의학석사 학위논문

Association between Pathologic Grade and Multiphase Contrast-enhanced Computed Tomography Attenuation Level for Pancreatic Neuroendocrine Tumor

췌장신경내분비종양에서의 병리학적 등급과 전산화 단층촬영 조영 증강 정도의 연관성

2017년 2월

서울대학교 대학원

의학과 내과학 전공

강 진 우

Abstract

Background/Aims: Pancreatic neuroendocrine tumors (PNETs) are rare diseases but gradually increasing in prevalence with different prognosis. Neuroendocrine tumors are classified into low-grade (G1), intermediate grade (G2), and high-grade (G3, neuroendocrine carcinoma) by WHO 2010 grading system. Prognostic validity of WHO grading system has been established by several studies. Multiphase contrast-enhanced computed tomography (CT) is known as the most useful imaging modality for the diagnosis of pancreatic tumors. We aimed to investigate whether CT enhancement pattern is associated with the pathologic tumor grades according to WHO classification and can predict those of pancreatic neuroendocrine tumor.

Methods: Between January 2011 and December 2015, Ninety patients who underwent multi-phase contrast-enhanced CT and were diagnosed as pancreatic NETs histopathologically were retrospectively reviewed. The diagnosis of a PNETs were established by histopathological examination and immunohistochemistry on tissue samples, based on the 2010 WHO classification.

Results: Ninety pancreatic NETs included sixty-two G1 (68.9%),

twenty-one G2 (23.3%), seven G3 (7.8%). The enhancement values of the early arterial phase were significantly different among three groups (G1 vs. G2; p=0.043, G1 vs. G3; p=0.001, G2 vs. G3; p=0.027). In the late arterial phase, there was a difference between grade 1 and grade 3, grade 2 and 3, but no significant difference between grade 1 and grade 2 (G1 vs. G2; p=0.804, G1 vs. G3; p=0.016, G2 vs. G3; p=0. 0.022). The enhancement value of the portal phase did not differ significantly between the three groups. In G1 and G2, mean CT attenuation values highly increased in arterial phases and after which declined in portal phase. Enhancement values of G3 tumors showed no statistical difference between late arterial and portal phases. ROC analysis of the early arterial enhancement value for the differentiation of the grade 1 tumors was comparable to the tumor size.

Conclusion: CT enhancement value of early arterial phase and degree of change among arterial phases can be help for the differentiation of pathologic grade of pancreatic neuroendocrine tumors.

Key words: pancreatic neuroendocrine tumors, pathologic grade, MDCT, attenuation value

Student Number: 2015-21966

Contents

Abstract i

Contents iii

List of tables iv

List of figures v

List of abbreviations vi

Introduction 1

Methods 3

Results 6

Discussion 22

References 28

Abstract in Korean 31

List of tables

Table 1. Characteristics of 90 patients with pancreatic neuroendocrine tumor 11

Table 2. Difference of characteristics based on pathological grades of NET 13

Table 3. Comparisons of CT findings among pathologic grades of pancreatic neuroendocrine tumors 14

Table 4. Differences in the enhancement value and its ratio according to the tumor grades 15

List of figures

Figure 1. Multiphase contrast-enhanced CT imaging of pancreatic neuroendocrine tumor 16

Figure 2. Mean CT attenuation values of pancreatic neuroendocrine tumors 17

Figure 3. The rate of change of enhancement value 18

Figure 4. Differences in the enhancement value between grade 1/2 and grade 3 19

Figure 5. ROC analysis to predict NET G1 according to early arterial enhancement value (A) and tumor size (B).....20

Figure 3. Kaplan-Meier curves for overall survival (A) and progression-free survival (B) based on the WHO 2010 grade 21

List of abbreviations

PNET, pancreatic neuroendocrine tumor; WHO, World Health Organization; G, grade; AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; CT, computed tomography; NEC, neuroendocrine carcinoma; OS, overall survival; PFS, progression-free survival; ROC, receiver-operating characteristic; AUC, Area under the curve

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare diseases that account for 1 to 3% of primary pancreatic tumors.[1] Overall, the PNETs tend to grow slower than pancreatic ductal adenocarcinomas, but aggressive variants are not uncommon.

Histologic grades and various classifications have evolved for attempting to stratify patients into different prognostic groups. The World Health Organization (WHO) 2010 grading system has been proposed to define a new pathologic grade stratification, and the system categorized neuroendocrine tumors into low-grade (G1), intermediate grade (G2), and high-grade (G3) based on their proliferative rate using the mitotic activity and/or a Ki-67 labeling index.[2]

Several studies evaluated the prognosis of PNETs according to pathological grade. In a study which evaluated the clinical consistency of the WHO 2010 grading system and 2006 ENETS staging system, survival rates at 5 years for G1, G2, G3 tumor and mixed adenoneuroendocrine carcinoma were 82.6%, 52.7%, 25.7%, and 0%, respectively.[3] In the report comparing the AJCC/ENETS staging and WHO 2010 grade systems of 425 PNETs, 5-year OS rates for G1, G2, and G3 tumors were 75%, 62%, and 7%, respectively.[4]

Endoscopic ultrasonography-guided fine needle aspiration has been

used for histopathological diagnosis of a pancreatic neuroendocrine tumor. However, the preoperative biopsy could be less reliable in the identification of grade because Ki-67 index is not uniform throughout tumor, especially in a relatively large tumor.[5] Multiphase contrast-enhanced computed tomography (CT) is currently the most useful and reliable imaging modality for detection and characterization of various pancreatic tumors. Pancreatic neuroendocrine tumors are known to exhibit a well-circumscribed mass with early strong enhancement on the arterial phase because they are composed of a dense and specialized capillary network.[6]

Although such characteristics could be useful findings for identification of PNETs from other pancreatic tumors, there were few studies on the differentiation of tumor grade among PNETs. We aimed to investigate whether CT enhancement pattern is associated with the pathologic tumor grades according to WHO classification and can predict those of pancreatic neuroendocrine tumor.

