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Can we predict recurrence in WHO G1-G2 pancreatic neuroendocrine neoplasms? Results from a multi-institutional Spanish study

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ABSTRACT

Introduction: Pancreatic neuroendocrine neoplasms (PNEN) are rare tumours and well differentiated PNEN are associated with relatively indolent physiological behaviour. For this reason, only few studies have investigated those factors associated with recurrence in this group of patients. The aim of this study is to analyse whether it is possible to predict tumour recurrence in World Health Organization (WHO) 2017 G1-G2 PNEN patients.

Methods: This is a retrospective multi-institutional study. Patients submitted to pancreatic resection from 7 Spanish centres were reviewed. Only patients with WHO G1-G2 PNEN were included. Demographic and clinicopathological variables were analysed.

Results: Data from 137 patients were reviewed. Median age was 59.2 (25–84) years. Recurrence of disease occurred in 19 (13.9%) patients. Median DFS was 55 months. At multivariate analysis, tumour size >20 mm, lymphnode metastasis and a new tumour grade 2 incorporating Ki-67 labelling index (LI) > 5% and mitotic index (MI) > 2 were independently associated with recurrence. We developed a risk score model with these three factors. High-risk patients had a significantly lower 5-year disease-specific survival compared to low-risk patients (70% vs 100%).

Conclusion: We propose a novel risk score for recurrence based on lymphnode metastasis, tumour size > 20 mm and a new grade 2 based on Ki-67 LI >5% and MI > 2. If 2 factors are present, patients have a higher risk for recurrence and a significantly poorer DSS, and therefore they should be closely monitored during follow-up. The role of adjuvant chemotherapy in these patients needs to be evaluated in clinical trials.

Introduction

Well-differentiated pancreatic neuroendocrine neoplasms (PNEN) are considered a relatively indolent disease. However, the recurrence rate reported after curative surgery can reach 17% of resected patients with consequences on survival [1]. Currently, there is no indication for adjuvant treatment in this group of patients and no surveillance protocols exist.

It has been recently suggested that a Ki-67 Labelling Index (LI) 5% cut-off level is independently associated with recurrence and with poorer disease-specific survival in patients with non-functioning PNEN [2–5] and therefore it might be a useful tool to predict survival. The same authors have reported a novel score to predict disease-specific survival based on World Health Organization (WHO) 2010 tumour grade (G1 and G2), lymph node metastasis, and perineural invasion [1]. However, the 2017 WHO tumour grade classification still utilize a Ki-67 LI < 3% cut-off level to differentiate G1 from G2 PNEN patients [6,7]. Mitotic count (MC) is

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also considered and the final grade is based on whichever index places the tumour in the higher-grade category.

The aim of our study is to investigate those factors associated with tumour recurrence in a Spanish multi-institutional analysis and the value of a risk score to predict recurrence in WHO G1-G2 PNEN patients.

Methods

All patients referred to 7 Spanish referral centres for PNEN from January 2006 to December 2016 were reviewed. Patients who underwent curative resection of histologically proven PNEN were considered for this study. Those patients with distant metastasis, unresectable PNEN at diagnosis or with PNEN associated with a genetic predisposition were excluded. Both functional and non-functional tumours were included. Tumours were staged according to the 8th edition of AJCC/UICC TNM system. Only G1 and G2 patients were included, i.e. those with Ki-67 < 20% LI and MC < 20 high power fields (HPF) (G2: Ki-67 3–20 or MC 2–10/10 HPF). The final grade was based on whichever index placed the tumour in the higher-grade category. Since the 8th edition was introduced in January 2018, all specimens were reviewed by pathologists dedicated to neuroendocrine malignancies from each centre. For all patients, manual counting of printed images was performed to assess Ki-67 and number of mitosis, indicating an exact number and not the category only. Resection margin was assessed according to the Classification of the Royal College of Pathologists [8]. All types of pancreatic resections were considered. Lymphadenectomy was not routinely performed in case of parenchyma-sparing surgery.

Data of patients with PNEN are collected in a prospectively maintained database from each centre and they include: demographics, histopathology of the tumour, operation data, complications and follow-up. Postoperative complications were defined according to Clavien-Dindo classification [9]. Pancreatic leak was defined according to ISGPF classification (grade B and C) [10].

