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Efficacy of Quantitative Analysis for Differentiating Pancreatic Solid Lesions Using Contrast-Enhanced Endoscopic Ultrasonography

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Abstract Aim: To evaluate the efficacy of quantitative analysis for differentiating pancreatic ductal adenocarcinoma (PDAC) and inflammatory pancreatic masses (IPM) using time intensity curve (TIC) analysis based on contrast-enhanced endoscopic ultrasonography (CE-EUS). Methods: We reviewed 89 patients who had undergone CE-EUS for pancreatic solid lesions at our department between August 2012 and January 2016. CE-EUS images were recorded for 2 minutes after injection of the contrast agent. The diagnostic abilities of the enhanced patterns and TIC analysis were assessed. Results: The enhanced patterns of PDAC were mainly hypovascular and heterogeneous (66/77), while IPM were mainly isovascular and homogeneous (6/12). In PDAC, sensitivity was 77.9%, specificity 83.3%, and accuracy was 78.7%. In TIC analysis, the intensity reduction rate was significantly different at 10 and 30 seconds after peak intensity. After creating a cutoff value (49%) based on the receiver operating characteristic curve for the intensity reduction rate after 30 seconds, diagnosing PDAC with TIC analysis had a sensitivity of 67.5%, specificity of 100%, and accuracy of 71.9%. Combining enhanced pattern analysis with TIC analysis had a sensitivity of 90.9%, specificity of 83.3%, and accuracy of 89.9%. Conclusion: Combining TIC analysis with CE-EUS improved diagnostic accuracy when differentiating between PDAC and IPM.

Key words: contrast-enhanced endoscopic ultrasonography, pancreatic ductal adenocarcinoma, inflammatory pancreatic mass, time intensity curve analysis, quantitative analysis

Introduction

Endoscopic ultrasonography (EUS) is a modality with high spatial and contrast resolution that is excellent for conducting detailed observations of the pancreas and detecting small lesions. EUS is indispensable for evaluating pancreatic diseases because it has higher sensitivity for microlesions than CT or MRI, involves no radiation exposure, and is associated with very few complications.[1] However, differentiating pancreatic ductal adenocarcinoma (PDAC) and inflammatory pancreatic mass (IPM) are complicated, even when using EUS, CT, and MRI.

The recent development of a second-generation ultrasound contrast agent (Perflubutane: Sonazoid®, GE Healthcare Pharma, Tokyo, Japan) has made contrast-enhanced endoscopic ultrasonography (CE-EUS) a useful examination method, according to many reports.[2-11] With first-generation ultrasound contrast agents, the energy released in high-sound pressure ultrasonic waves destroys bubbles,

making it impossible to evaluate hemodynamics over a long period. Sonazoid® consists of microbubbles of perflubutane of about 3 μm long covered with a phospholipid membrane. Low sound pressure ultrasonic waves generate resonance among the microbubbles without destroying them, allowing for observation of blood flow dynamics chronologically over long periods.[1,2]

We compared CE-EUS to B-mode observation for differentiating between PDAC and IPM. Observing changes over time with CE-EUS, we found that diagnostic accuracy was higher in the late phase (70-90 seconds) compared with the early phase (30-50 seconds) and reported that diagnostic ability was significantly higher with CE-EUS.[3]

Recently, time intensity curve (TIC) analysis of CE-EUS images has been reported as a useful method of quantitative evaluation. Previous reports have compared: intensity reduction rates after 1, 3, and 5 minutes[2]; the rise in intensity, intensity rise rate, and other factors[4]; and the time until peak intensity.[5] However, no studies have made detailed comparisons of the time phases within 1 minute of the start of contrast enhancement.

The purpose of the present study was to perform differential diagnosis of PDAC and IPM by capturing changes in blood flow dynamics in more detail.

Subjects and Methods

Data for consecutive 89 patients who underwent CE-EUS for the differential diagnosis of a pancreatic mass previously detected by abdominal ultrasonography, computed tomography, or magnetic resonance imaging from August 2012 to January 2016 at the Yamaguchi University Hospital, and whose images could be subjected to time intensity curve analysis (TIC). In all cases histological diagnoses were made using surgery or EUS-guided fine-needle aspiration. The 89 cases included 77 cases of PDAC and 12 cases of IPM (autoimmune pancreatitis: 6 cases, mass-forming pancreatitis: 6 cases). Patient characteristics were analyzed statistically by Mann-Whitney test, chi-squared test, and Fisher's exact test, as appropriate. The IPM cases showed no signs of malignancy in diagnostic imaging performed after a 6-month follow-up period after the initial examination (Table 1).