Methods

Patient Selection

Between January 2011 and December 2015, One hundred and forty-three patients were pathologically diagnosed as pancreatic NETs. Ninety patients who underwent multi-phase contrast-enhanced CT by pancreatobiliary protocol in our hospital before pathologic diagnosis were retrospectively reviewed. Data collected included the patient's age, gender, tumor location, functioning status of tumor, metastasis. In case of surgically confirmed patients, data on the tumor stage based on TNM staging, vascular invasion, lymphatic invasion, perineural invasion were also recorded. The stage of the tumor was recorded according to the AJCC TNM staging classification. The diagnosis of PNET was established by histopathological examination and immunohistochemistry on tissue samples, based on the 2010 WHO classification.

CT image analysis

CT images were obtained by various multi-detector CT scanners. The following CT machines were used: 16-channel scanner (Sensation 16, Siemens Healthcare, Erlangen, Germany), 64-

channel scanners (Somatom Definition, Siemens Healthcare, Erlangen, Germany and Brilliance 64, Philips Healthcare, Best, the Netherlands), 128-channel scanner, (Ingenuity, Philips Healthcare, Best, the Netherlands), 320-channel scanner (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan). Non-enhanced, early arterial, late arterial, portal phase images were obtained in all patients. Early arterial phase was automatically obtained 6-9sec after achieving 100HU attenuation of the abdominal aorta. The mean imaging time delay was 23s for the early arterial phase, 40sec for the late arterial phase, and 70 sec for the portal phase after triggering. We assessed following findings; tumor calcification, pancreatic duct dilatation, heterogeneity, cystic degeneration, demarcation. Hounsfield Unit values of PNETs during each phase on CT were measured and enhancement ratio was calculated based on attenuation value of tumor on non-contrast phase. A round region of interest (ROI) cursor was placed on relatively homogeneous part of the targeted lesion. (Figure 1) We analyzed the association between pathologic grades and findings on CT including attenuation values at each phase.

Statistical analysis

The significance of differences among three groups was assessed using Chi-square test, one-way analysis of variance (ANOVA),

Fisher's extract test, Kruskal–Wallis test, and Mann–Whitney's U test, as appropriate. Overall survival and progression–free survival curves were constructed Kaplan–Meier method and compared using the log rank test. ROC analysis was performed to evaluate the sensitivity and specificity for enhancement value. Statistical significance was assumed at a confidence level of 0.05. The statistical analyses were performed using SPSS 23 (SPSS, Chicago, IL).

Results

Patient Characteristics

Characteristics of the 90 PNETs patients are summarized in Table 1. There were 45 male and 45 female patients, with age ranging from 20 to 86 years (59.8±11.6, mean±SD). Tumors were located as follows; 35 in the head of the pancreas, 26 in the body, 29 in the tail. Tumor size ranged from 5 to 150mm (26.3±21.4, mean±SD). Functioning tumor was found in 15 patients; 8 insulinoma, 5 somatostatinoma, 1 glucagonoma, 1 serotoninoma. 62 tumors were G1 NETs, 21 were G2 NETs, and 7 were G3 NECs based on the 2010 WHO classification. 82 patients conducted surgical resection for NETs. In 8 patients with biopsy alone, 4 patients had grade 1 tumor with a size of 9 to 13mm and did not undergo surgery. The remaining 4 patients with grade 2 and 3 had distant metastasis at the time of diagnosis. During follow-up, metastases were newly found among 17 patients. Patients' demographics were not different statistically according to grade of tumor, but chemotherapy, TNM stage of tumor were statistically different. (Table 2).

Multi-phase CT features

Most of the tumors had no calcification (7.8%, 7/90) and were well-demarcated (78/90, 86.7%). Pancreatic duct dilatation was found among 22 patients (24.4%, 22/90). More than half of the tumors showed heterogeneity (58.9%, 53/90). 21 tumors had cystic degeneration (23.3%, 21/90). Tumor size tended to increase as tumor grade went up. Mean size of grade 1 tumor was 21.1mm, grade 2 was 32.7mm, and grade 3 was 53.9mm. (p=0.005) (Table 3)

Analysis of CT attenuation values

CT attenuation values for 90 PNETs in each phase were calculated and time-dependent graphs are represented in Figure 2. When the enhancement values at each phase according to the tumor grade were compared, the values of the early arterial phase were significantly different among the three groups, (G1 vs. G2; p=0.043, G1 vs. G3; p=0.001, G2 vs. G3; p=0.027) In the late arterial phase, there was a difference between grade 1 and grade 3, grade 2 and 3, but no significant difference between grade 1 and grade 2 (G1 vs. G2; p=0.804, G1 vs. G3; p=0.016, G2 vs. G3; p=0. 0.022). The enhancement value of the portal phase did not differ significantly between the three groups (G1 vs. G2; p=0.867, G1 vs. G3; p=0.227, G2 vs. G3; p=0.444).

The rate of change of enhancement value (HU) was obtained by using time delay between phases. (Figure 3). Changes in enhancement

value from the pre-contrast phase to the early arterial phase were statistically significant between grade 1 and grade 3, and between grade 2 and grade 3, but not between grade 1 and grade 2. (G1 vs G2; p=0.196, G1 vs. G3; p=0.002, G2 vs. G3; p=0.036) In the interval from the early arterial phase to the late arterial phase, the change in enhancement value per second did not show any significant difference between the three groups. (G1 vs. G2; p=0.777, G1 vs. G3; p=0.279, G2 vs. G3; p=0.189) There was a statistically significant difference between grade 1 and grade 3, grade 2 and grade 3, but grade 1 and grade 2 did not showed difference during the late arterial phase to the portal phase (G1 vs. G2; p=0.608, G1 vs. G3; p=0.009, G2 vs. G3; p=0.014). Basically, the attenuation values of PNETs G1 and G2 increased from the early arterial phase, peaked during late arterial phase, after which they declined in portal phase. In case of G3 (NEC), enhancement value increased much more slowly during the arterial phases and showed no statistical difference between late arterial phase and portal phase.