All patients were followed up in the outpatient clinic by the operating surgeon and received a contrast enhanced CT-scan every six months during the first 2 years and yearly thereafter. After two years, patients received a CT-scan annually. Tumour markers were not routinely assessed. Additional radiologic imaging was requested in case of unclear results from CT-scan or tumour markers. Follow-up time was defined as the time to the last known date the patient was alive or the time until death. Recurrence was defined as local recurrence in the pancreas, a new location in lymph nodes, or the development of distant metastases.

Patients lost at follow-up or deceased for postoperative complications following pancreatic resection (in hospital or 30-day mortality) were excluded.

Ethical approval for this study was obtained from each participating centre.

Statistical analysis

Frequencies were compared using $\times 2$ or Fisher's exact tests. Continuous data were compared using the independent samples *t*-test or the Mann–Whitney *U* test, depending on whether they were normally distributed or not, respectively. Data were previously tested for normality by the Kolmogorov–Smirnov test. These univariate analyses identified those variables associated with recurrence. Multivariate analysis of statistically significant variables ($p < 0.05$) was performed using binary logistic regression. Those factors independently associated with recurrence were used to develop a risk score. Receiver operating characteristic (ROC) analysis with area under curve (AUC) determination was performed to detect best cut-off values.

Kaplan–Meier survival analyses with log-rank testing were performed to investigate disease-specific survival. Youden's index was used to maximize sensitivity and specificity.

A two-tailed P-value less than 0.05 was considered significant. SPSS 19.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Data from 137 patients were reviewed (see Flowchart). Patient and tumour characteristics are reported in Table 1. Recurrence of disease occurred in 19 (13.9%) patients. Median time to recurrence was 44 (5–100) months. Median follow-up was 64 months.

At univariate analysis, tumour size, lymphnode metastasis, vascular and perineural invasion, Ki-67 LI, MC and WHO G2 were significantly associated with recurrence ($p < 0.05$) (Table 2). ROC analysis was used to identify cut-off point for continuous variables. For tumour size, cut-off at 20 mm was chosen (AUC 0.754, Sensitivity 82%, Specificity 70%). Best cut-off point for Ki-67 LI was 5% (AUC 0.661, Sensitivity 48%, Specificity 88%) and for MC was 2 HPF (AUC 0.73, Sensitivity 48%, Specificity 84%).

At multivariate analysis, tumour size >20 mm, lymphnode metastasis, MC > 2 and Ki-67 > 5% were independently associated with recurrence (Table 3). A new grade 2 was calculated by allocating those patients with MC > 2 or Ki-67 > 5% in grade 2. All remaining patients including those with a 2% < Ki67 > 5% were allocated in grade 1. In total, 39 patients were allocated to grade 2: 28 patients in no-recurrence group, and 11 in recurrence group (23.7% vs 57.9%, $p = 0.02$). By multivariate analysis, new grade 2, tumour size >20 mm and positive nodes were independently associated to recurrence (Table 3). When tested in multivariate analysis, WHO Grade 2 was not independently associated with recurrence ($p = 0.358$, OR 1.813, 95% IC 0.51–6.43).

Table 1
Tumour and patient characteristics.

	n. (%)
Age, median (range)	59.2 (25–84)
Male Gender	79 (57)
Tumour size, mm, median (range)	27 (2–120)
Tumour location	45 (32.8)
• Head	44 (32.2)
• Body	48 (35)
• Tail	
Functioning tumour	33 (24.1)
Type of pancreatectomy	27 (19.7)
• PD	65 (48.4)
• DP	45 (31.9)
• Other	
Lymphadenectomy	93 (67.9)
N. of metastatic lymphnodes, median (range)	0.5 (0–9)
N. of retrieved lymphnodes, median (range)	8.3 (1–43)
LNR	0.4 (0.06–1)
Vascular invasion	18 (13.1)
Perineural invasion	24 (17.5)
MC, HPF, median (range)	2.2 (0–20)
Ki-67 LI, %, median (range)	3.8 (0–20)
Residual disease (R1)	16 (11.7)
Pancreatic fistula	38 (27)
Postoperative complications	82 (59.9)
Recurrence	19 (13.9)
Site of recurrence	15
• Liver	4
• Local (in the pancreas)	0
• Nodal	
Overall deaths	15 (10.9)
Disease-related deaths	7 (5.1)

PD: pancreaticoduodenectomy; DP: distal pancreatectomy; LI: labelling Index; MC: mitotic count; HPF: high power fields.

Table 2
Univariate analysis.

