb 1;26(2):227–239. PubMed PMID: 30540557.
28. Collot T, Fumet JD, Klopfenstein Q, et al. Bevacizumab-based chemotherapy for poorly-differentiated neuroendocrine tumors. *Anticancer Res*. 2018 Oct;38(10):5963–5968. PubMed PMID: 30275226.
29. Klöppel G ea. *WHO Classification of Tumours of Endocrine Organs: WHO/IARC Classification of Tumours*. fourth ed. vol. 10. 2017, 2017.
30. Galleberg RB, Knigge U, Tiensuu Janson E, et al. Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol*. 2017 Sep;43(9):1682–1689. PubMed PMID: 28522174.
31. Deng HY, Li G, Luo J, et al. The role of surgery in treating resectable limited disease of esophageal neuroendocrine carcinoma. *World J Surg*. 2018 Jan 16;42(8):2428–2436. PubMed PMID: 29340724.
32. Maire F, Hammel P, Kianmanesh R, et al. Is adjuvant therapy with streptozotocin and 5-fluorouracil useful after resection of liver metastases from digestive endocrine tumors? *Surgery*. 2009 Jan;145(1):69–75. PubMed PMID: 19081477.
33. Ramella Munhoz R1 dMRJ, de Celis Ferrari AR, Ignez Braghiroli M, et al. Combination of irinotecan and a platinum agent for poorly differentiated neuroendocrine carcinomas. *Rare Tumors*. 2013;5(3):e39.