Between G1/2 and G3, enhancement value were significantly different in the early arterial and late arterial phase (G1/2 vs. G3; 107.9±38.3 vs. 64.8±19.9 in the early phase, 151.0±50.8 vs. 94.1±39.2 in the late arterial phase, 114.8±26.2 vs. 92.4±30.7 in the portal phase, p<0.001, p=0.007, and p=0.105, respectively). (Figure 4)

The difference in attenuation values according to patients and tumor characteristics was analyzed. There was no statistical significance according to the characteristics except functioning status of the tumor. In functioning tumors, the enhancement value itself was not statistically significant but the enhancement ratios based on the pre-contrast phase were significantly higher than non-functioning tumor along the whole phase. When analyzed by grade, only grade 1 showed a significant difference between the two groups.

Optimal cutoff value for the differentiation of the pathologic grade

ROC analysis was performed to evaluate whether early arterial enhancement value can be used as a parameter to identify NET G1. The optimal cut-off value was 100HU and the sensitivity, specificity and area under the curve (AUC) were 60.7%, 64.3% and 0.685, respectively. (Figure 5A) In the analysis according to the tumor size, cutoff value of 22mm showed sensitivity of 64.5%, specificity of 67.9%, and AUC of 0.714, respectively (Figure 5B).

Association between other CT findings and WHO grades

Association between specific CT findings (calcification, heterogeneity, pancreatic ductal dilatation, tumor demarcation and

cystic degeneration) and tumor grades according to the WHO classification of PNETs were statistically analyzed. In the analysis, pancreatic duct dilatation and tumor heterogeneity were statistically significant predictable factor for G3 NECs ($p<0.001$ and $p=0.039$, respectively). Pancreatic duct dilatation also showed statistical significance in the differentiation between G1 and G2 ($p=0.03$, Table 4)

Survival Outcomes

Overall survival and progression free survival according to pathological grade were analyzed using Kaplan-Meier analysis. Overall survival was calculated from the date of diagnosis by biopsy or surgery to the date of death, the date of the most recent follow-up. During median follow-up period of 60 months, a total of 2 patients died and 8 patients were lost to follow-up. Median OS of G1 tumor was 63.4 month, G2 55.3 month, and G3 34.1month. 5-year OS rates for WHO classification were 95%, 86% and 43%, respectively ($p<0.001$, Figure 6A). A total of 15 patients had disease progression. Median PFS of each grade were as follows; grade 1 64.1 month, grade 2 38.5 month, and grade 3 23.6 month. 5-yrear PFS rates were 97%, 62%, and 29%, respectively ($p<0.001$, figure 6B).

Table 1. Characteristics of 90 patients with pancreatic neuroendocrine tumor

Characteristics	N	%
Median age, y (range)	60.0	(20-86)
Tumor size, mm (range)	26.3	(7-150)
Gender		
Male	45	50.0
Female	45	50.0
DM		
No	64	71.1
before diagnosis	16	17.8
Postop.	10	11.1
MEN		
No	84	93.3
Yes	6	6.7
Type of Surgery		
No (Biopsy only)	8	8.9
Total pancreatectomy	2	2.2
Pancreaticoduodenectomy	24	26.7
Distal pancreatectomy	42	46.7
Partial resection	13	14.4
Enucleation	1	1.1
Pathologic grade		
Grade 1	62	68.9
Grade 2	21	23.3
Grade 3	7	7.8
Functioning status		
Non-functioning	75	83.3
Functioning	15	16.7
Insulinoma	8	8.9
Somatostatinoma	5	5.6
Glucagonoma	1	1.1
Serotoninoma	1	1.1
Tumor location		
Head	35	38.9
Body	26	28.9

Tail	29	32.2
T stage		
1	36	40.0
2	31	34.4
3	21	23.3
4	2	2.2
N stage		
0	80	88.9
1	10	11.1
M stage		
0	81	90.0
1	9	10.0

Table 2. Difference of characteristics based on pathological grades of NET

	G1	G2	G3	p-value
Gender				0.867
Male	30 (48.4%)	12 (57.1%)	3 (42.9%)	
Female	32 (51.6%)	9 (42.9%)	4 (5.1%)	
DM				0.14
No	42 (67.7)	16 (76.2%)	6 (85.7%)	
previous	11 (17.7%)	4 (19.0%)	1 (14.3%)	
Postop.	9 (14.5%)	1 (4.8%)	0 (0%)	
MEN				0.074
No	60 (96.8%)	18 (85.7%)	6 (85.7%)	
Yes	2 (3.2%)	3 (14.3%)	1 (14.3%)	
Functioning status				0.94
No	52 (83.9%)	17 (81.0%)	6 (85.7%)	
Yes	10 (16.1%)	4 (19.0%)	1 (14.3%)	
Tumor location				0.353
Head	21 (33.9%)	11 (52.4%)	3 (42.9%)	
Body	20 (32.3%)	4 (19.0%)	2 (28.6%)	
Tail	21 (33.9%)	6 (28.6%)	2 (28.6%)	
T stage				<0.001
1	32 (51.6%)	3 (14.3%)	1 (14.3%)	
2	21 (33.9%)	8 (38.1%)	2 (28.6%)	
3	9 (14.5%)	9 (42.9%)	3 (42.9%)	
4	0 (0%)	1 (4.8%)	1 (14.3%)	
N stage				<0.001
0	59 (95.2%)	19 (90.5%)	2 (28.6%)	
1	3 (4.8%)	2 (9.5%)	5 (71.4%)	
M stage				<0.001
0	61 (98.4%)	15 (71.4%)	5 (71.4%)	
1	1 (1.6%)	6 (28.6%)	2 (28.6%)	

Table 3. Comparisons of CT findings among pathologic grades of pancreatic neuroendocrine tumors