	No recurrence (118 patients)	Recurrence (19 patients)	p-value
Age, median (range)	59.4 (25.84)	57.4 (29–83)	0.552
Male gender	69 (58.5)	10 (52.6)	0.632
Tumour size, mm, median (range)	25.2 (2–120)	40.5 (4–70)	0.007
Tumour location	38 (32.2)	7 (36.8)	0.832
• Head	39 (33.1)	5 (26.3)	
• Body	41 (34.7)	7 (36.8)	
• Tail			
Functioning tumour	31 (26.3)	2 (10.5)	0.136
Type of pancreatectomy	21 (17.8)	6 (31.6)	0.16
• PD	55 (46)	10 (52.7)	
• DP	42 (35.5)	3 (16.7)	
• Other			
Lymphadenectomy	78 (66.1)	15 (78.9)	0.266
LNR	0.2 (0.06–1)	0.5 (0.07–1)	0.07
N. of mitosis, median (range)	1.9 (0–20)	3.8 (1–12)	0.005
Ki 67 LI, %, median (range)	4 (0–20)	9 (1–18)	0.001
WHO G2	46 (39)	12 (63.2)	0.048
Vascular invasion	12 (10.2)	6 (31.6)	0.010
Perineural invasion	17 (14.4)	7 (36.8)	0.017
Residual disease (R1)	13 (11)	3 (15.8)	0.548
Postoperative complications	71 (60.2)	11 (57.9)	0.851
Pancreatic fistula	31 (26.3)	7 (36.8)	0.339
Metastatic Lymphnodes	10 (8.5)	9 (47.4)	< 0.001
Tumour Size > 20 mm	52 (44.1)	17 (89.5)	< 0.001
Ki67 LI >5%	15 (12.7)	9 (47.4)	< 0.001
MC > 2 HPF	20 (16.9)	9 (47.4)	0.003

PD: pancreaticoduodenectomy; DP: distal pancreatectomy; LI: labelling Index; MC: mitotic count; HPF: high power fields.

Table 3
Multivariate analysis.

	p-value	OR	95% CI
T > 20 mm	**0.012**	8.112	1.581–41.624
Positive nodes	**0.002**	10.374	2.32–46.381
Vascular invasion	0.246	0.343	0.056–2.095
Perineural invasion	0.06	4.703	0.8–17.928
Grade 2 (Ki-67 > 5% or MC > 2 HPF)	**0.044**	3.785	1.034–13.855

LI: labelling Index; MC: mitotic count; HPF: high power fields.

We developed a risk score with these 3 factors as shown in Table 4. ROC analysis showed an AUC 0.824, with best cut-off at 11 (Sensitivity 74%, Specificity 81%). Patients scoring ≥11 were considered at high-risk for recurrence. Since the cut-off score can be reached with 2 out of 3 factors, the presence of 2 factors itself is sufficient to allocate patients in the high-risk category. Out of 19 patients with recurrence, 14 reported a score ≥3 (high-risk) (73.7% vs 19.5% in no recurrence group, $p < 0.001$).

Kaplan–Meier analysis showed significantly less recurrence within 5 years after surgery for the patients with high-risk score than for the patients with low-risk score. The 5-year disease-free survival rate was 97% for the patients with low-risk and 65% for the patients with high-risk score ($p < 0.001$; Fig. 1).

Median DSS was 55 (3–132) months. In all cases of disease-specific death, patients had a high-risk score. No disease-related deaths were observed in low-risk patients. Five-year disease-specific survival was 75% for high-risk vs 100% for low-risk patients ($p < 0.001$; Fig. 2).

