Clinical value of contrast-enhanced harmonic endoscopic ultrasonography in differential diagnosis of pancreas and gall bladder mass

Ga Lam Leem

Department of Medicine

The Graduate School, Yonsei University

Clinical value of contrast-enhanced harmonic endoscopic ultrasonography in differential diagnosis of pancreas and gall bladder mass

Directed by Professor Seung Woo Park

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Ga Lam Leem

June 2016

This certifies that the Master's Thesis of
Ga Lam Leem is approved.

Thesis Supervisor : Seung Woo Park

Thesis Committee Member#1 : Kyung Sik Kim

Thesis Committee Member#2 : Jin Young Choi

The Graduate School
Yonsei University

June 2016

ACKNOWLEDGEMENTS

First of all, I am grateful to my God for leading me to this medical field and letting me achieve this master's degree.

I wish to express my deep sense of gratitude to professor Seung Woo Park for encouraging and inspiring me at all the stages of this work and providing all the necessary facilities and guiding me to complete this study.

I am also very grateful to professor Kyung sik Kim and professor Jin Young Choi for their valuable guidance, keen interest and encouragement at various stages of this work.

This study is based on 5 excellent gastroenterology endoscopic specialists' dedication to the patients; I am extremely thankful to professor Si Young Song, Seungmin Bang, Jeong Youp Park, and Moon Jae Chung for their dedication to the patients and their works.

Ga Lam Leem

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Clinical value of contrast-enhanced harmonic endoscopic ultrasonography in differential diagnosis of pancreas and gall bladder mass

Ga Lam Leem

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Seung Woo Park)

Recent studies reveal that contrast enhanced harmonic endoscopic ultrasonography (CEH-EUS) is beneficial in differential diagnosis of malignant neoplasms of pancreas and gall bladder (GB) from benign mass in aspects of evaluation of microvasculature and real time perfusion. However, in Korea, CEH-EUS is not widely used as EUS is.

Therefore, in this study, I aimed to prove the clinical value of CEH-EUS in differential diagnosis of pancreas and GB mass by direct comparing to that of conventional EUS.

I reviewed sonographic images and medical information of 471 patients who underwent conventional EUS and CEH-EUS for diagnosis of pancreas and gall bladder mass at a single medical center; Severance Hospital, Seoul, Korea, between March 2010 and March 2016.

For the pancreas solid mass, the enhancement pattern of CEH-EUS showed high sensitivity (82.0%) and specificity (87.9%) and the area under the ROC curve was higher than that of conventional EUS. However, for the GB mass, CEH-EUS was not superior to the conventional EUS.

Key words : contrast-enhanced harmonic endoscopic ultrasonography, EUS, pancreas solid mass, gall bladder neoplasm

Clinical value of contrast-enhanced harmonic endoscopic ultrasonography in differential diagnosis of pancreas and gall bladder mass

Ga Lam Leem

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Seung Woo Park)

I. INTRODUCTION

According to the statistical research announced by the Ministry of health and welfare in March, 2015, the crude incidence rate of pancreatic cancer and gall bladder cancer has been increased gradually since 1999; from 6.4 over 100,000 to 10.2 over 100,000 (pancreatic cancer) and 5.5 over 100,000 to 10.7 over 100,000 (gall bladder cancer). And compare to other digestive tract cancers, their 5-year survival rates are relatively low; 8.8% and 28.3%, each. Therefore,

the early detection of those cancers and distinguish them from benign mass are getting more important.

Endoscopic ultrasonography (EUS) is widely used to diagnose pancreas and gall bladder diseases because of its higher spatial resolution than other imaging methods.[1-4] But without evaluating their hemodynamics, the vascularity, EUS has limitations of diagnosis. Therefore, many tries have been attempted to complement those limitations; such as, doppler EUS and contrast-using EUS.[5-10] Doppler EUS is limited in dynamic perfusion imaging and cannot depict very slowly flowing microscopic vessels and parenchymal perfusion.[11-12] In contrast, contrast-enhanced harmonic (CEH) technology allows real-time perfusion imaging without Doppler-related artifacts[11-12], and evaluation for both blood flow in small vessels (2 or 3 mm in minimum diameter) and parenchymal microvasculature[13].

Recently, CEH-EUS has been widely used to characterize solid pancreatic cancer and gastrointestinal stromal tumors[14-15]. US contrast agents consist of gas microbubbles covered by the shell of a biocompatible material such as a protein, lipid, or polymer[17]. Until recently, contrast enhanced imaging techniques for EUS were impossible to develop because all available echo-endoscope transducers were too small to produce sufficient acoustic power for contrast-enhanced harmonic imaging using first-generation US contrast agents[16-17]. However, second-generation US contrast agents such as SonoVue (Bracco Inc., Milan, Italy), Definity (Lantheus Medical Imaging, North

Billerica, MA, USA), and Sonazoid (Daiichi-Sankyo, Tokyo, Japan) are composed of stabilized microbubbles containing perfluorocarbons or sulfur hexafluoride, an echogenic and poorly soluble gas[16-18]. They are markedly improved in peripheral circulation[18]. These second-generation US contrast agents produce harmonic signals at lower acoustic power and are suitable for CEH-EUS imaging[15].

A recent meta-analysis on contrast enhanced endoscopic ultrasonography (CE-EUS) that analyzed reports on both contrast-enhanced Doppler and contrast-enhanced harmonic EUS showed that this method differentially diagnoses pancreatic adenocarcinomas with a pooled sensitivity and specificity of 94% and 89%, respectively[19]. And for gall bladder (GB) neoplasms, a retrospective study of using contrast enhanced harmonic endoscopic ultrasonography (CEH-EUS) for differentiating GB adenomas from cholesterol polyps showed that it was useful to differentially diagnose GB adenomas with the sensitivity and specificity of 75.0% and 66.6%, respectively[20].