The ultrasonic endoscope was an electronic radial EUS (GF-UE260-AL5: Olympus Co. Ltd., Tokyo, Japan), and the observation device was the Prosound alpha-10 (Aloka Co. Ltd., Tokyo, Japan). The second-generation ultrasonic contrast agent Sonazoid® was used. B-mode observations were performed with a mechanical index of 0.15, and during contrast enhancement, the extended pure harmonic detection method was used with a mechanical index of 0.35.

The subjects were placed in the left lateral recumbent position, supervised with an ECG monitor, and were sedated with intravenous midazolam or propofol during the EUS observations. B-mode observations were performed before and after the lesion was depicted on contrast imaging with Sonazoid®. Sonazoid® 16 μL was suspended in 2 ml of injectable water, of which 0.5 ml was administered intravenously. Observations were conducted for 120 seconds after intravenous injection of Sonazoid®, and the images were evaluated using the enhanced patterns and TIC analysis.

First, the CE-EUS enhanced patterns were evaluated macroscopically to compare the

Table 1 Patient Characteristics

	PDAC (n = 77)	IPM (n = 12) AIP (n = 6) MFP (n = 6)
Median Age, yr (range)	70 (46 - 90)	67.5 (37 - 73)
Sex (Males.F emales)	39 : 38	8 : 4
Location (Head:B ody:T ail)	41 : 24 : 12	7 : 3 : 2
Median Size, mm (range)	29.6 (7 - 74)	36.7 (19 - 50)

hemodynamics of the lesion and surrounding pancreatic tissue. The enhanced patterns were evaluated via the inner echo pattern and blood flow distribution after contrast enhancement by one investigator: M.Y. The inner echo patterns were evaluated as hypovascular when enhancement of the lesion was weaker than the pancreatic parenchyma in the vicinity, as isovascular when it was similar, and hypervascular when it was stronger. Inner blood flow distribution patterns were classified as heterogeneous or homogeneous.

Next, the quantitative evaluation was performed. After the examination, digital data stored on the ultrasound device hard disk was played to designate a region of interest in the lesion, and quantitative analysis was performed using the preinstalled CHE analysis software (Aloka Co. Ltd., Tokyo, Japan). The location of the region of interest was determined as large as possible while correcting for movement of the examiner's hands and subject's respiratory variations to create a TIC. The intensity value before the start of contrast enhancement was used as the base intensity. Intensity was measured at the peak of contrast enhancement and 10, 30, 60, and 90 seconds after the peak. The intensity values were base intensity subtracted from intensity measurements (peak, 10, 30, 60, and 90 seconds). We also calculated the time from the start of contrast enhancement to peak, the peak intensity value, and the intensity reduction rates 10, 30, 60, and 90 seconds after peak intensity (Fig. 1). The Student's t-test was used to the compare the intensity reduction rates of the PDAC group to that of the IPM group. JMP Pro 12 (SAS Institute Inc., Caly, NC, USA) was used for the statistical analysis. P values less than 0.05 were considered significant.

The study protocol was approved by the Institutional Review Board for Human Research at the Yamaguchi University Hospital (No. H24-160). The study was conducted in accordance with the human and ethical principles of research set forth in the Declaration of Helsinki.

Results

When comparing the PDAC group and IPM group, the median ages were 70 and 67.5 years, male:female ratios were 39:38 and 8:4, lesion sites (head: body: tail) were 41: 24: 12 and 7: 3: 2, and maximum tumor diameters were 29.6 mm and 36.7 mm, respectively. There were no significant differences between any of these measures.

