Outcome after pancreatectomy for neuroendocrine neoplams according to the WHO 2017 grading system: A retrospective multicentric analysis of 138 consecutive patients

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Short title/Running head
Pancreatectomy for NEN & WHO 2017

Authors

Regis Souche MD[1], Antoine Coignac MD[1], Marie Dupuy MD[2], Martin Bertrand MD, PhD[3], Isabelle Raingeart MD[4], Boris Guiu MD, PhD[5], Astrid Herrero MD, PhD[1], Fabrizio Panaro MD, PhD[1], Stephane Obled MD[6], Fabienne Portales MD[7], Benjamin Riviere MD[8], Jeanne Ramos MD, PhD[8,] Frederic Borie MD, PhD[3], Francois Quenet MD[9], Pierre-Emmanuel Colombo MD, PhD[9], Michel Prudhomme MD, PhD[3], Eric Assenat MD, PhD[2], Jean-Michel Fabre MD, PhD[1].

[1] Department of Digestive Surgery and Transplantation, Centre hospitalier-universitaire. Université de Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

[2] Department of Medical Oncology, Centre hospitalier-universitaire. Université de Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

[3] Department of Digestive Surgery, Carémeau Hospital, University of Montpellier - Nîmes, Place du professeur Debré, 30900, Nîmes, France

[4] Department of Endocrinology, Centre hospitalier-universitaire. Université de Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

[5] Department of Radiology, Centre hospitalier-universitaire. Université de Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

[6] Department of Gastroenterology, Carémeau Hospital, University of Montpellier - Nîmes, Place du professeur Debré, 30900, Nîmes, France

[7] Oncology - Institut du Cancer de Montpellier (ICM). Université de Montpellier-Nîmes, Parc Euromédecine - 208 rue des Apothicaires - 34298 Montpellier, France

[8] Department of Pathology, Centre hospitalier-universitaire. Université de Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

[9] Digestive & Oncologic Surgery - Institut du Cancer de Montpellier (ICM). Université de Montpellier- Nîmes, Parc Euromédecine - 208 rue des Apothicaires - 34298 Montpellier, France

Renaten Languedoc-Roussillon study group - Réseau de Référence Clinique pour les Tumeurs Endocrines Malignes Sporadiques et Héréditaires

Corresponding author

Dr. Regis Souche

Digestive and Mini-invasive Surgery unit, Department of digestive surgery and transplantation, St Eloi Hospital, 80 avenue Augustin Fliche, 34295, Montpellier, France. University of Montpellier- Nîmes, 641 avenue du Doyen Gaston Giraud, 34090, Montpellier, France

Tel: +33467337072.

Mail: fr-souche@chu-montpellier.fr

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Synopsis

The aim of this study was to evaluate the new World Health Organization (WHO) 2017 grading system and the others clinicopathological factors in pancreatic neuroendocrine tumor (panNET) operated patients. 138 patients underwent surgical resection with a severe morbidity and mortality rates of 14.5% and 0.7% respectively. Our findings confirm several specific issues related to the management of panNET and the prognostic value of the recent WHO-AJCC 2017 grading system in a real-life setting, even with a relative limited sample size.

Abstract

Aim: The aim of this study was to evaluate the new World Health Organization (WHO) 2017 grading system and the others clinicopathological factors in pancreatic neuroendocrine tumor (panNET) operated patients.

Methods: Histological staging was based on the WHO 2017 grading system. Outcome after surgery and predictors of overall survival (OS) and disease free survival (DFS) were evaluated.

Results: 138 patients underwent surgical resection with a severe morbidity and mortality rates of 14.5% and 0.7% respectively. 5-years OS differed according to WHO 2017: 95% among 58 patients with NETG1, 82% in 68 patients with NETG2, 35% in 7 patients with NETG3 and 0% in 5 patients with NECG3 ($p<0.0001$). Independent predictors of worse OS were age > 60 y.o ($p=0.014$), synchronous metastasis ($p=0.005$) and WHO 2017 with significant differences between NETG1 versus NETG2 ($p=0.005$), NETG3 ($p<0.001$) and NECG3 ($p<0.001$). Independent predictors of worse DFS were symptomatic NET ($p=0.038$), pN+ status ($p=0.027$) and WHO 2017 with significant differences between NETG1 versus NETG3 ($p=0.014$) and NECG3 ($p=0.009$).