However, in Korea, CEH-EUS is not widely used as EUS is. There would be some reasons for that; some are technical problems and others are lack of studies for Korean population with CEH-EUS. In fact, there was no meta-analysis to prove the clinical value of CEH-EUS in differential diagnosis of pancreas and gall bladder disease.

Therefore, in this study, I aimed to prove the clinical value of CEH-EUS in differential diagnosis of pancreas and gall bladder solid mass by direct

comparing the usefulness of CEH-EUS to that of conventional EUS.

II. MATERIALS AND METHODS

1. Study design

I retrospectively reviewed sonographic images and medical information of 471 patients who underwent conventional EUS and CEH-EUS for diagnosis of pancreas and gall bladder mass at a single medical center; Severance Hospital, Seoul, Korea, between March 2010 and March 2016. All those endoscopic sonographies were done by 5 pancreatobiliary endoscopy specialists; SW Park, SY Song, SM Bang, MJ Chung and JY Park, and those images were reviewed by one medical doctor, GL Leem.

2. Ultrasonography equipment

A radial echo-endoscope developed for CEH-EUS (GF-UE260, Olympus Medical Systems Co., Ltd., Tokyo, Japan) and a low acoustic power setting (mechanical index = 0.2) were used. Ultrasonography image analysis were performed by using an Aloka ProSound alpha-10 system (Aloka Co., Ltd., Tokyo, Japan). After the fundamental B-mode EUS investigated the mass, the setting was changed to the extended pure harmonic detection mode, which combines the filtered fundamental and second harmonic component frequencies with a transmitting frequency of 5–7.5 MHz. Then, 2.5 mL of the contrast agent was injected into the antecubital vein in a bolus fashion through a 20-gauge IV

cannula, followed by flushing with 5 mL of normal saline. SonoVue (Bracco Inc., Milan, Italy) was used for contrast agents. 1 ample (2.5ml) of SonoVue contains 25mg of lyophilised sulphur hexafluoride powder. The vascular structures were assessed in real time by examining continuous 0–90s images after contrast agents are injected.

3. Ultrasonography image analysis

The echogenic patterns of conventional EUS were classified into four categories; anechoic, hypoechoic, isoechoic and hyperechoic. For the pancreas solid mass, those echogenic patterns were defined by comparing to those of normal pancreas parenchyme. And for the GB mass, those echogenic patterns were defined by comparing to those of GB wall.

The enhancement patterns of CEH-EUS were classified into four categories; nonenhancement, hypoenhancement, isoenhancement and hyperenhancement. Those enhancement patterns were also defined by comparing to those of normal pancreas parenchyme, in pancreas solid mass, and those of GB wall, in GB mass.

The other parameters that I could describe with sonographic images such as duct dilatation, tumor size, tumor demarcation, tumor marginal irregularity, hypoechoic foci, and focal wall thickness were obtained and used for analysis commonly.

4. Statistical analysis

All analysis were performed using the statistical software SPSS v20. First, I compared those two diagnostic tools with the sensitivities and the specificities that were calculated with echogenic patterns and enhancement patterns. Those discrimination abilities were performed with the classification table. And then, with the other parameters, by logistic regression, I figured out the variables which were statistically significant and obtained the ROC curve and the area under the curve (AUC). They were calibrated with hosner-lemeshow test. With pairwise comparison of those AUCs, I figured the clinical value of CEH-EUS. When the *P* value was < 0.05, the difference was regarded as significant.

5. Patient population

Among 471 patients reviewed, 279 patients were diagnosed as pancreas mass and 192 patients were diagnosed as GB mass. Among 279 patients of pancreas mass, 72 patients of cystic neoplasm of pancreas were excluded. Among 192 patients of GB mass, 24 patients of nonenhancment in CEH-EUS were excluded when analyzing and all those 24 cases were non-neoplasm.

III. RESULTS

1. Patient characteristics

Table 1 and Table 2 show the baseline characteristics of patients with pancreas solid mass and GB mass. Their mean age was 58.7 and 55.9 each, and all patients were underwent conventional EUS and CEH-EUS for diagnosis. For the pancreas solid mass, ductal carcinoma was most common (45.9%), and neuroendocrine tumor (27.5%) and mass forming pancreatitis (10.1%) were following. For the GB mass, cholesterol polyps were most common (30.7%), and then carcinoma (18.2%) and adenoma (7.8%) were following. For the GB mass, I divided them into two groups, neoplasm and non-neoplasm with their pathologic diagnosis; carcinoma and adenoma as neoplasm (26.0%) and others as non-neoplasm (74.0%).