	G1 (n=62)	G2 (n=21)	G3 (n=7)	p-value
Tumor size, mm (mean±SD)	21.1±12.8	32.7±19.9	53.9±49.4	0.005
Calcification				0.425
No	58 (93.5%)	19 (90.5%)	6 (85.7%)	
Yes	4 (6.5%)	2 (9.5%)	1 (14.3%)	
Heterogeneity				0.136
No	27 (43.5%)	10 (47.6%)	0 (0%)	
Yes	35 (56.5%)	11 (52.4%)	7 (100%)	
Pancreatic duct dilatation				<0.001
No	53 (85.5%)	13 (61.9%)	2 (2.9%)	
Yes	9 (14.5%)	8 (38.1%)	5 (71.4%)	
Demarcation				0.101
No	6 (9.7%)	4 (19.0%)	2 (16.7%)	
Yes	56 (90.3%)	17 (81.0%)	5 (71.4%)	
Cystic degeneration				0.211
No	45 (72.6%)	18 (85.7%)	6 (85.7%)	
Yes	17 (27.4%)	3 (14.3%)	1 (7.8%)	

Table 4. Differences of the CT findings according to the tumor grades

	G1/2	G3	p-value
Calcification			0.444
No	77 (92.8%)	6 (85.7%)	
Yes	6 (7.2%)	1 (14.3%)	
Pancreatic duct dilatation			0.009
No	66 (79.5%)	2 (28.6%)	
Yes	17 (20.5%)	5 (71.4%)	
Heterogeneity			0.039
No	37 (44.6%)	0 (0%)	
Yes	46 (55.4%)	7 (100%)	
Demarcation			0.234
No	10 (12.0%)	2 (28.6%)	
Yes	73 (88.0%)	5 (71.4%)	
Cystic degeneration			0.558
No	63 (75.9%)	6 (85.7%)	
Yes	20 (24.1%)	1 (14.3%)	
	G1	G2	p-value
Calcification			0.64
No	58 (93.5%)	19 (90.5%)	
Yes	4 (8.5%)	2 (9.5%)	
Pancreatic duct dilatation			0.03
No	53 (85.5%)	13 (61.9%)	
Yes	9 (14.5%)	8 (38.1%)	
Heterogeneity			0.803
No	27 (43.5%)	10 (47.6%)	
Yes	35 (56.5%)	11 (52.4%)	
Demarcation			0.264
No	6 (9.7%)	4 (19.0%)	
Yes	56 (90.3%)	17 (81.0%)	
Cystic degeneration			0.227
No	45 (72.6%)	18 (85.7%)	
Yes	17(27.4%)	3 (14.3%)	

Figure 1. Multiphase contrast-enhanced CT imaging of pancreatic neuroendocrine tumor. (A) grade 1, (B) grade 2, (C) grade 3. A round region of interest cursors were placed on the target lesion to calculate the attenuation value.

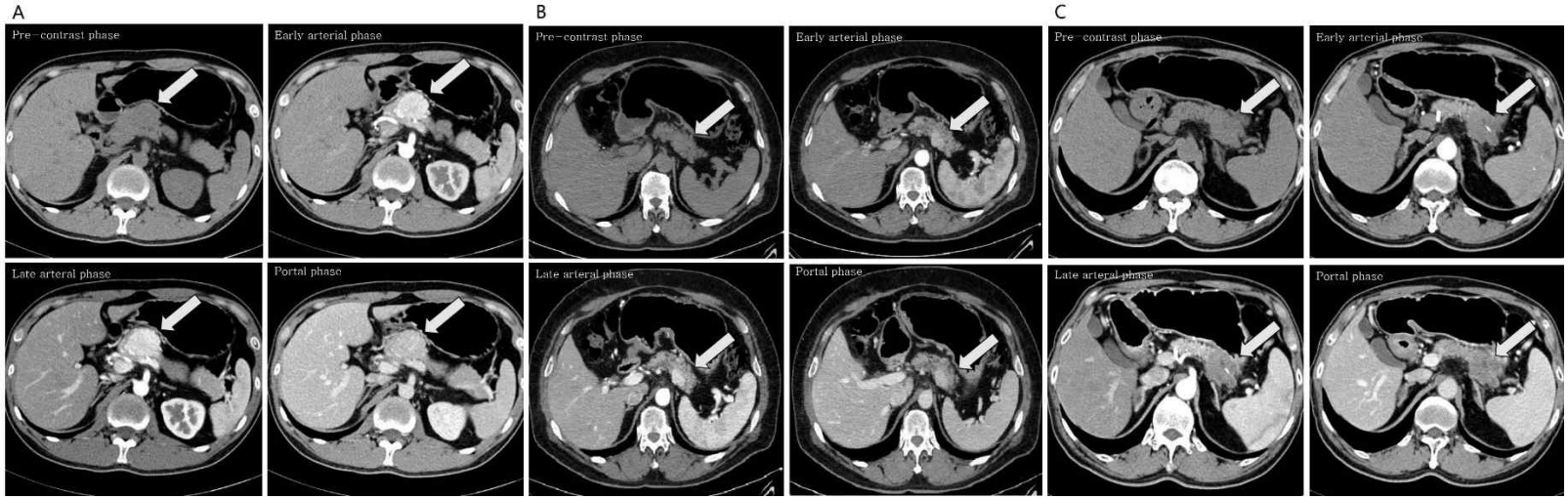
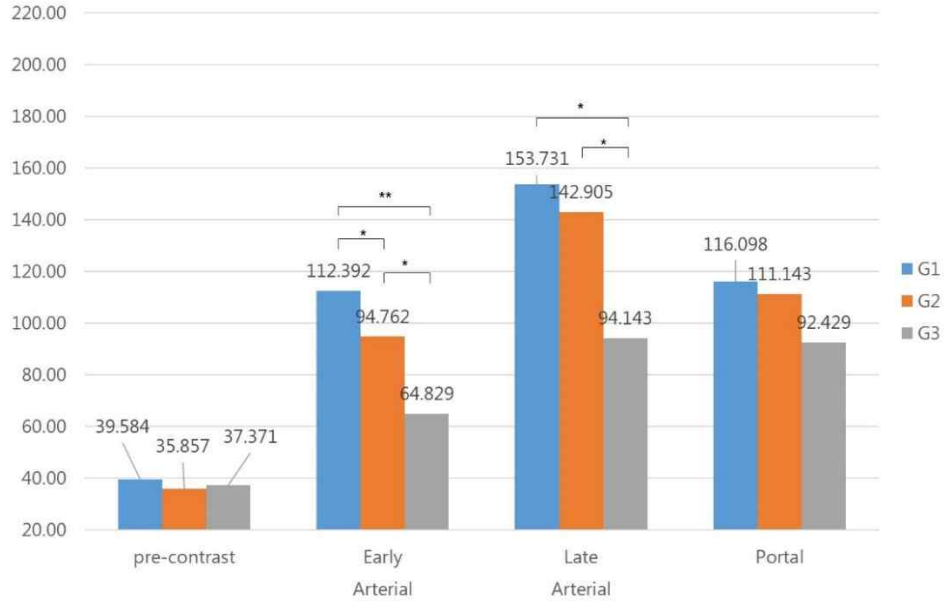