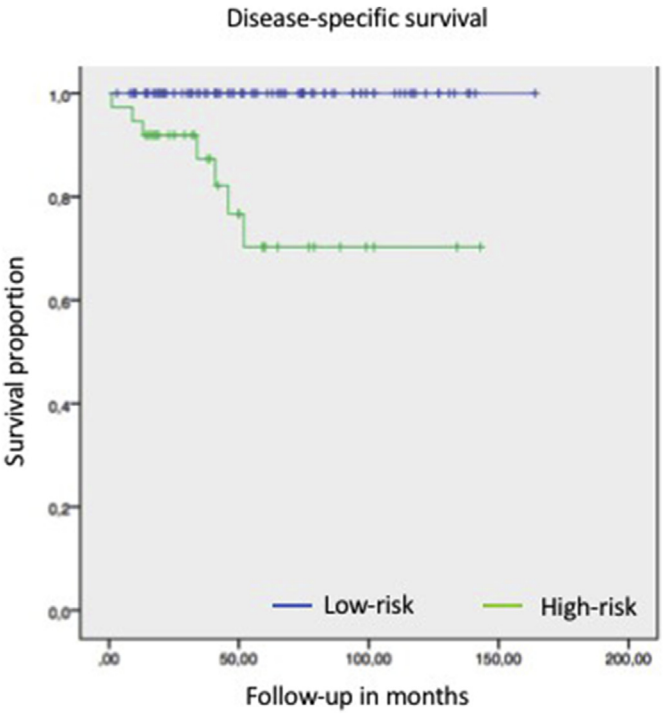

Fig. 1. Disease-specific survival for high- and low-risk patients.

Table 4
Risk score to identify patients with high-risk of tumour recurrence.

	Points
T > 20 mm	8.1
Positive nodes	10.3
Grade 2 (Ki-67 > 5% or MC > 2 HPF)	3.7

LI: labelling Index; MC: mitotic count; HPF: high power fields.

Discussion

Pancreatic neuroendocrine neoplasms (PNEN) are rare lesions. They include a broad family of tumours that exhibit heterogeneous

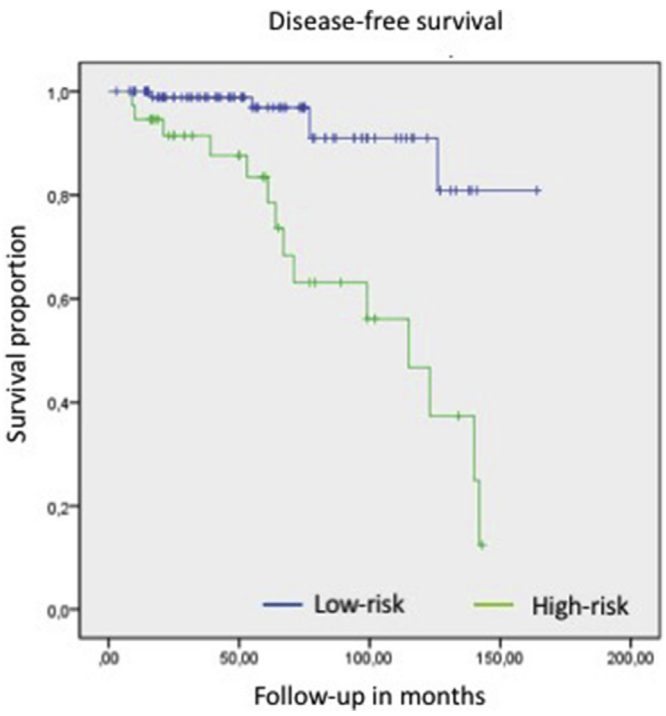

Fig. 2. Disease-free survival for high- and low-risk patients.

biologic behaviour [11]. These tumours are increasingly being found in cross sectional imaging performed for other unrelated reasons [12], and surgical resection can be curative in patients with localized PNEN and also it can increase survival in patients with metastatic PNEN [13,14]. Resection in case of non-functioning PNEN < 20 mm is controversial since non-operative management is advocated by some authors [15]' although even in these cases an aggressive behaviour can be found [16,17]. Regional lymph node resection is a matter of debate because available literature consist of retrospective series with small number of cases [18].

Our study contributes to the assumption of tumour heterogeneity even among patients with a WHO 2017 G1-G2 PNEN. Three different parameters, namely, tumour size >20 mm, lymphnode metastasis and a new grading obtained combining Ki-67 LI >5% or MC > 2 should be considered together to identify those patients with higher risk for recurrence. As the cut-off score was 11, and this could be reached with 2 out of 3 factors, there is no need to make any score calculation. When 2 factors are present, patient can be classified as high-risk for recurrence. This represents a very simple way to stratify G1-G2 PNEN patients. Our result suggests that more intensive follow-up and adjuvant chemotherapy needs be considered in high-risk patients and perhaps long-term and intensive follow-up is not necessary in low-risk patients. No specific follow-up programs have been reported by PNEN guidelines. Follow-up visits are usually scheduled every 6 months for the first 2–3 years and once a year after that. In case of high-risk PNEN, this could be intensified to 3 monthly outpatient visits checking for CgA (chromogranin A) levels and alternating CT and MRI scan during the first 5 years.