Table 1. Patient characteristics for pancreas solid mass (n=207)

Age (mean ± SD)	58.7 ± 13.9
Sex (M/F)	110/97 (53.1%/46.9%)
Diagnostic modality	n (%)
EUS (Conventional and CEH)	207 (100)
CT	205 (99.0)
MRI	163 (78.7)
PET-CT	144 (69.6)
Tumor size (mm) (mean ± SD)	25.3 ± 15.0
Tumor location	n (%)
Head/Uncinate	82 (39.6)
Neck	25 (12.1)
Body	48 (23.2)
Tail	52 (25.1)
Pathology	n (%)
Ductal carcinoma	95 (45.9)
Neuroendocrine tumor	57 (27.5)
Mass forming pancreatitis	23 (11.1)
Solid pseudopapillary neoplasm	14 (6.8)
Others	20 (9.7)

Table 2. Patient characteristics for gall bladder mass (n=192)

Age (mean ± SD)	55.9 ± 15.0
Sex (M/F)	77/115 (40.1%/59.9%)
Diagnostic modality	n (%)
EUS (Conventional and CEH)	192 (100)
CT	102 (53.1)
MRI	39 (20.3)
PET-CT	47 (24.5)
Tumor size (mm) (mean ± SD)	15.7 ± 10.6
Tumor location	n (%)
Neck	32 (16.7)
Fundus	63 (32.8)
Body	97 (50.5)
Pathology	n (%)
Neoplasm (carcinoma and adenoma)	50 (26.0)
Non-neoplasm	142 (74.0)

2. Pancreas solid mass

Table 3 shows the vascular enhancement patterns of all 207 cases in the view of CEH-EUS. According to the table 3, ductal carcinoma show mostly hypoenhancement pattern and neuroendocrine tumors show mostly hyperenhancement pattern, as revealed by previous studies. Assuming that those enhancement patterns are diagnostic, I measured the sensitivity and specificity for ductal carcinoma and neuroendocrine tumor, each. The sensitivity and the specificity for ductal carcinoma was 82.0% and 87.9%, respectively. For neuroendocrine tumor, the sensitivity and the specificity was 81.1% and 90.9%, respectively. Table 4 shows the echogenic patterns of all 207 cases on conventional EUS. According to the table 4, both ductal carcinoma and neuroendocrine tumors were mostly hypoechoic, so when I calculated their sensitivity and specificity, they show very low sensitivity and relatively high specificity; sensitivity and specificity of 49.0% and 93.3% each, for ductal carcinoma and of 26.6% and 60.0% each, for neuroendocrine tumors.

Table 3. Vascular enhancement patterns on CEH-EUS for pancreas solid mass

	Vascular enhancement patterns				
	None	Hypo	Iso	Hyper	Total
DC	10	82	1	2	95
NET	0	5	9	43	57
SPN	3	5	6	0	14
Pancreatitis	5	5	12	1	23
Metastasis	0	0	2	5	7
GIST	0	0	1	1	2
Lipoma	3	0	0	0	3
Lymphoma	1	0	0	0	1
Accessory spleen	0	3	1	1	5
Total	22	100	32	53	207

DC, ductal carcinoma; SPN, solid pseudopapillary neoplasm; GIST, gastrointestinal submucosal tumor.

Table 4. Echogenic patterns on conventional EUS for pancreas solid mass

	Echogenic patterns				
	Anechoic	Hypoechoic	Isoechoic	Hyperechoic	Total
DC	0	94	1	0	95
NET	0	51	5	1	57
SPN	0	14	0	0	14
Pancreatitis	0	19	4	0	23
Metastasis	0	6	0	1	7
GIST	0	2	0	0	2
Lipoma	0	1	0	2	3
Lymphoma	0	1	0	0	1
Accessory spleen	0	4	1	0	5
Total	0	192	11	4	207

DC, ductal carcinoma; SPN, solid pseudopapillary neoplasm; GIST, gastrointestinal submucosal tumor.

When considered the enhancement texture and echogenic texture together with enhancement or echogenic pattern (Table 5, 6), the diagnostic ability can be improved. When classifying the ductal carcinoma as hypoenhancement and heterogenic pattern in CEH-EUS, the sensitivity and the specificity are estimated as 85.7% and 89.4% respectively. With conventional EUS, when ductal carcinoma

is classified as hypoechoic and heterogenic pattern, the sensitivity and the specificity are estimated as 52.1% and 78.74%, respectively. For the cases of neuroendocrine tumor, when they are classified as hyperenhancement and homogeneous pattern in CEH-EUS, the sensitivity and the specificity are 85.3% and 91.0%, each. In conventional EUS, when they are classified as hypoenhancement and homogeneous pattern, the sensitivity and the specificity are 52.1% and 84.9%, each.

Table 5. Vascular enhancement pattern with texture on CEH-EUS for pancreas solid mass

	Vascular pattern								
	None		Hypo		Iso		Hyper		Total
	Hom	Het	Hom	Het	Hom	Het	Hom	Het	
DC	7	0	**0**	**42**	0	1	0	1	51
NET	0	0	1	2	5	2	**29**	**0**	39
SPN	2	0	0	3	2	3	0	0	10
Pancreatitis	11	0	1	2	3	5	0	0	22
GIST	0	0	0	0	0	0	1	0	1
Lipoma	3	0	0	0	0	0	0	0	3
Metastasis	0	0	0	0	1	1	4	0	6
Lymphoma	1	0	0	0	0	0	0	0	1
Accessory spleen	0	0	1	0	0	0	0	0	1
Total	24	0	3	49	11	12	34	1	134

DC, ductal carcinoma; NET, neuroendocrine tumor; SPN, solid pseudopapillary neoplasm; GIST, gastrointestinal submucosal tumor.

Table 6. Echogenic patterns with texture on conventional EUS for pancreas solid mass

	Echogenic pattern								
	Anoechoic		Hypoechoic		Isoechoic		Hyperechoic		Total
	Hom	Het	Hom	Het	Hom	Het	Hom	Het	
DC	0	0	**12**	**38**	0	1	0	0	51
NET	0	0	26	7	5	0	**1**	**0**	39
SPN	0	0	1	9	0	0	0	0	10
Pancreatitis	1	0	4	15	1	1	0	0	22
GIST	0	0	1	0	0	0	0	0	1
Lipoma	0	0	0	1	0	0	2	0	3
Metastasis	0	0	3	2	0	0	1	0	6
Lymphoma	0	0	0	1	0	0	0	0	1
Accessory spleen	0	0	1	0	0	0	0	0	1
Total	1	0	48	73	6	2	4	0	134

DC, ductal carcinoma; NET, neuroendocrine tumor; SPN, solid pseudopapillary neoplasm; GIST, gastrointestinal submucosal tumor.