Figure 2. Mean CT attenuation values of pancreatic neuroendocrine tumors.



*p<0.05, **p=0.001

Figure 3. The rate of change of enhancement value

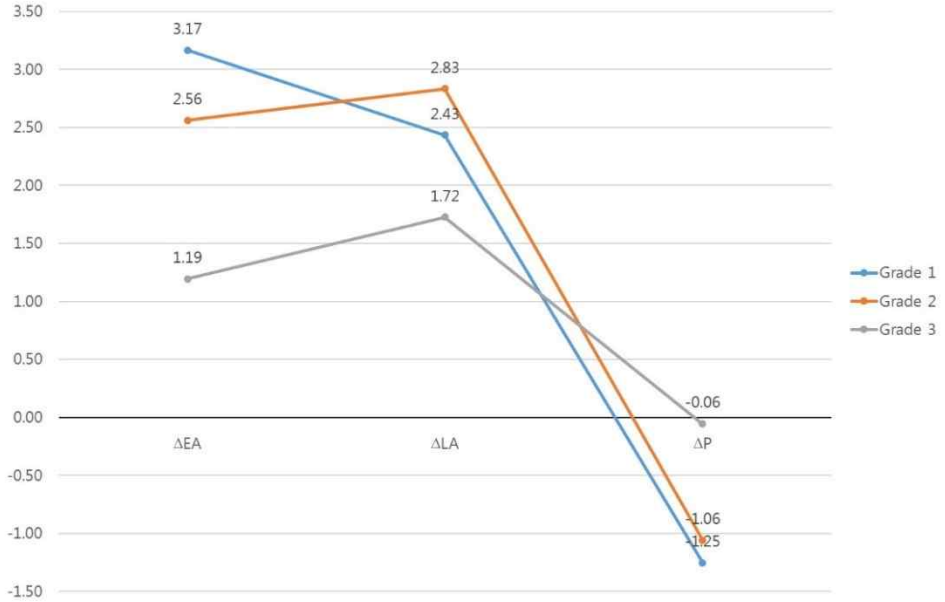
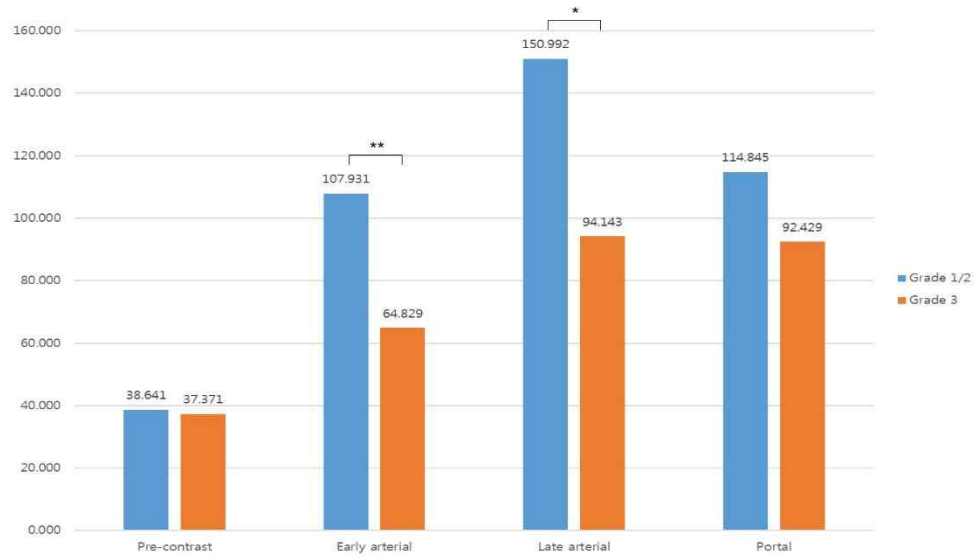


Figure 4. Differences in the enhancement value between grade 1/2 and grade 3.