In the evaluation of enhanced patterns, 60 of the 77 PDAC cases (77.9%) were hypovascular and heterogeneous. In contrast, half of cases in the IPM group were isovascular and homogenous (6/12, 50.0%). Two cases in the IPM group (16.7%) were hypovascular and heterogeneous, which was the most common

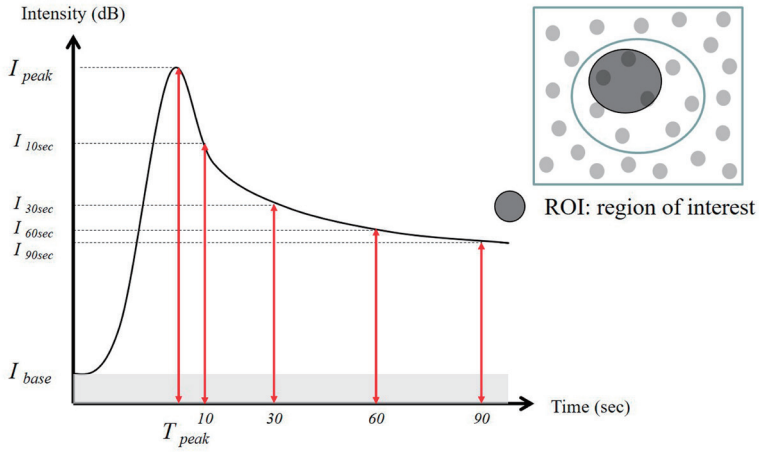

Fig. 1 Schematic presentation of time intensity curve
A time intensity curve is generated by creating an ROI (region of interest) inside the tumor.

enhanced pattern in PDAC (Table 2). When cases evaluated macroscopically as hypovascular and heterogeneous were diagnosed as PDAC, there was 77.9% sensitivity, 83.3% specificity, and 78.7% accuracy in diagnosing pancreatic cancer.

Quantitative analysis using TIC was performed for the PDAC and IPM groups. Fig. 2 and 3 show typical cases of pancreatic cancer and an autoimmune pancreatitis, respectively. The mean time from the start of contrast enhancement to peak intensity was 24.2 seconds for PDAC and 22.4 seconds for IPM, which was not significantly different (Fig. 4A). The peak intensity values were 10.6 dB in PDAC and 12.5 dB in IPM, which were not significantly different (Fig. 4B). The mean intensity reduction rates at 10, 30, 60, and 90 seconds after peak intensity were 41.3%, 56.0%, 63.6%, and 71.7% in PDAC, and 27.1%, 36.4%, 55.0%, 63.2% in IPM, respectively. The intensity reduction rates at 10 and 30 seconds after peak intensity were significantly higher in PDAC (p-values < 0.01: Fig. 4C). The receiver operating characteristic (ROC) curves were prepared with data of the intensity reduction rate at 10 and 30 seconds after peak intensity. The area under the curve (AUC) of the ROC analysis of the intensity reduction rate at 10 and 30 seconds after peak intensity was 0.731 and 0.829, respectively (Fig. 5). When optimal cut-off value of the reduction rate at 30 seconds after peak intensity was accepted as 49%, the sensitivity, specificity and accuracy for diagnosing PDAC was 67.5%, 100%, and 71.9%, respectively.

Next, we examined the diagnostic ability of combining macroscopic and quantitative evaluations for pancreatic cancer. We diagnosed PDAC, which presents with hypovascular and heterogeneous macroscopic patterns, as typical tumors. Diagnosis by CE-EUS images only showed sensitivity: 77.9%, specificity: 83.3%, and accuracy: 78.7%. When cases that were detected as hypovascular and heterogeneous by CE-EUS or had an intensity reduction rate of 49% or more at 30 seconds after peak intensity were diagnosed as PDAC, sensitivity was 90.9%, specificity was 83.3%, and accuracy was 89.9% (Table 3).

Table 2 Inner echo and Distributio

	Hypovascularity		lsovascularity	
	Heterogeneous	Homogeneous	Heterogeneous	Homogeneous
PDAC n = 77	60 (77.9%)	6 (7.8%)	5 (6.7%)	6 (7.8%)
IPM n = 12	2 (16.7%)	2 (16.7%)	2 (16.7%)	6 (50%)

PDAC: pancreatic ductal adenocarcinoma, IPM: inflammatory pancreatic mass

Table 3 Diagnostic Accuracy

	Sensitivity [95%CI]	Specificity [95%CI]	Accuracy [95%CI]	PPV [95%CI]	NPV [95%CI]
Image pattern	77.9 % [0.687-0.872]	83.3 % [0.622-1.04]	78.7 % [0.701-0.872]	96.8 % [0.928-1.01]	37.0 % [0.188-0.553]
TIC	67.5 % [0.571-0.780]	100 % [1.00 1.00]	71.9 % [0.626-0.812]	100 % [1.00-1.00]	32.4 % [0.173-0.475]
Image pattern +TIC	90.9 % [0.845-0.973]	83.3 % [0.622-1.04]	89.9 % [0.836-0.962]	97.2 % [0.934-1.01]	58.8 % [0.354-0.822]