Regarding adjuvant treatment, clinical trials are needed to demonstrate the potential benefit in these patients.

Other authors have previously demonstrated similar results. Genç at al evaluated a multicentric retrospective series of 241 patients and showed that a Ki67 rate higher than 5%, tumour larger than 4 cm and lymph node metastases were independently associated with recurrence [2]. In our study, a 20 mm tumour size cut-off was identified after ROC analysis, which is in line with available literature considering a diameter > 20 mm as an indicator of poorer prognosis [19]. As previously commented, in agreement with other authors, Ki-67 LI > 5% is a very useful tool to identify those patients at high risk for recurrence. In our study, when considered with a 2% cut-off as in WHO classification, Ki-67 LI was not significantly associated with recurrence at univariate analysis ($p = 0.089$), whilst 5% cut-off showed a statistically significant association. Whether different categories could be identified in the 5–20% LI range needs to be validated in larger studies. We decided to include MC in our grading since there was a statistically significant association at univariate analysis. The Ki- 67 LI and the MC have proved to be extremely useful prognostic markers in PNEN patients, and have been incorporated into international grading systems [20]. However, there is a lack of consensus regarding the best marker and the most appropriate cutoff to define grade. As shown by some authors, grade according to Ki-67 is better in predicting prognosis than MC [21]; however, one should not assume agreement between Ki-67 and MC. In our study, only 14 (58%) patients out of 24 with a Ki-67 > 5 showed a MC > 2. Also, 15 out of 29 patients with MC > 2 showed a Ki67 < 5%. Therefore, we agree that both factors should be used and the final grade should be based on whichever index placed the tumour in the higher-grade category.

In our study, pathology specimens were reviewed by each centre pathologist at the time of the study; Ki-67 values and number of mitosis were counted manually on printed images, thus allowing a more accurate classification compared to previous retrospective reports. This is the first study analysing the association between tumour recurrence in WHO G1-G2 PNEN patients and Ki-67 LI/MC assessed as continuous variables as opposed to categories.

We decided to consider as a recurrence both local and distant disease. One could argue that these 2 types of recurrence may be related to different parameters; however, all the authors we have previously mentioned did not make such a distinction. In fact, in our population there was no association between local recurrence (in the pancreas) and R1 resection (15.8% vs 11% in the group with R0 resection, $p = 0.548$). In this study, microscopic positive resection margins were seen in 11% after pancreatic resection. Frozen sections during surgery were nor routinely performed. However, they were nor associated to recurrence and similar results have been reported by other authors [1]. Therefore, the role of resection margins remains unclear.

This study has several limitations. Firstly, although our data were extracted form a prospective database, this is a retrospective study and therefore data were not collected for this analysis. Secondly, we decided to include both functioning and non-functioning tumours, making our study population very heterogeneous. Although surgical treatment for NF-PNEN < 20 mm is controversial, surgery is always indicated in functioning tumours. However, there is no clear evidence that when stratified for Ki-67 and mitosis, these tumours have a different biological behaviour. In fact, no specific staging system for functional tumours exist and they are classified together with non-functioning tumours [22]. Regarding pathology, data were reviewed from each centre, thus implying the risk of interobserver variability. Furthermore, other clinical variables could not be assessed. For instance, treatment of recurrence was not considered and this might have affected disease-specific survival. Also, lymphadenectomy was not systematically performed and the median number of retrieved lymphnodes was 8, which is lower than expected in lymphadectomy for pancreatic cancer [23]. However, these problems are difficult to overcome, especially until specific guidelines for PNEN staging and treatment will be available.

Despite the limitations of this study, we showed that tumour

size, Ki-67 or MC, and lymphnode metastasis allow the identification of a group of patients with WHO G1-G2 PNEN who have a high-risk of recurrence and therefore a considerably lower survival. Further trials should review the role of adjuvant chemotherapy in these patients.

References

[1] Genç CG, Jilesen AP, Partelli S, Falconi M, Muffatti F, van Kemenade FJ, van Eeden S, Verheij J, van Dieren S, van Eijck CHJ, Nieveen van Dijkum EJM. A new scoring system to predict recurrent disease in grade 1 and 2 nonfunctional pancreatic neuroendocrine tumors. Ann Surg 2018 Jun;267(6):1148–54.

[2] Genç CG, Falconi M, Partelli S, Muffatti F, van Eeden S, Doglioni C, Klümpen HJ, van Eijck CHJ, Nieveen van Dijkum EJM. Recurrence of pancreatic neuroendocrine tumors and survival predicted by Ki67. Ann Surg Oncol 2018 Aug;25(8):2467–74.