*p<0.05, **p<0.001

Figure 5. ROC analysis to predict NET G1 according to early arterial enhancement value (A) and tumor size (B)

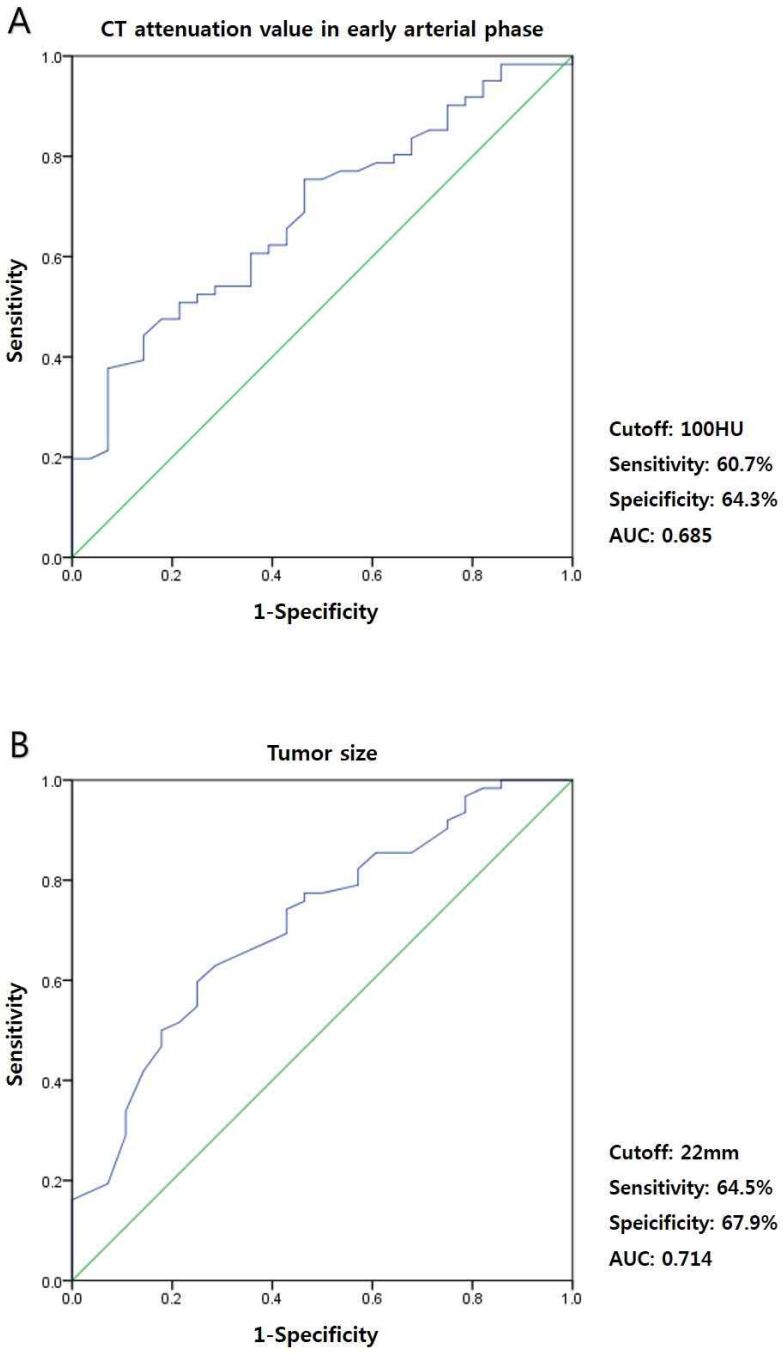
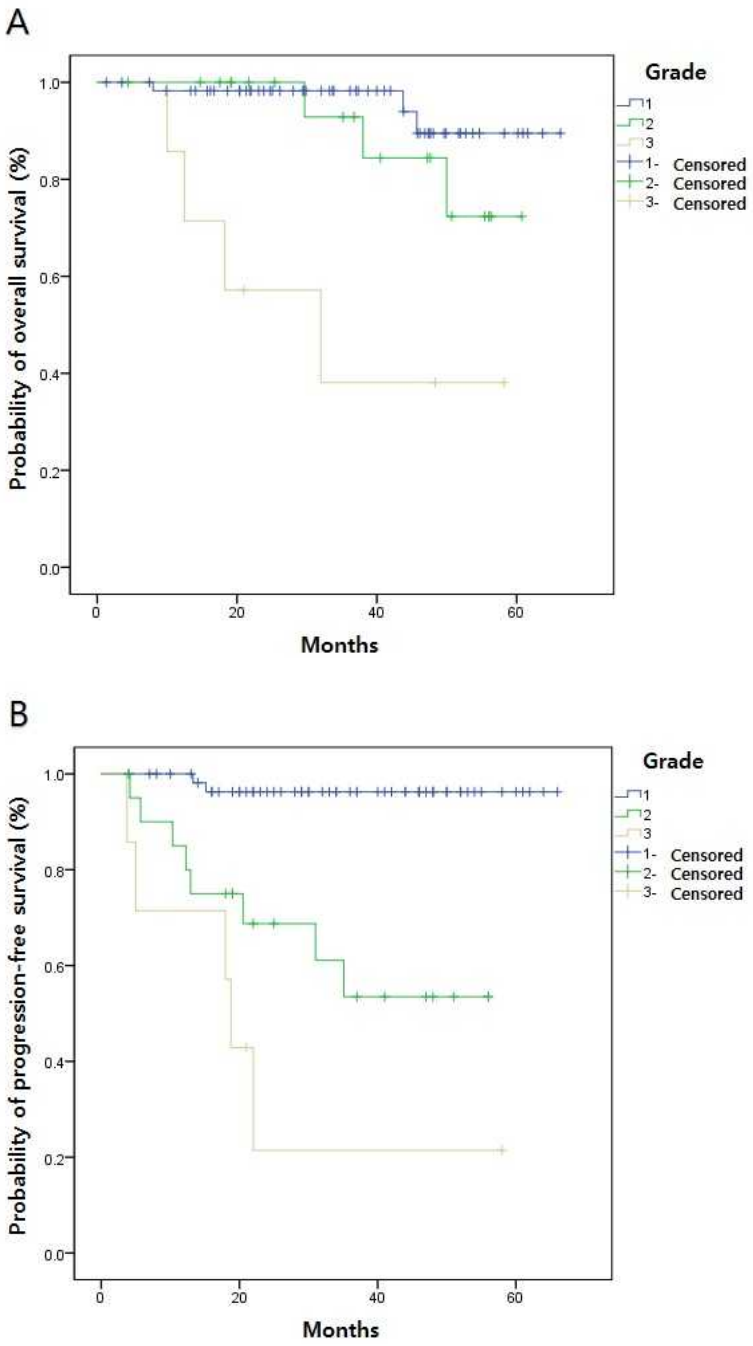


Figure 6. Kaplan-Meier curves for overall survival (A) and progression-free survival (B) based on the WHO 2010 grade



Discussion

Our results demonstrate that tumor size, pancreatic duct dilatation, arterial enhancement value are statistically significant predictors in the differentiation of pancreatic neuroendocrine tumors. Interesting observation of this study is the association between early arterial enhancement value and tumor grade, particularly enabling the differentiation between grade 1 and grade 2 NETs.