PPV: positive predictive value, NPV: negative predictive value, TIC: time intensity curve

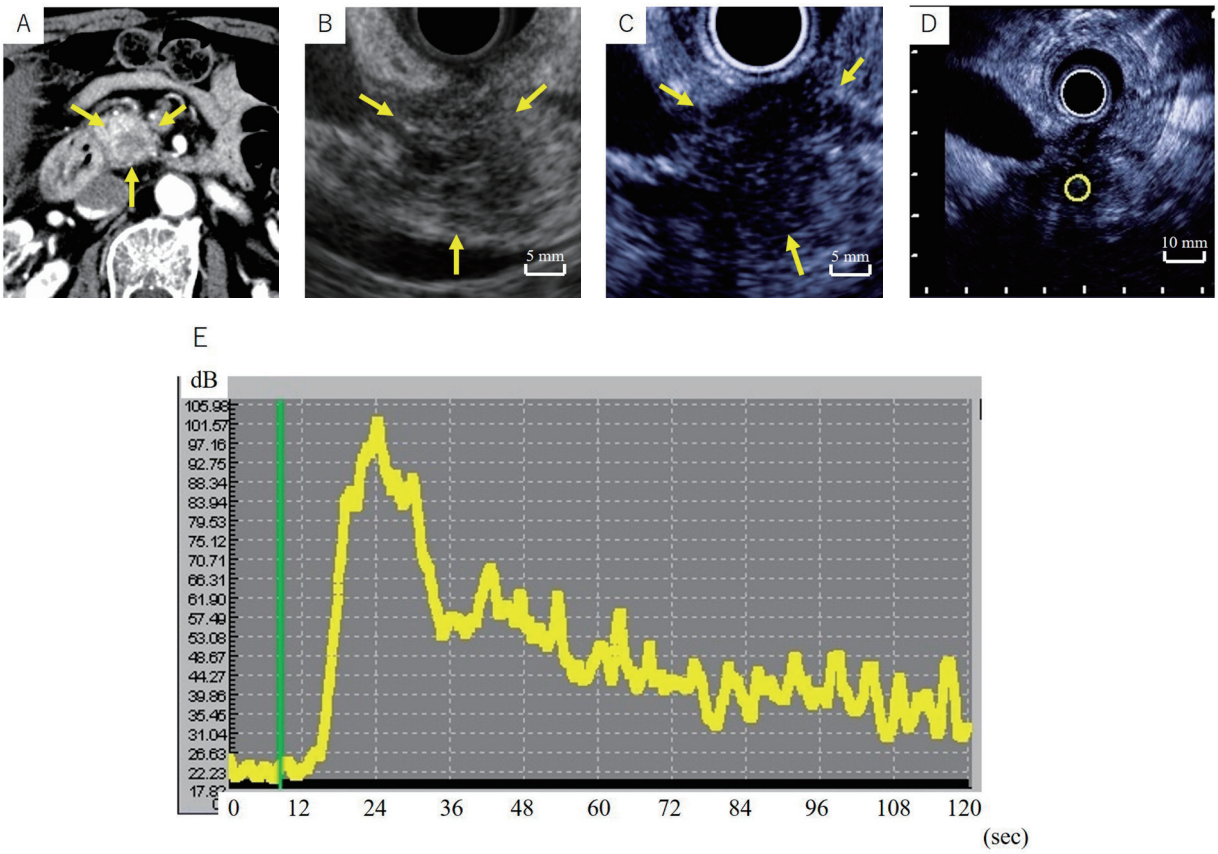

Fig. 2 Pancreatic cancer
A. Contrast-enhanced CT shows a hypovascular mass Φ16 × 21 mm in the pancreatic head (arrows).
B. EUS (B-mode) shows a hypoechoic mass with obscure boundaries (arrows).
C. CE-EUS shows a hypovascular and heterogeneous mass (arrows).
D. An ROI is created inside the tumor (yellow circle).
E. TIC analysis shows a 62% intensity reduction rate after 30 seconds and a typical pattern for pancreatic ductal adenocarcinoma. Pancreatic ductal adenocarcinoma is diagnosed with EUS-FNA.
CE-EUS, contrast-enhanced endoscopic ultrasonography; CT, computed tomography; EUS, endoscopic ultrasonography; EUS-FNA, EUS-guided fine-needed aspiration; ROI, region of interest; TIC, time intensity curve.