A. Ductal carcinoma

To evaluate the clinical value of CEH-EUS, I analyzed the enhancement patterns and echogenic patterns with other parameters that I can obtain from

endoscopic ultrasonography. To diagnose the ductal carcinoma with sonographic images, I analyzed those parameters with logistic regression to find out which variables are statistically significant (Table 7).

Table 7. Univariate analysis of variables for ductal carcinoma

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Age	1.049	1.025	1.073	<0.001
Sex	0.785	0.466	1.325	0.365
Duct dilatation	6.657	2.606	17.008	<0.001
Tumor size	1.043	1.021	1.065	<0.001
Tumor demarcation	3.442	1.729	6.852	<0.001
Tumor marginal irregularity	13.372	6.782	26.366	<0.001
Hypoechoic	13.429	1.732	104.144	0.013
Hypoenhance	35.249	16.155	76.912	<0.001

Table 7 shows that age, duct dilatation, tumor size, tumor demarcation, tumor marginal irregularity, hypoechoic on conventional EUS, and hypoenhancment on CEH-EUS are significant factors in univariate analysis. I made two groups and verified those factors with multivariate analysis; one group with hypoechoic pattern and the other with hypoenhancement pattern (Table 8, 9).

Table 8. Multivariate analysis of variables with echogenic pattern of conventional EUS for ductal carcinoma

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Age	1.053	1.024	1.084	<0.001
Hypoechoic	15.955	1.167	218.136	0.038
Duct dilatation	5.748	1.829	18.060	0.003
Tumor size	1.029	1.003	1.056	0.030
Tumor demarcation	0.608	0.210	1.760	0.359
Tumor marginal irregularity	14.805	5.859	37.408	<0.001

Table 9. Multivariate analysis of variables with enhancement pattern of CEH-EUS for ductal carcinoma

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Age	1.058	1.018	1.100	0.004
Hypoenhance	35.071	12.261	100.315	<0.001
Duct dilatation	6.344	1.470	27.379	0.013
Tumor size	1.016	0.984	1.049	0.333
Tumor demarcation	0.446	0.112	1.771	0.251
Tumor marginal irregularity	19.167	5.678	64.705	<0.001

Table 8 reveals that age, hypoechoic pattern on conventional EUS, duct dilatation, tumor size, and tumor marginal irregularity are statistically significant. On the other hand, Table 9 reveals that age, hypoenhancement pattern on CEH-EUS, duct dilatation, and tumor marginal irregularity are statistically significant in multivariate analysis of CEH-EUS setting. With logistic regression, I obtained a predicted probability formula for each, and ROC curves for them (Figure1).

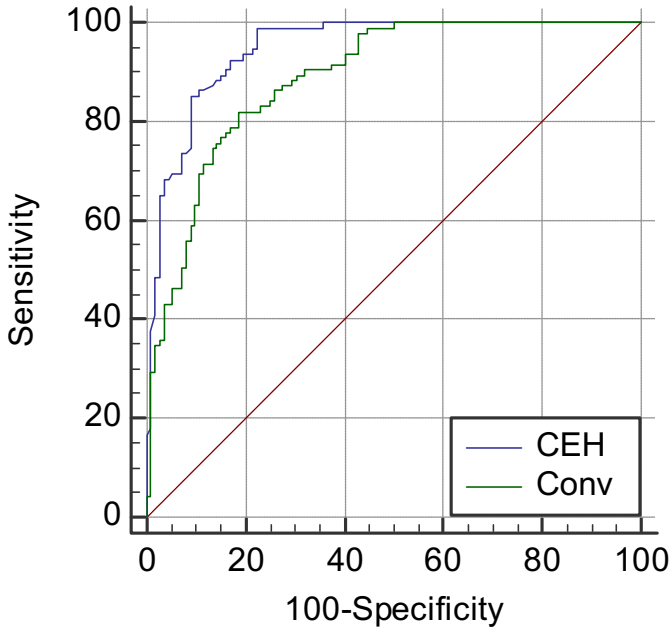

Figure 1. Comparison of ROC curve with predicted probabilities from CEH-EUS and Conventional EUS for ductal carcinoma. AUROC for CEH-EUS is 0.949 (SE 0.0140), and AUROC for conventional EUS is 0.889 (SE 0.0220).

With pairwise comparison of ROC curves for ductal carcinoma, the difference between areas under ROC curves was 0.0602, and it was statistically significant (p=0.001).

In real clinical field, clinicians usually do conventional EUS first and then, do CEH-EUS for the lesions observed in conventional EUS. Therefore, at this time, I analyzed the parameters that I could measure from conventional EUS and CEH-EUS together.

Table 10. Multivariate analysis of variables with EUS for ductal carcinoma

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Age	1.059	1.019	1.101	0.003
Hypoenhance	32.117	11.176	92.299	<0.001
Hypoechoic	14.633	0.111	1927.415	0.281
Duct dilatation	6.090	1.402	26.461	0.016
Tumor size	1.015	0.982	1.048	0.371
Tumor demarcation	0.421	0.104	1.710	0.226
Tumor marginal irregularity	19.704	5.662	68.571	<0.001

When I analyzed those parameters from conventional EUS and CEH-EUS together, enhancement pattern of CEH-EUS was single powerful parameter, so echogenic pattern in conventional EUS lost its power in diagnosis and was no more significant in diagnosis (Table 10).