After publication of the 2010 WHO classification, several researches on prognostic validity of grading system based on mitotic count and Ki-67 index, AJCC and ENETS staging system has been conducted. Although there has been some differences among researches, prognostic value of this grade-based classification system has been accepted. We also analyzed survival outcome according to grade, and as shown in previous studies, higher grade was associated with poorer survival outcome. Grade 3 NET is classified as carcinoma (NEC) and aggressive chemotherapy is often needed because many of these tumors are initially on advanced stage unresectable or accompanying with metastases. Grade 1 and grade 2 NETs are considered benign compared with grade 3 NECs, but grade 2 NETs show poorer prognosis and often need more radical treatment than grade 1. Therefore, early differential diagnosis between grade 1 and 2 is important.

Our study demonstrated that enhancement value on arterial phases can be one of deciding factor in differentiation of tumor grades. In general, angiogenesis is considered important in most cancer development and works as one of the major prognostic factor in some types of cancer. [7-10] But several research revealed that neuroendocrine tumor has a tendency to be hypervascular and relationship between intratumoral angiogenesis and prognosis appears to be inverse compared with other types of tumors.[11, 12] Contrast enhancement of CT examination as a predictor of PNETs is thought to be distinguishing parameter. Several studies have reported on the relevance of preoperative CT findings to predict characteristics and prognoses of PNETs.[10, 11] Rodallec et al [13] showed that low-enhancing PNETs using helical CT were correlated with poorly differentiated PNETs and a worse overall survival. Similarly, d'Assignies et al[14] reported that tumor blood flow values assessed with perfusion CT were significantly higher in tumors with a Ki-67 index of 2% or less. This study showed that enhancement value on arterial phase increases as tumor grade lowers and it corresponded with previous studies. Considering the difference of survival outcome and arterial enhancement value according to tumor grade, arterial enhancement value could be one of the important prognostic factor, and it should be evaluated by further studies.

Tatsumoto et al[15] classified PNETs into subgroups based on their preoperative CT enhancement patterns and reported that there was a correlation between the washout pattern and prognosis. Yamada el al[16] reported that the CT enhancement in the pancreatic phase were significant predictors of NET G2 in the study of 37 cases of PNET. In this study, statistically significant difference of enhancement value on arterial phases, especially early arterial phase was confirmed. In comparison of grade 1 and grade 2, enhancement value of grade 2 tumor rather gradually increased than those of grade 1 on early arterial phase and caught up on late arterial phase. This finding insists that not only value itself but also enhancement pattern should be helpful in differentiation between grade 1 and grade 2 tumors. Enhancement pattern of grade 1 and 2 is shown as fill-up on arterial phase and washout on portal phase. In case of grade 3, enhancement value increases more slowly throughout arterial phase, and showed no definite washout on portal phase in comparison with late arterial phase. This could be one of the major point for the differentiation of grade 1/2 and grade 3, neuroendocrine carcinoma.

Comparing enhancement values in early arterial phase, the enhancement value in early arterial phase was significantly different according to the pathology. Based on this result, we performed ROC analysis to evaluate whether enhancement value of the early arterial phase can differentiate pathologic grade, particularly grade 1. Grade

1 NET can be differentiated with approximately 60% of sensitivity and specificity at the cutoff point of 100HU. There has been no reliable factor other than tumor size for the prediction of malignancy in several previous reports. Thus, we calculated ability of the tumor size for the differentiation of grade 1 tumor first, then evaluated the power of the enhancement value in the early arterial phase. Our study showed that enhancement value was comparable to the tumor size for the prediction of grade 1 tumor.

The presence of pancreatic duct dilatation were associated with high grade tumors, not only G3 NECs but also G2 tumors. Although this is common feature of pancreatic ductal adenocarcinoma and PNETs are known to show a higher resectability and a better response to chemotherapy, patients with higher grade tumors need more aggressive treatment and frequent follow-up like PDAC. In case of patients with pancreatic mass and ductal dilatation, differential diagnosis could be made in combination with attenuation value and pattern considering possibility of at least higher grade of NETs. The accuracy of predicting the pathologic grade can be increased when the absolute value of enhancement value in the early arterial phase, the change pattern of enhancement value in the arterial phases and the presence or absence of pancreatic ductal dilatation are combined.

Association between grade and stage was reported in one study which sought correlation between ENETS staging system and

grading system according to 2010 WHO classification.[17] In our study, the tumor size correlated significantly with the tumor grade based on the 2010 WHO classification. Tumor size is major factor for determining T stage. Therefore, as tumor size increases AJCC/ENETS stage follows. Our study showed the association between tumor grade and size as well as stage of the tumor.

Our study had several limitations. First, we could not obtain inter-observer variability of the qualitative image analysis due to consensus review by radiologists. There is possibility to show clear difference between grade 1 and grade 2 like previous studies based on more accurate data if we could get consensus review. Second, we used various CT scanners and contrast media with different concentrations. Therefore, obtained value in this study should not be applied directly. But considering that purpose of this study is to provide information for prompt decision making, results of this study could be applicable in clinical practice if further studies followed. Third, the number of the G3 tumors was small among all PNETs. Many of the G3 tumors were unresectable with metastases at the time of diagnosis, and follow-up was conducted using CT with different protocol. Fourth, we included 8 biopsy-proven cases into our study population. Preoperative biopsy could be less reliable in the identification of WHO classification because Ki-67 index is not uniform throughout tumor, especially in a relatively large tumor,

resulting in underestimation of the grading. However, most of the NETs included in this study was confirmed by surgical resection and the other NETs diagnosed by biopsy were small tumors (less than 10mm). Therefore, diagnostic reliability may not be a confound factor. Fifth, sensitivity, specificity and AUC by ROC analysis were not as high as previous reports. Further studies should be followed for the diagnostic reliability of the difference in the enhancement value.