Conclusion: The WHO 2017 grading system is a useful tool for patient prognosis after panNET resection and the tailoring of therapeutic strategy. Surgery could provide good results in NETG3 patients.

INTRODUCTION

Neuroendocrine neoplams of the pancreas (panNET) are neoplasms that originate from the endocrine portion of the pancreas. These tumors, which newly affect 2–3 per 100,000 individuals per year, constitute only about 1% to 2% of all pancreatic neoplasms [1, 2]. PanNET can be classified as functioning and non-functioning [3]. At least 50% of panNET are non-functioning and hence asymptomatic. Prognosis of panNET depends on clinico-pathological factors including tumor size, differentiation and proliferative index that give an indication of the biological aggressiveness of the tumor and likelihood of lymph node involvement [4-6]. Complete surgical resection plays an important role in the curative treatment of patients with panNET. Several guidelines exist for the treatment of functioning and non-functioning panNET [7, 8]. It is generally accepted that tumors > 2 cm and functioning tumors should be resected but the management of non-functioning tumors < 2 cm remains controversial. Further controversy exists as to the surgical approach (open vs. laparoscopic) and the lymphadenectomy. PanNET are associated with synchronous liver metastasis in 30-80% of patients and require dedicated multidisciplinary staff discussion [9]. The prognostic classification of NET has been challenging due to their relative rarity. The WHO 2010 grading system adopted the Ki-67 index and/or mitotic index to divide digestive system NEN into 3 main types: NET G1, NET G2 NEC G3. Several studies leading to the new WHO 2017 grading system had reported that NEC G3 is a heterogeneous category that can be separated into two

subcategories with significantly different prognosis and more importantly, therapeutic strategies seem to be distinct [10-13]. The new WHO 2017 classification (dividing G3 tumors in well differentiated NET G3 or poorly differentiated NEC G3) validation is ongoing for its ability to predict disease-free survival (DFS) and overall survival (OS) for panNET [14].

Therefore, we aimed to explore the clinicopathological characteristics, short-term and survival outcome on the basis of 138 consecutive patients with panNET, as well as to evaluate the prognostic value of the proposed new WHO 2017 classification.

PATIENTS AND METHODS

Patient selection and study design

This was a retrospective review of a prospectively maintained database including all consecutive patients requiring a pancreatic resection for panNET at 3 tertiary referral centers for pancreatic surgery in France, between January 1998 and December 2017. The 3 centers were Digestive Surgery Units of Montpellier, Nimes and Institute of Cancer of Montpellier. The University Institutional Review board approved the study (N°: 2019_IRB-MTP_01-02), which was registered on Clinicaltrials.gov registry (NCT03791346).

The inclusion criteria were patients with histologically proven panNET who underwent pancreatic resection (by open, laparoscopic or robotic approach) with no previous or concurrent malignancy. Specimens of patients with incomplete

pathological records were re-analyzed by pathologists. Patients with tumors diagnosed as adenocarcinoma with scattered neuroendocrine cells or with focal neuroendocrine component were excluded of this study.

Surgical management and postoperative outcomes

In each centers, indications for surgery were established during NET dedicated multidisciplinary meeting (Réseau National de Référence pour la prise en charge des Tumeurs neuro-Endocrines Malignes Rares Sporadiques et Héréditaires - RENATEN) including surgeons, gastroenterologists, radiologists, and TENpath labeled pathologists (TENpath: national network of expertise for the pathological diagnosis of adult and sporadic NET).

Functional and hereditary lesions were diagnosed on the basis of the distinct clinical syndromes, serum elevation and positive immunohistochemistry of the relevant hormones. Computed tomography, magnetic resonance imaging, somatostatin receptor scintigraphy and endoscopic ultrasound were used for preoperative assessment of tumor location as deemed necessary.

Patients with panNET that was symptomatic, functional, size ≥2 cm or with presence of aggressive features like pancreatic duct dilation underwent systematic pancreatic resection [7, 15]. During the second part of the study period, small panNET (<2 cm)

that were slow growing with indolent course were considered to observation regardless their location [16, 17]. Patients with synchronous distant metastasis and G1 or G2 panNET, functioning tumor, resectable liver metastasis and absence of extra-hepatic metastasis were considered to surgery after systematic multidisciplinary discussion.