B. Neuroendocrine tumor

With the same ways used for ductal carcinoma, I repeated the analysis for neuroendocrine tumors (Table 11).

Table 11. Univariate analysis of variables for neuroendocrine tumor

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Age	0.986	0.964	1.007	0.195
Sex	1.635	0.920	2.906	0.094
Duct dilatation	0.069	0.009	0.515	0.009
Tumor size	0.922	0.889	0.955	<0.001
Tumor demarcation	0.182	0.062	0.533	0.002
Tumor marginal irregularity	0.047	0.014	0.158	<0.001
Hypoechoic	0.543	0.184	1.600	0.268
Hyperenhance	43.000	17.826	103.722	<0.001

As mentioned before, the sensitivity for neuroendocrine tumor with hypoechoic pattern was too low. Therefore at this time, hypoechoic pattern was not statistically significant. At this time, duct dilatation, tumor size, tumor demarcation, tumor marginal irregularity, and hyperenhancement pattern were statistically significant in univariate analysis.

Table 12. Multivariate analysis of variables with echogenic pattern of conventional EUS for neuroendocrine tumor

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Hypoechoic	1.186	0.349	4.035	0.784
Duct dilatation	0.093	0.011	0.758	0.026
Tumor size	0.946	0.914	0.978	0.001
Tumor demarcation	0.777	0.193	3.135	0.723
Tumor marginal irregularity	0.075	0.020	0.281	<0.001

Table 13. Multivariate analysis of variables with enhancement pattern of CEH-EUS for neuroendocrine tumor

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Hyperenhance	26.771	9.633	74.397	<0.001
Duct dilatation	0.125	0.012	1.292	0.081
Tumor size	0.945	0.908	0.983	0.005
Tumor demarcation	0.933	0.180	4.826	0.934
Tumor marginal irregularity	0.183	0.040	0.840	0.029

Table 12 and Table 13 revealed the factors that were statistically significant in multivariate analysis; duct dilatation, tumor size, tumor marginal irregularity for conventional EUS, and hyperenhancement pattern, tumor size, tumor marginal irregularity for CEH-EUS.

With logistic regression, I obtained a predicted probability formula for each, and ROC curves for them (Figure2).

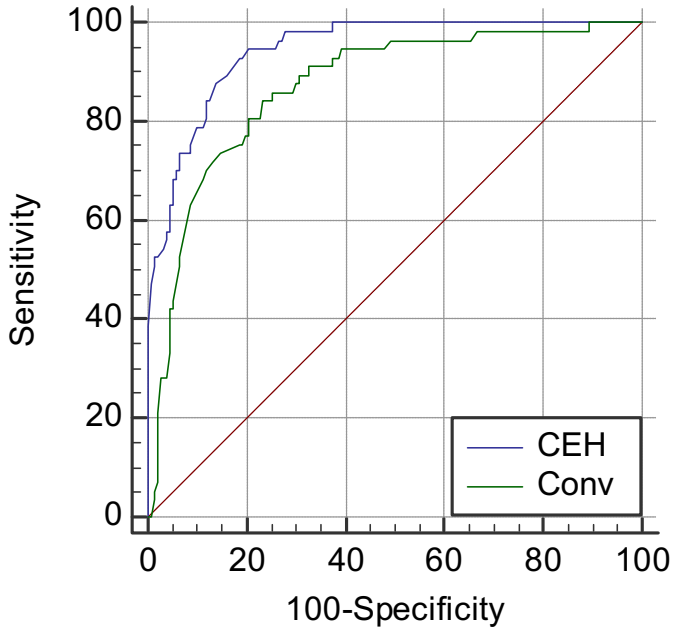

Figure 2. Comparison of ROC curve with predicted probabilities from CEH-EUS and Conventional EUS for neuroendocrine tumor. AUROC for CEH-EUS is 0.945 (SE 0.0145), and AUROC for conventional EUS is 0.870 (SE 0.0274).

With pairwise comparison of ROC curves for neuroendocrine tumor, the difference between areas under ROC curves was 0.0744, and it was statistically significant (p=0.0014).

3. Gall bladder mass

I divided all gall bladder mass into two groups; neoplasm (carcinoma, adenoma) and non-neoplasm. Unlike pancreas solid mass, neoplasm and non-neoplasm did not show specific echoic or enhancement pattern (Table 14, Table 15). Therefore, I categorized them with vascular and echogenic texture; homogeneous or heterogeneous. Neoplasm showed mostly heterogenic enhancement pattern (80%) but non-neoplasm was not characterized by CEH-EUS. So, with heterogenic enhancement pattern, the sensitivity for neoplasm was only 40.4% and the specificity was 85.5%. On the other hand, on conventional EUS, at this time, non-neoplasm mostly showed homogenous echoic pattern, but neoplasm did not show specific pattern. With heterogenic echoic pattern, the sensitivity for neoplasm was 60.9%, and the specificity was 82.0%, still inappropriate for diagnostic tool.

Table 14. Vascular enhancement patterns on CEH-EUS for gall bladder mass

	Vascular enhancement pattern						
	Hypo		Iso		Hyper		Total
	Hom	Het	Hom	Het	Hom	Het	
Neoplasm	1	12	3	17	6	11	50
Non-neoplasm	21	27	28	31	10	1	118
Total	22	39	31	48	16	12	168

Hom, Homogeneous; Het, Heterogeneous.