In conclusion, CT enhancement value of early arterial phase and degree of change among arterial phases can be help for the differentiation of pathologic grade of pancreatic neuroendocrine tumors.

References

1. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121:589-597.

2. Rindi G, Arnold R, Bosman F, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. WHO Classification of Tumours of the Digestive System, ed. 2010;4:13-14.

3. Yang M, Tian BL, Zhang Y, et al. Evaluation of the World Health Organization 2010 grading system in surgical outcome and prognosis of pancreatic neuroendocrine tumors. Pancreas. 2014;43:1003-1008.

4. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol. 2011;29:3044-3049.

5. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol. 2011;35:853-860.

6. Horton KM, Hruban RH, Yeo C, Fishman EK. Multi-detector

row CT of pancreatic islet cell tumors. Radiographics. 2006;26:453-464.

7. Vermeulen PB, Verhoeven D, Hubens G, et al. Microvessel density, endothelial cell proliferation and tumour cell proliferation in human colorectal adenocarcinomas. Ann Oncol. 1995;6:59-64.

8. Ellis LM, Takahashi Y, Fenoglio CJ, Cleary KR, Bucana CD, Evans DB. Vessel counts and vascular endothelial growth factor expression in pancreatic adenocarcinoma. Eur J Cancer. 1998;34:337-340.

9. Weidner N, Folkman J, Pozza F, et al. Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma. J Natl Cancer Inst. 1992;84:1875-1887.

10. Duarte IG, Bufkin BL, Pennington MF, et al. Angiogenesis as a predictor of survival after surgical resection for stage I non-small-cell lung cancer. J Thorac Cardiovasc Surg. 1998;115:652-658; discussion 658-659.

11. Takahashi Y, Akishima-Fukasawa Y, Kobayashi N, et al. Prognostic value of tumor architecture, tumor-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumors. Clin Cancer Res. 2007;13:187-196.

12. Marion-Audibert AM, Barel C, Gouysse G, et al. Low microvessel density is an unfavorable histoprognostic factor in pancreatic endocrine tumors. Gastroenterology. 2003;125:1094-1104.

13. Rodallec M, Vilgrain V, Couvelard A, et al. Endocrine pancreatic tumours and helical CT: contrast enhancement is correlated with microvascular density, histoprognostic factors and survival. Pancreatology. 2006;6:77-85.

14. d'Assignies G, Couvelard A, Bahrami S, et al. Pancreatic endocrine tumors: tumor blood flow assessed with perfusion CT reflects angiogenesis and correlates with prognostic factors. Radiology. 2009;250:407-416.

15. Tatsumoto S, Kodama Y, Sakurai Y, Shinohara T, Katanuma A, Maguchi H. Pancreatic neuroendocrine neoplasm: correlation between computed tomography enhancement patterns and prognostic factors of surgical and endoscopic ultrasound-guided fine-needle aspiration biopsy specimens. Abdom Imaging. 2013;38:358-366.

16. Yamada S, Fujii T, Suzuki K, et al. Preoperative Identification of a Prognostic Factor for Pancreatic Neuroendocrine Tumors Using Multiphase Contrast-Enhanced Computed Tomography. Pancreas. 2016;45:198-203.

17. Ricci C, Casadei R, Taffurelli G, et al. Validation of the 2010 WHO classification and a new prognostic proposal: A single centre retrospective study of well-differentiated pancreatic neuroendocrine tumours. Pancreatology. 2016;16:403-410.

국문초록

배경: 췌장 신경내분비종양은 최근 유병율이 서서히 증가하고 있으며 다양한 예후를 지닌 질환이다. 신경내분비종양은 국제보건기구 2010 분류법에 따라 저등급, 중간등급, 고등급으로 분류된다. 췌장의 종양을 진단하는데 있어 조영 증강 전산화 단층촬영이 가장 유용한 영상 기법으로 알려져 있다. 본 연구에서는 전산화 단층촬영에서의 조영 증강 정도 및 양상과 국제보건기구 분류법에 따른 병리학적 등급과의 연관성을 살펴보고자 하였다.

방법: 2011년 1월부터 2015년 12월까지, 조영 증강 전산화 단층촬영을 시행하고 병리학적으로 췌장 신경내분비종양을 진단받은 90명의 환자들의 의무기록을 후향적으로 분석하였다.

결과: 90명의 췌장 신경내분비종양 중 저등급은 62명 (68.9%), 중간등급 21명 (23.3%), 고등급 7명 (7.8%) 였다. 초기 동맥기의 조영 증강 정도는 세 등급간 모두 유의한 차이를 보였으며, 후기 동맥기에서의 조영 증강 정도는 저등급과 중간등급 사이에서는 통계적으로 유의한 차이를 보이지 않았다. 저등급과 중간등급의 경우 평균 조영 증강 수치가 동맥 조영기에서 크게 증가하였고 문맥 조영기에서 감소하는 경향을 보였다. 고등급의 경우 문맥 조영기에서의 조영 증강 수치는 동맥 조영기의 그것과 유사하였다. 초기 동맥기 조영 증강 정도의 등급 구분 능력은 종양 크기에 따른 그것과 유사함을 확인하였다.

결론: 초기 동맥기에서의 조영 증강 값 및 동맥기에서의 조양 증강 변화 정도가 신경내분비 종양의 등급을 예측할 수 있는 유용한 인자가 될 수 있을 것이다.

주요어 : 췌장신경내분비종양, 조영증강, 전산화단층촬영, 병리학적 등급

학 번 : 2015-21966