Only patients with well-controlled comorbidities and American Society of Anesthesiologist grade I, II, or III were candidates for surgery. All procedures were performed by at least one experienced (> 40 procedures) pancreatic surgeon.

Lymph node dissection was systematically discussed with the exception of some insulinomas. In case of a reassuring prognosis (panNET G1 at biopsy, no tumor growth over time, absence of suspicious lymph node on CT scan, positive ^{111}In-octreotide scintigraphy and recently, the absence of FDG PET scan hypermetabolism, these last two suggesting a well-differentiated panNET), a parenchymal sparing pancreatectomy with lymph node picking was performed when feasible. During the first decade of the present study, lymph node pathological examination was not routine in case of G1 panNET.

After surgery, all patients were seen daily by a physician until hospital discharge. Thoracoabdominopelvic CT scan with intravenous contrast injection was performed selectively in patients with suspected abdominal or thoracic complications. Pancreatic fistula (PF) was defined and classified according to the ISGPF [18]. Early postoperative hemorrhage was defined according to the ISGPS [19]. Postoperative complications were stratified according to the Dindo–Clavien classification which

defines major complications by a score of III or more [20]. Complications, readmissions, and operative mortality were considered as those occurring within 90 days of surgery, or at any time during the postoperative hospital stay [21, 22].

Histopathologic analysis

Resection margin status was graded R0 (complete resection with no microscopic residual tumor), R1 (complete macroscopic resection but margins microscopically positive) or R2 (grossly residual tumor).

Histological grading and staging was based on the WHO-AJCC 2010 grading system and ENETS classification [23]. Histological examination included regular haematoxylin and eosin staining, and additional immunolabelling using the standard avidin-biotin peroxidase method with antibodies against neuroendocrine markers (synaptophysin (27G12 - Novocastra), chromogranin A (LK2H10 – Ventana)), and Ki67/MIB1 (Dako). Tumor grade (G) was determined by mitotic countin and by Ki-67-labeling index. The mitotic rate was determined by counting mitotic figures in 50 high power fields (at 400x on an Leica microscope) and averaged to 10 high power fields. The Ki67 labeling index was determined by manual counting in the most intensely labeling regions (hot spots), by microscopic examination. At least 500 tumor cells were counted, for each case. All specimens were re-evaluated and re-graded according to the WHO-AJCC 2017 grading system for PanNET by 2 expert TENpath pathologists [14, 24].

Data collection and Follow-up

Demographic details, surgical treatment (enucleation, anatomic resection, multi-visceral resection), pathological variables and follow-up information regarding survival and disease status were evaluated.

After pancreatic resection, all patients were followed-up every 3 months by clinical examination, chromogranin A levels determination, and chest/abdomen computed tomography scan for the first 2 years, and every 6 months thereafter. Follow-up data were collected during routine clinic visits or by contact with the referring physicians. The end of follow-up was considered on December 31, 2017 or at the time of death. During the follow-up, data regarding site, type, and treatment of panNET recurrence were recorded as well.

Statistical analysis

Categorical variables were expressed as percentages, and compared by Chi-square test or Fisher's exact test when appropriate. Continuous variables were expressed as median with range and compared using Student's t test or Mann–Whitney U-test as appropriate. Overall survival (OS) was calculated from the date of diagnosis to the date of death or of last follow-up. Disease-free survival (DFS) was calculated from date of surgery to time of first radiological evidence of local, regional, or distant relapse, or death due to panNET. OS were assessed using Kaplan Meier method and comparisons were performed using the log-rank test, for all characteristics of patients. Patients were censored as of their last follow-up visit if they were alive

and/or disease-free throughout the study period. A P value <0.05 was considered statistically significant. Hazard ratios, with 95% confidence intervals (CI), were estimated using Cox proportional hazard models. For univariate and multivariate analyses, relevant clinicopathological variables were used to determine the association of each parameter with OS, DFS and N+ status. Only variables clinically or statistically relevant (p value of <0.05 at univariate analysis) were introduced in the multivariate model analysis. Data were analyzed with SPSS 21 (IBM, Armonk, USA).