Table 15. Echogenic patterns on conventional EUS for gall bladder mass

	Echogenic pattern						
	Hypo-echoic		Iso-echoic		Hyper-echoic		Total
	Hom	Het	Hom	Het	Hom	Het	
Neoplasm	2	13	18	12	2	3	50
Non-neoplasm	36	6	55	11	9	1	118
Total	38	19	73	23	11	4	168

Hom, Homogeneous; Het, Heterogeneous.

To find out which variables are significant to diagnose neoplasm at gall bladder, I analyzed the parameters that I obtained from sonographic images with logistic regression (Table 16).

Table 16. Univariate analysis of variables for gall bladder neoplasms

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
Sex	1.142	0.583	2.238	0.699
Age	1.079	1.047	1.112	<0.001
Hypoechoic foci	20.222	7.506	54.485	<0.001
Tumor size	1.100	1.057	1.145	<0.001
Multi-lobulated	2.991	1.451	6.164	0.003
Presence of Neck	>1000	<0.001	<-3000	0.998
Number of Lesion	10.537	2.428	45.723	0.002
Focal wall thickness	10.608	1.386	81.200	0.023
ConvEUS hetero	7.071	3.337	14.980	<0.001
CEH-EUS hetero	4.000	1.831	8.737	0.001

Table 16 shows that age, hypoechoic foci, tumor size, multi-lobulated, multiple number of lesions, focal wall thickness, echogenic heterogeneity and heterogenic enhancement are significant in univariate analysis. I separated them into two groups with conventional EUS and CEH-EUS, and verified those factors with multivariate analysis (Table 17, 18).

Table 17 is for variables with conventional EUS and Table 18 is for variables with CEH-EUS. Age and hypoechoic foci are only statistical significant variables in both groups. This reveals that CEH-EUS is not superior to conventional EUS in

diagnose of neoplasm at gall bladder.

Table 17. Multivariate analysis of variables with echogenic pattern of conventional EUS for gall bladder neoplasms

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
ConvEUS hetero	1.512	0.461	4.952	0.495
Age	1.038	1.002	1.074	0.037
Hypoechoic foci	4.993	1.414	17.629	0.012
Tumor size	1.046	0.992	1.103	0.097
Multi-lobulated	1.893	0.697	5.146	0.211
Number of Lesion	4.039	0.837	19.495	0.082
Focal wall thickness	7.977	0.901	70.587	0.062

Table 18. Multivariate analysis of variables with echogenic pattern of CEH-EUS for gall bladder neoplasm

Variables	Odds ratio	95% C.I for OR		p-value
		Lower	Upper	
CEH-EUS hetero	1.802	0.689	4.717	0.230
Age	1.037	1.002	1.074	0.040
Hypoechoic foci	5.212	1.658	16.377	0.005
Tumor size	1.049	0.997	1.105	0.067
Multi-lobulated	1.788	0.655	4.879	0.256
Number of Lesion	4.362	0.901	21.119	0.067
Focal wall thickness	7.099	0.800	62.987	0.078

IV. DISCUSSION

To prove the clinical value of CEH-EUS in differential diagnosis of pancreas and gall bladder solid mass, I designed the study with two approaches; compare of the sensitivity and the specificity, and compare the ROC curves in diagnosis. In this study, I proved the superiority of CEH-EUS in differential diagnosis of pancreas mass compared to conventional EUS with higher sensitivity and specificity, and higher AUROC, for the cases of ductal carcinoma and neuroendocrine tumor. In contrast, for gall bladder mass, CEH-EUS did not show any superior ability in differential diagnosis to conventional EUS.

For the pancreas solid mass, with comparison of the diagnostic ability of enhancement pattern and echogenic pattern, the enhancement pattern showed higher sensitivity (82.0%) and higher specificity (87.9%) for ductal carcinoma, compared to relatively low sensitivity (49.0%) and high specificity (93.3%) from echogenic pattern. Past studies revealed that only with enhancement pattern, the sensitivity and specificity can be improved up to 95%[1, 3-4]. But in real clinical field, it was not that precise. To improve the sensitivity and specificity, I considered the enhancement and echogenic texture, together. Most cases of ductal carcinoma showed heterogenic texture, so I think that if I consider heterogenic texture together with enhancement pattern, the diagnostic ability could get better. When I classify ductal carcinoma as hypoenhancement and heterogenic pattern on CEH-EUS, the sensitivity and the specificity increases up to 85.7% and 89.4%, respectively. With conventional EUS, when ductal carcinoma is classified as hypoechoic and heterogenic pattern, the sensitivity and the specificity increases up to 52.1% and 78.74%, respectively. In the cases of neuroendocrine tumor, it changes more dramatically. If neuroendocrine tumor is classified as hyperenhancement and homogeneous pattern in CEH-EUS, the sensitivity and the specificity changes from 81.1% to 85.3%, from 90.9% to 91.0%, respectively, compared to classified just with hyperenhancement pattern. In conventional EUS, if the neuroendocrine tumor is classified as hypoenhancement and homogeneous pattern, the sensitivity and the specificity changes from 26.6% to 52.1%, from 60.0% to 84.9%, respectively, compared to classified just with hyperenhancement

pattern.

However, there is no standardized definition for enhancement and echogenic texture, defined as homogeneous and heterogeneous. So, I didn't consider the echogenic texture as a diagnostic parameters, because I thought that it would not be reproducible and would be easily biased by physicians. If we can make a standard definition for the texture, I think the diagnostic performance would be improved.