[3] Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010;23:824–33.

[4] Pelosi G, Bresaola E, Bogina G, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor pro- tein immunostaining, mitotic index, and other clinicopathologic variables. Hum Pathol 1996;27:1124–34.

[5] Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst 2012;104:764–77.

[6] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010;39:707–12.

[7] Farrell JM, Pang JC, Kim GE, Tabatabai ZL. Pancreatic neuroendocrine tumors: accurate grading with Ki-67 index on fine- needle aspiration specimens using the WHO 2010/ENETS cri- teria. Cancer Cytopathol 2014;122:770–8.

[8] Stephenson TJ, Cross SS, Chetty R. Standards and datasets for reporting cancers: dataset for neuroendocrine tumors of the gas- trointestinal tract including pancreas, 3rd ed. R Coll Pathol. 2013. p. 12–3.

[9] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205–13.

[10] Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. International study group on pancreatic surgery (ISGPS). The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. Surgery 2017 Mar;161(3):584–91.

[11] Jensen RT. Pancreatic neuroendocrine tumors: overview of recent advances and diagnosis. J Gastrointest Surg 2006 Mar;10(3):324–6.

[12] Vagefi PA, Razo O, Deshpande V, McGrath DJ, Lauwers GY, Thayer SP, Warshaw AL, Fernández-Del Castillo C. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. Arch Surg 2007 Apr;142(4):347–54.

[13] Saxena A, Chua TC, Perera M, Chu F, Morris DL. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. Surg Oncol 2012 Sep;21(3):e131–41.

[14] Hill JS, McPhee JT, McDade TP, Zhou Z, Sullivan ME, Whalen GF, Tseng JF. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009 Feb 15;115(4):741–51.

[15] Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A, Falconi M. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011 Jul;150(1):75–82.

[16] Fischer L, Bergmann F, Schimmack S, Hinz U, Prieß S, Müller-Stich BP, Werner J, Hackert T, Büchler MW. Outcome of surgery for pancreatic neuroendocrine neoplasms. Br J Surg 2014 Oct;101(11):1405–12.

[17] Kim MJ, Choi DW, Choi SH, Heo JS, Park HJ, Choi KK, Jang KT, Sung JY. Surgical strategies for non-functioning pancreatic neuroendocrine tumours. Br J Surg 2012 Nov;99(11):1562–8.

[18] Ferrone CR. Lymphadenectomy for pancreatic neuroendocrine tumors: is that the relevant debate? Ann Surg 2014 Feb;259(2):213–4.

[19] Rosenberg AM, Friedmann P, Del Rivero J, Libutti SK, Laird AM. Resection versus expectant management of small incidentally discovered nonfunctional pancreatic neuroendocrine tumors. Surgery 2016 Jan;159(1):302–9.

[20] Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, Corrie P, Davar J, Davies AH, Lewington V, Meyer T, Newell-Price J, Poston G, Reed N, Rockall A, Steward W, Thakker RV, Toubanakis C, Valle J, Verbeke C, Grossman AB. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61(1):6–32.

[21] Khan MS, Luong TV, Watkins J, Toumpanakis C, Caplin ME, Meyer T. A comparison of Ki-67 and mitotic count as prognostic markers for metastatic pancreatic and midgut neuroendocrine neoplasms. Br J Canc 2013 May 14;108(9):1838–45.

[22] Cho JH, Ryu JK, Song SY, Hwang JH, Lee DK, Woo SM, Joo YE, Jeong S, Lee SO, Park BK, Cheon YK, Han J, Kim TN, Lee JK, Moon SH, Kim H, Park ET, Hwang JC, Kim TH, Jeon TJ, Cho CM, Choi HS, Lee WJ. Prognostic validity of the American joint committee on cancer and the European neuroendocrine tumors staging classifications for pancreatic neuroendocrine tumors: a retrospective nationwide multicenter study in South Korea. Pancreas 2016 Aug;45(7):941–6.

[23] Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, Andrén-Sandberg A, Asbun HJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fingerhut A, Friess H, Hartwig W, Izbicki JR, Lillemoe KD, Milicevic MN, Neoptolemos JP, Shrikhande SV, Vollmer CM, Yeo CJ, Charnley RM, International Study Group on Pancreatic Surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014 Sep;156(3):591–600.