RESULTS

Patient characteristics

A total of 138 patients underwent pancreatic resection for panNET in our 3 centers. The age at surgery was 56 (13-77) years, and 48.5% (67/138) were female. ASA score at diagnosis was I/II in 86.5% of the patients. Diagnosis was incidental in 57 (41%) patients. panNET was sporadic in 132 patients (96%) and associated to Multiple Endocrine Neoplasia syndrome type 1 in 5 (3.5%) patients and Von Hippel-Lindau in 1 (0.5%) patients. Primary locations were equally distributed in the pancreas: head (32.5%), neck/body (32%) and tail (35.5%). Nineteen patients had synchronous metastasis at diagnosis (14%). Main metastatic sites were liver only (11%) and distant lymph nodes (2%). A preoperative biopsy was performed in 87 (63%) of the patients and was positive for panNET in 78 (89%). Key demographics, surgical and

preoperative tumor characteristics are summarized in **Table 1**. Six patients (4%) received neoadjuvant treatment for locally advanced non metastatic lesions with cisplatine-etoposide (n=4) or doxorubicine-streptozocine (n=2). Seven metastatic patients (5%) with panNET G2 (n=5) or panNEC (n=2) received preoperative chemotherapy (doxorubicine-streptozocine (n=5) or cisplatine-etoposide (n=2)).

Surgical data

On 138 patients, surgical procedure was pancreaticoduodenectomy (29%), distal pancreatectomy (58%), enucleation (9%) and central pancreatectomy (4%). An open approach was used in 56% of patients and laparoscopy was used in 44% of patients with a rate of open conversion of 3%. Adjacent organ resection was required in 6 patients (4%): partial gastrectomy (n=1), small bowel resection (n=1), transverse colic resection (n=1) and liver resection (n=3; 1 right hepatectomy, 1 left lobectomy + wedge resection, 1 wedge resection).

In the 19 patients with synchronous metastasis, 4 symptomatic patients (aged of 49, 49, 39 and 43 years old) with preoperative jaundice due to a cephalic PanNET and potentially resectable liver metastasis underwent a pancreaticoduodenectomy after discussion in multidisciplinary meeting.

The 5 patients with PanNEC were under 65 years old and symptomatic. Two of them had potentially resectable liver metastasis and received a preoperative chemotherapy. Three patients underwent a distal pancreatectomy and 2 a pancreaticoduodenectomy for panNEC.

Postoperative outcome

The postoperative outcome data are presented in **Table 2**. The overall complication rate was 44%. A postoperative pancreatic fistula (POPF) occurred in 23% of the patients and was mostly clinically relevant (grade B/C) (n=27/33). A major complication Clavien-Dindo ≥ 3 occurred in 14.5% of the patients and the reoperation rate was 10% essentially due to pancreatic fistula. The overall postoperative mortality rate was 0.7% (n=1). The cause of the postoperative death in one patient was grade C POPF after pancreaticoduodenectomy complicated by massive hemorrhage.

Pathological tumour characteristics

The pathology results are presented in **Table 3**. Resection of the panNET was complete (R0) in 92.5 % of cases. The median tumor size was 31 mm (+/-23, range: 2-140mm). The median number of harvested lymph nodes was 8 (range 1 - 43) in 92 patients who underwent lymphadenectomy. Seven of 12 panNET graded NEC G3 according to the WHO 2010 grading system were well differenciated and re-graded as panNET G3 according to the new proposal WHO 2017 grading system. Of 24 asymptomatic patients with nonfunctional panNET smaller than 2 cm, 7 patients had tumors graded G2, and 5 of 10 patients who underwent lymphadenectomy had lymph node metastasis.

Factors associated with lymph node metastasis

In the sub group of patients with lymphadenectomy, factors associated with N+ status at univariate analysis were Ki67 > 2% (p = 0.028), tumor size > 2 cm (p = 0.044) and microvascular invasion (p = 0.005). None of them were independent predictors of N+ status after logistic regression.