After considering the texture with echogenic and enhancement pattern, still, CEH-EUS was better to diagnosis of ductal carcinoma and neuroendocrine tumor than conventional EUS, but the sensitivity and the specificity were not that high as previous studies, reported nearly 95%. Therefore, I put the parameters that physicians actually considered to diagnosis in analysis together. And with logistic regression, calculated area under the ROC curve (AUROC) in CEH-EUS was 0.949 for ductal carcinoma, and 0.945 for neuroendocrine tumor. Considering that we usually think of a model as a powerful predictable model if the AUC is over 0.75, I can say that the predictive model with the parameters of CEH-EUS is very powerful and quite precise. Even though the model is not validated externally and the total patient numbers were not enough to make a scoring model, there would be an agreement that it is powerful to diagnose ductal carcinoma and neuroendocrine tumor precisely with the parameters of CEH-EUS. When I calculated AUROC in conventional EUS for ductal carcinoma and neuroendocrine tumor, it was 0.890 and 0.871. Still useful predictive models but less powerful

than those of CEH-EUS with statistical significance.

To prove the clinical value of CEH-EUS, I made possibility equations with logistic regression for ductal carcinoma and neuroendocrine tumor with parameters of CEH-EUS. For ductal carcinoma, the possibility equation is 1 / (1 + exp (-A)), where A = -7.074 + (0.056 x Age) + (3.557 x hypoenhancement) + (1.848 x Duct dilatation) + (0.016 x Tumor size) + (-0.808 x Tumor demarcation) + (2.953 x Tumor marginal irregularity). And for neuroendocrine tumor, the possibility equation is 1 / (1 + exp (-A)), where A = -0.259 + (3.287 x hyperenhancement) + (-2.081 x Duct dilatation) + (-0.057 x Tumor size) + (-0.070 x Tumor demarcation) + (-1.699 x Tumor size).

Here are two cases. First case is 34 years old male, presenting abdominal pain for 1 month. He had no family history of pancreatic cancer and tumor markers, CEA and CA 19-9, were within normal ragne. In CT scan, a pancreatic mass, size of 15mm, was found. When consider his age, tumor markers, and the size, it was less likely pancreatic cancer, rather likely pancreatitis or something else benign. He underwent CEH-EUS and showed hypoenhancement pattern, dilated pancreatic duct, and poorly demarcated and rough margin of mass. With the possibility equation I made to predict ductal carcinoma and neuroendocrine tumor, his pancreatic lesion had a possibility of 93.2% for ductal carcinoma and 0.7% for neuroendocrine tumor. Therefore, he got surgery and the pathology revealed that it was pancreas ductal adenocarcinoma. Another case is 78 years old female, also presenting abdominal pain for 2 weeks. She had no family history of pancreatic

cancer and also had normal range of tumor markers. In CT scan, a pancreatic mass, size of 15mm, was found. Unlike the previous case, she was old enough to doubt pancreatic cancer. With CEH-EUS, she had hyperenhancement pattern, normal pancreatic duct, and well demarcated and smooth margin of mass. With the possibility equation I made to predict ductal carcinoma and neuroendocrine tumor, her pancreatic lesion had a possibility of 7.8% for ductal carcinoma and 89.8% for neuroendocrine tumor. Due to her old age, we planned the surgical resection of it, and the pathology revealed that it was neuroendocrine tumor.

These two patients have same sizes of pancreatic mass. However, some features on CEH-EUS were different, and despite their unmatched age, the possibility equation proved its precise ability of predicting ductal carcinoma and neuroendocrine tumor. This would provide physicians more information in diagnosis of pancreatic mass and help us decide how to treat it.

For the gall bladder mass, when I classify neoplasm with enhancement pattern, like I classified for pancreas solid mass, it did not seem to have any specific enhancement pattern. This is similar result to past studies[20]. Therefore, for gall bladder mass, I used echogenic texture, heterogeneous or homogeneous, for diagnosis. However, unlike past studies, in this study, CEH-EUS was not superior to the conventional EUS. It showed low sensitivity and in the multivariate analysis, only age and hypoehoic foci were meaningful. As known before, the size is one of the most important factors to predict the malignancy, so as heterogenic texture is, but in this study, they were not statistically significant. I think that it is because as

this study is to prove the clinical value of CEH-EUS, I include all the pathologies in the same analysis tool. There are specific diagnostic parameters to diagnose non-neoplasms, such as presence of neck for cholesterol polyps, multi-lobulated, focal wall thickness and smooth marginal irregularity for adenomyomatosis. Therefore, if I make some flow chart and exclude those easily diagnosable disease, I can improve the accuracy of diagnosis with CEH-EUS.

And in past studies and in this study, the enhancement pattern was not specific for neoplasms. However, if we think of the pathophysiology of neoplasm and non-neoplasm, there should be some differences. For now, it was technically impossible, but if I can measure the quantitation of enhancement, I can figure the difference of enhancement amount between neoplasm and non-neoplasm.

V. CONCLUSION

In this study, I can figure out the clinical value of CEH-EUS in differential diagnosis of pancreas and gall bladder solid mass. There are some limitations in this study, of course. It was a retrospective data analysis and I didn't measure the texture of enhancement and echogenic pattern. It was also not a quantitative study. However, it was enough to prove its superior ability in differential diagnosis of pancreas solid mass to that of conventional EUS. For the gall bladder mass, even though this study did not prove the value of CEH-EUS, I expect that if I exclude easily diagnosable diseases with sonographic images and use quantitative data of how much the enhancement is, CEH-EUS would be valuable in differential

diagnosis of gall bladder mass, also.