Survival

The median follow-up, based on the Kaplan–Meier estimate of potential follow-up, was 79 months (range: 3-245 months). Overall (OS) and Disease free Survival (DFS) were 98, 89, 81, 68% and 93, 88, 79, 67% at 1, 3, 5 and 10 years, respectively (**Figure 1**). The median OS was not reached. On 118 non metastatic patients, recurrence was experienced by 22.9 % of patients (n=27/118), with a median time interval until disease recurrence not reached (range: 12-245 months). OS and DFS according to WHO 2017 classification are displayed in Figure 2A and 2B respectively. Five-year overall survival differed according to WHO 2017 grading system: 95% among 58 patients with panNET G1, 82% in 68 patients with NETG2, 35% in 7 patients with NETG3 and 0% in 5 patients with pancreatic neuroendocrine carcinomas NECG3 (p<0.0001).

Prognostic factors analysis

Overall survival As shown in **Table 4** resuming all significant variables at univariate analysis in the whole study cohort, independent factors associated with

overall survival were age > 60 y.o (p=0.014), synchronous metastasis (p=0.005) and WHO-AJCC 2017 grading system with significant differences between NETG1 versus NETG2 (p=0.005), NETG3 (p<0.001) and NECG3 (p<0.001).

Disease-free survival Independent factors associated with Disease free survival were symptomatic NET (p=0.038), pN+ status (p=0.027) and WHO-AJCC 2017 grading system with significant differences between NETG1 versus NETG3 (p=0.014) and NECG3 (p=0.009). No significant difference was found between NETG1 and NETG2 in multivariate analysis (p=0.064).

DISCUSSION

This study, which involved three centers with the same clinical RENATEN network, has many strengths: only panNET patients were included, standardization of work-up across our centers and systematic pathological review by 2 TENpath labeled experts. Pancreatic neuroendocrine neoplasms were majority non-functioning, sporadic, single lesion of 31 mm in median size, non-metastatic with homogenous stage distribution. Our findings confirm several specific issues related

to the management of panNET and the prognostic value of the recent WHO-AJCC 2017 grading system in a real-life setting, even with a relative limited sample size.

Surgery for panNET provides good results on OS and DFS, both higher than 80% at 5 years. Median recurrence time was not reached in the present study. However, pancreatic resection remains a challenging procedure and its morbidity must be systematically considered in therapeutic strategy with benefits/risks evaluation. Morbidity after pancreatectomy is closely related to pancreatic fistula (23%) which is classically high due to (i) the soft texture of pancreas, (ii) an usual small diameter of main pancreatic duct and (iii) a larger number of patients who benefits of parenchymal sparing pancreatectomy [25, 26].

The present study found that WHO-AJCC 2017 grading system provides good discrimination between panNET G1, NETG2, NETG3 and NEC for OS and DFS. In line with the Rindi et al international cohort study, we found that OS and DFS following the resection of panNET G3 vs PNEC G3 significantly differed, thereby suggesting distinct aggressive behavior [27]. DFS following the resection of panNET G3 vs G2 was statistically different whereas OS was not probably due to the low statistical power resulting from the relatively low number of panNET G3. These data reinforces this new subgroup of panNET G3 is the most aggressive form of well differentiated pancreatic neuroendocrine neoplasms, and as such should be carefully diagnosed and benefit from a dedicated treatment [27]. These findings could suggest that resection may be considered as a treatment option for patients with panNET G3

contrary to panNEC G3. Progress in diagnosis tools to distinguish panNET G3 vs. panNEC are required in order to provide a better tailoring in the management of patients for personalized therapy. Larger prospective series dedicated to G3 tumors are required to explore this question.

In addition to the WHO-AJCC grading system, age and distant metastasis were independent predictors of worse survival in the present study; symptomatic panNET, lymph node metastasis were independently associated with disease recurrence.

We found that age over 60 years at diagnosis was an independent factor associated with poor survival as in the National Cancer Data Base study by Bilimoria et al. including 3851 patients. The group of patients aged 55 to 75 years and those over 75 had a worse survival than patients younger than 55 years (HR 1.57 and 3.04 respectively, $p < 0.0001$) [28].

The incidence of panNET has increased in recent years, particularly for small lesions [29, 30]. In multivariate analysis, we found that a symptomatic lesion (59% of cases) was an independent factor of poor DFS compared to incidental panNET. In the same way, the study by Cheema et al. reports a significant difference in 5-year disease-free survival rate between incidental panNET (86%) and symptomatic panNET (59% , $p = 0.007$) [31].

The present study included 86% of nonfunctional panNET in line with previous data [32]. In asymptomatic patients with nonfunctional panNET smaller than 2 cm, some patients had tumors graded G2, and 50% of patients who underwent

lymphadenectomy had lymph node metastasis. These findings results are in line with previous studies that found a potential malignancy for small lesions [30, 33]. Considering we did not find any influence of tumor size on OS or DFS, this data highlights that a 'watch-and-wait' strategy for nonfunctional panNET < 2 cm should be confronted to a strong benefits/risks discussion in order to avoid under/overtreatment.

The presence of liver metastases was an independent factor of poor prognosis [28, 34, 35]. Unlike other pancreatic carcinomas, patients with metastatic panNET can benefits of multimodal therapy and these patients justify expert multidisciplinary staff discussion.

The question of lymphadenectomy in modern parenchymal sparing era remains a major concern in patients with panNET. Although controversial, some studies have highlighted the impact of lymph node invasion on survival [35-39]. pN+ status was independantly asociated with poor DFS. Lymph node invasion was significantly associated with Ki67 > 2%, tumor size > 2 cm and microvascular invasion but logistic regression failed to identify independent predictors in the present study. A comprehensive analysis is difficult because of a high rate of surgery with unknown lymph node pNx status (46%) due to the selective lymphadenectomy and initial lymph node pathology examination policies of involved centers. The management and monitoring of N+ panNET remain a major concern such as they currently do not benefit from adjuvant treatment.

We are, of course, aware of some limitations of the present study. First, it is limited by its retrospective nature. Second, we have data only on resected patients, and it is unknown how many patients have been under surveillance during the same time period in our 3 centers. Third, the patient sample size, particularly in panNET with Ki67 > 20%, remains limited to provide meaningful subgroup survival analysis. However, our results were obtained from a homogeneous cohort of consecutive patients treated in the same clinical network and reflect real life. Missing data in our database were inferior to 5%.

In conclusion, the WHO 2017 grading system is a useful tool for patient survival prognosis after pancreatic resection and the tailoring of therapeutic strategy. PanNET G3 has an intermediate prognosis between panNET G2 and PNEC on DFS indicating that panNET G3 is the most aggressive panNET. Progress in diagnosis tools to distinguish panNET G3 vs. PNEC are required in order to provide a better management of patients in the era of personalized multimodal therapy.

All authors declare that has participated sufficiently in the work to take public responsibility for appropriate portions of the content, as defined in to the guidelines of the International Committee of Medical Journal Editors (ICMJE).

Authors' contributions: RS, AC, MD, JR, BR, MP, EA and JMF were responsible for study concept and design. RS, AC, MD, MB, IR, BG, AH, SO, FP, BR, FB, JR, FQ, PEC, MP, EA and JMF contributed for acquisition and interpretation of data. RS, AC, MD, MB, IR, BG, AH, SO, BR, FB, JR, FQ, PEC, MP, EA and JMF performed drafting of the manuscript. RS, AC, MD, MB, IR, BG, AH, SO, FP, BR, FB, JR, FQ, PEC, MP, EA and JMF contributed for critical revision. All authors have viewed and approved the final version of the manuscript.

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FIGURES AND TABLES

Table 1 - Demographic and clinicopathological characteristics of patients with pancreatic neuroendocrine neoplasms (n = 138)

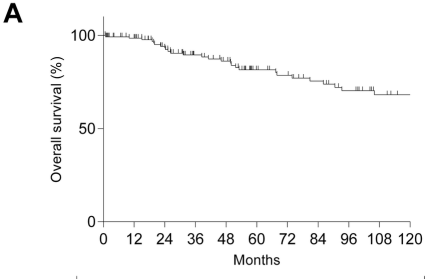
Table 2 – Surgical data and postoperative outcome of patients with pancreatic neuroendocrine neoplasms (n = 138)

Table 3 – Pathologic results of patients with pancreatic neuroendocrine neoplasms (n = 138)