REFERENCES

1. DeWitt J, Devereaux B , Chriswell M et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Internal Med 2004; 141: 753–63.

2. Ngamruengphong S, Zhou Y, Chak A et al. EUS and survival in patients with pancreatic cancer: a population-based study. Gastrointes Endosc 2010; 72: 78–83.

3. Khashab MA, Yong E, Lennon AM et al. EUS is still superior to multidetector computed tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc 2011; 73: 691–6.

4. Ishikawa T, Itoh A, Kawashima H et al. Usefulness of EUS combined with contrast-enhancement in the differential diagnosis of malignant versus benign and preoperative localization of pancreatic endocrine tumors. Gastrointes Endosc 2010; 71: 951–9.

5. Sakamoto H, Kitano M, Suetomi Y et al. Utility of contrast-enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. Ultrasound Med Biol 2008; 34: 525–32.

6. Becker D, Strobel D, Bernatik T et al. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. Gastrointest Endosc 2001; 53: 784–9.

7. S ft oiu A , Popescu C , Cazacu S et al. Power Doppler endoscopic

ultrasonography for the diff erential diagnosis between pancreatic cancer and pseudotumoral chronic pancreatitis. J Ultrasound Med 2006; 25: 363–72.

8. Hocke M , Schulze E , Gottschalk P et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol 2006; 12: 246–50.

9. Dietrich CF , Ignee A , Braden B et al. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. Clin Gastroenterol Hepatol 2008; 6: 590–7.

10. S ft oiu A , Iordache SA , Gheonea DI et al. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the diff erential diagnosis of focal pancreatic masses (with videos). Gastrointest Endosc 2010; 72: 739–47.

11. Kudo M . Various contrast-enhanced imaging modes after administration of Levovist . In Kudo M (ed). Contrast Harmonic Imaging in the Diagnosis and Treatment of Hepatic Tumors. Springer: Tokyo, 2003; 22–30.

12. Whittingham TA . Contrast-specific imaging techniques; technical perspective. In Quaia E (ed). Contrast Media in Ultrasonography. Basic Principles and Clinical Applications. Springer: Berlin, 2005; 43–84.

13. Hirooka Y, Itoh A, Kawashima H et al. Contrast-enhanced endoscopic ultrasonography in digestive diseases. J. Gastroenterol. 2012; 47: 1063–72.

14. Kitano M, Kudo M, Yamao K et al. Characterization of small solid tumors in the pancreas: the value of contrast-enhanced harmonic endoscopic

ultrasonography. Am J Gastroenterol 2012; 107: 303–10.

15. Sakamoto H, Kitano M, Matsui S et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc 2010; 73: 227–37.

16. Kitano M, Sakamoto H, Matsui U et al. A novel perfusion imaging technique of the pancreas: contrast-enhanced harmonic EUS (with video). Gastrointest Endosc 2008; 67: 141–50.

17. Kitano M, Kudo M, Sakamoto H et al. Endoscopic ultrasonography and contrast-enhanced endoscopic ultrasonography. Pancreatology 2011; 11(Suppl 2):28–33.

18. Schneider M, Arditi M, Barrau MB et al. BR1: a new ultrasonographic contrast agent based on sulfur hexafluoride-filled microbubbles. Invest Radiol 1995; 30: 451–57.

19. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: A meta-analysis. Gastrointest. Endosc. 2012; 76: 301–9.

20. CH Park, MJ Chung, TG Oh et al. Differential diagnosis between gallbladder adenomas and cholesterol polyps on contrast-enhanced harmonic endoscopic Ultrasonography. Surg Endosc 2013; 27: 1414–21.

ABSTRACT(IN KOREAN)

췌담도 종양의 감별진단에 있어 조영증강 하모닉 내시경 초음파의 임상적 가치

<지도교수 박 승 우 >

연세대학교 대학원 의학과

임 가 람

내시경적 초음파(EUS)는 췌담도질환의 진단에 있어 가장 널리 사용되고 있는 진단적 방법이다. 하지만, EUS 로는 종양의 미세 혈관 및 혈액학적 특성을 파악할 수 없기에 그 한계를 드러냈고, 그를 보완하기 위해 최근 들어, 조영증강 하모닉 내시경 초음파(CEH-EUS)의 유용성이 대두되기 시작하였다. 이는 실시간으로 미세 혈관 및 조직 실질의 혈액 관류를 확인할 수 있고, 도플러의 영상적 결함을 극복할 수 있다는 장점이 있다.

최근의 연구 결과들을 통해, CEH-EUS는 췌담관의 질병을 진단하는데 있어 기존의 내시경 초음파에 비해 그 우월성이 입증되고 있다. 하지만, 아직 한국에서는 많이 사용되고 있지 않다. 이는 기술적 문제도 있겠지만, 아직 한국사람에 있어서 CEH-EUS의 진단적 가치가 대규모 연구를 통해 입증되지 않았기 때문일 것이다.

그래서, 본 저자는 이 연구를 통해 CEH-EUS 의 임상적 유용성을, 한국사람에 있어 증명하고자 했다. 2010년 3월부터 2016년 3월까지 췌담도 종양의 진단에 있어 CEH-EUS 를 사용한 471명의 환자의 영상 및 의료 정보를 분석하여 이를 입증하여 보았다.

췌장의 고형종양에 있어서 CEH-EUS 가 EUS 에 비해 진단에 있어 우월한 것이 확인되었고, 담낭의 종양에 있어서는 우월성이 입증되지 않았다.

핵심되는 말 : 췌담도 종양, 조영증강 하모닉 내시경 초음파