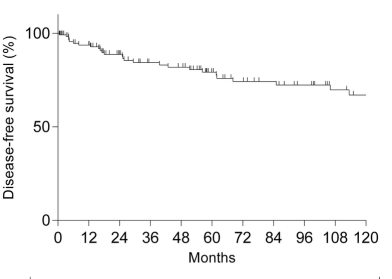
Table 4 - Multivariable Cox regression analysis of variables associated with overall survival and disease free survival after surgery for pancreatic neuroendocrine neoplasm

Figure 1 - (A) Overall survival of 138 patients after surgery for pancreatic neuroendocrine neoplasm and (B) Disease-free survival of 118 patients after surgery for non-metastatic pancreatic neuroendocrine neoplasm (color should be used)

Figure 2 - (A) Overall survival of 138 patients after surgery for pancreatic neuroendocrine neoplasm and (B) Disease-free survival of 118 patients after surgery for non-metastatic pancreatic neuroendocrine neoplasm according to the WHO 2017 grading system (color should be used)

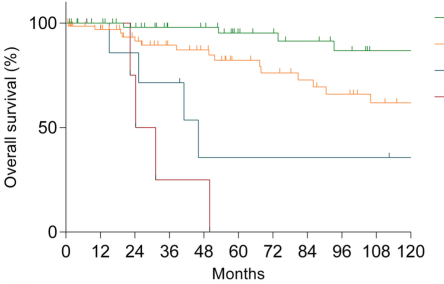


	0	12	24	36	48	60	72	84	96	108	120
Number at risk	138	124	104	86	78	60	54	47	41	33	30



	0	12	24	36	48	60	72	84	96	108	120
Number at risk	118	101	82	71	67	52	44	40	35	28	25

A

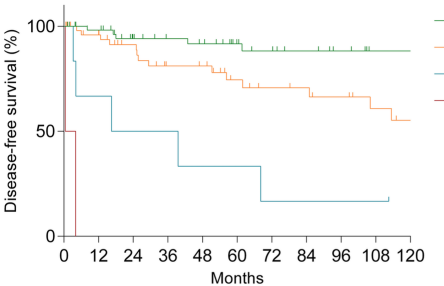


NETG1 vs. NETG2	p =0.007
NETG1 vs. NETG3	p < 0.0001
NETG1 vs. NECG3	p < 0.0001
NETG2 vs. NETG3	p = 0.120
NETG2 vs. NECG3	p < 0.0001
NETG3 vs. NECG3	p = 0.028

Number at risk

	0	12	24	36	48	60	72	84	96	108	120
NET G1	58	54	47	39	37	28	26	24	20	16	15
NET G2	68	60	49	41	37	29	26	23	20	16	13
NET G3	7	7	7	6	3	3	3	3	3	3	2
NEC G3	5	5	3	2	2	0	0	0	0	0	0

B



NETG1 vs. NETG2	p = 0.002
NETG1 vs. NETG3	p < 0.0001
NETG1 vs. NECG3	p< 0.0001
NETG2 vs. NETG3	p = 0.005
NETG2 vs. NECG3	p < 0.0001
NETG3 vs. NECG3	p = 0.046

Number at risk

	0	12	24	36	48	60	72	84	96	108	120
NET G1	57	53	42	39	37	30	25	23	20	16	16
NET G2	53	45	37	29	28	21	18	17	14	12	10
NET G3	6	5	4	3	3	3	2	2	2	1	1
NEC G3	2	0	0	0	0	0	0	0	0	0	0

Table 1 - Demographic and cliniopathologial characteristics of patients with pancreatic neuroendocrine neoplasms (n = 138)

		(n,%)
Patients		138
Gender		
	Female	67 (48.5)
	Male	71 (51.5)
Period		
	1997-2007	48 (35)
	2008-2017	90 (65)
Age, years		
	median (range)	56 (13-77)
ASA score		
	Grade I	46 (33)
	Grade II	74(53.5)
	Grade III	17 (12)
	Grade IV	1 (0.8)
Functional tumor		19 (14)
Fortuitous diagnosis		57 (41)
Preoperative biospy		87 (63)
Tumor localization		
	Head	45 (32.5)
	Neck/Body	44 (32)
	Tail	49 (35.5)
Synchronous metastasis		20 (14.5)
Site of metastasis		
	Liver only	15 (11)
	Liver and other site	4 (3)
	Other	1 (0.8)

SD: standard deviation; BMI: body mass index; DM: diabetes mellitus

Table 2 – Surgical data and postoperative outcome of patients with pancreatic neuroendocrine neoplasms (n = 138)

	(n,%)
Procedure	
Pancreaticoduodenectomy	40 (29)
Distal pancreatectomy	80 (58)
with spleen preservation	36 (26)
without spleen preservation	44 (31)
Central pancreatectomy	6 (4)
Enucleation	12 (9)
Adjacent organ resection	6 (4%)
Approach	
open	77 (56)
laparoscopic	61 (44)
Conversion to open	4 (3)
Postoperative outcome	
Pancreatic fistula *	33 (23)
Clinically relevant Pancreatic fistula (grade B/C)*	27 (19.5)
Postoperative transfusion	6 (4)
Reoperation	14 (10)
90-days readmission	27 (19.5)
90-days postoperative complications	61 (44)
Major complications (Clavien-Dindo ≥ 3)	20 (14.5)
90-days postoperative mortality	1 (0.7)
Duration of hospitalization (days), median (range)	12 (2-67)

* according to the ISGPF classification

Table 3 – Pathologic results of patients with pancreatic neuroendocrine neoplasms (n = 138)

	(n,%)
Tumor size, mm, median (range)	31 (2-140)
Differentiation	
Well	133 (96)
Poor	5 (4)
According to ENETS staging	
pT	
T1	53 (38)
T2	41 (30)
T3	35 (25)
T4	9 (6.5)
pN	
N1	37 (27)
N0	55 (40)
Nx	46 (33)
ENETS STAGE	
I	49 (35.5)
IIa	29 (21)
IIb	17 (12.5)
IIIa	1 (0.5)
IIIb	22 (16)
IV	20 (14.5)
Surgical margin	
R0	129 (93.4)
R1	9 (6.6)
WHO 2010	
NET G1	58 (42)
NET G2	68 (49)
NEC G3	12 (9)
WHO 2017	
NET G1	58 (42)
NET G2	68 (49)
NET G3	7 (5)
NEC G3	5(4)
Perineural invasion	34 (25)
Microvascular invasion	41 (30)
Macrovascular invasion	2 (1.5)

Table 4 - Multivariable Cox regression analysis of variables associated with overall survival and disease free survival after surgery for pancreatic neuroendocrine neoplasm

Variables*	HR	95% CI	P value
Overall survival			
Gender (male)	1.660	0.785 - 3.510	0.185
Age > 60 y.o	2.554	1.207 - 5.405	0.014
Synchronous metastasis	3.365	1.430 - 7.916	0.005
Microvascular invasion	1.633	0.671 - 3.973	0.280
Surgical margin (R1)	1.214	0.145 - 10.193	0.858
WHO 2017			<0.001
NET G1**	_	_	_
NET G2	3.084	1.048 - 9.075	0.041
NETG3	10.758	2.863 - 40.422	<0.001
NECG3	29.747	6.236 - 141.889	<0.001
Disease free survival			
Symptomatic NET	3.044	1.065 - 8.703	0.038
Functional tumor	0.161	0.020 -1.267	0.083
pN			0.015
N0**	_	_	_
Nx	0.354	0.074 - 1.704	0.195
N1	2.739	1.123 - 6.682	0.027
Tumor size	0.		0.702
< 20 mm**	_	_	_
20-39 mm	1.721	0.371 - 7.975	0.488
> 40 mm	1.935	0.410 - 9.129	0.404
Microvascular invasion	1.962	0.809 - 4.757	0.136
Surgical margin (R1)	1.834	0.470 - 7.159	0.383
WHO 2017			0.031
NET G1**	_	_	_
NET G2	3.042	0.935 - 9.892	0.064
NETG3	5.703	1.429 - 22.767	0.014
NECG3	15.139	1.998 - 114.718	0.009

CI: confidence interval; HR : hazard ratio; *Variables with p value < 0.100 in univariate analysis; **statistical reference, WHO : World Heatlh Organisation