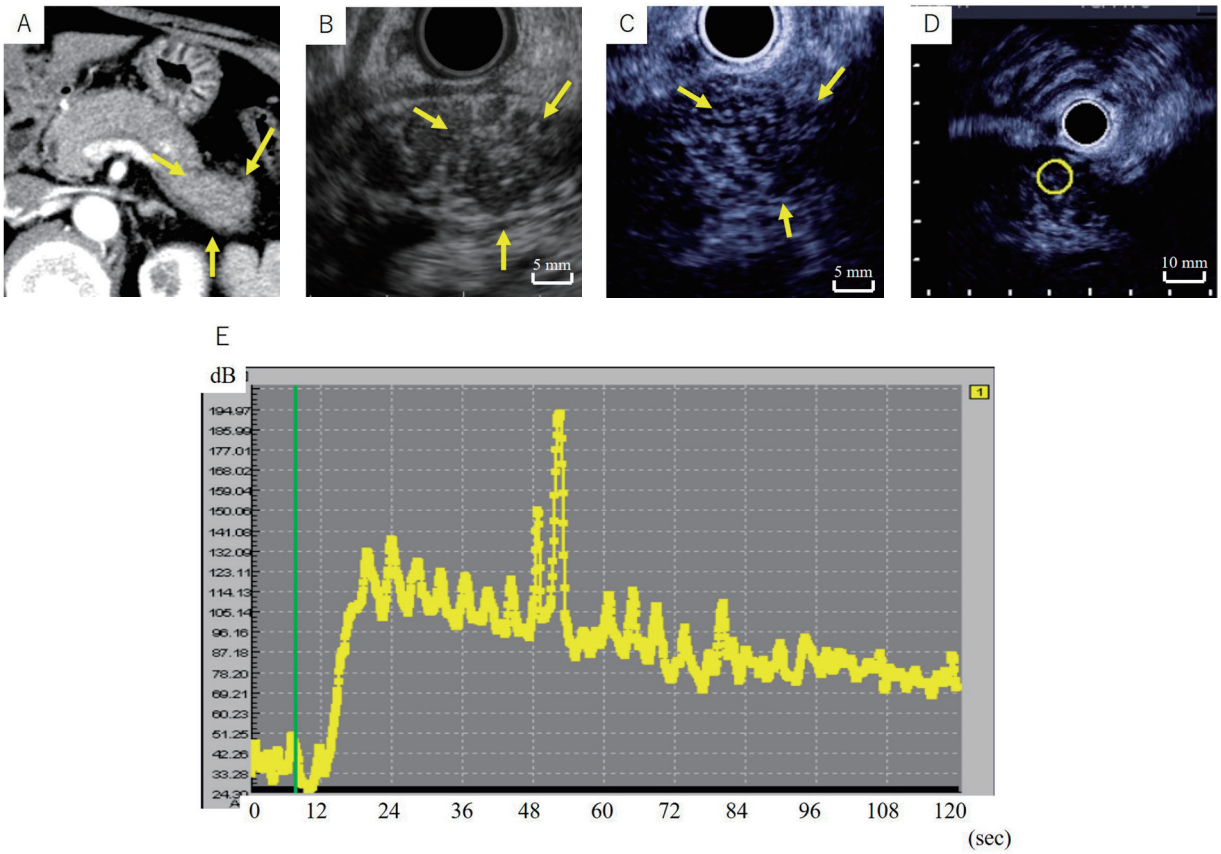

Fig. 3 Autoimmune pancreatitis
A. Contrast-enhanced CT shows swelling in the pancreatic body and tail (arrows).
B. EUS (B-mode) shows diffuse hypoechoic to isoechoic (arrows).
C. CE-EUS shows an isovascular and homogeneous pattern (arrows).
D. An ROI is created inside the tumor (yellow circle).
E. TIC analysis shows a 23% intensity reduction rate after 30 seconds. The contrast pattern and TIC are both different from typical pancreatic ductal adenocarcinoma. Autoimmune pancreatitis is diagnosed with EUS-FNA.
CE-EUS, contrast-enhanced endoscopic ultrasonography; CT, computed tomography; EUS, endoscopic ultrasonography; EUS-FNA, EUS-guided fine-needed aspiration; ROI, region of interest; TIC, time intensity curve.

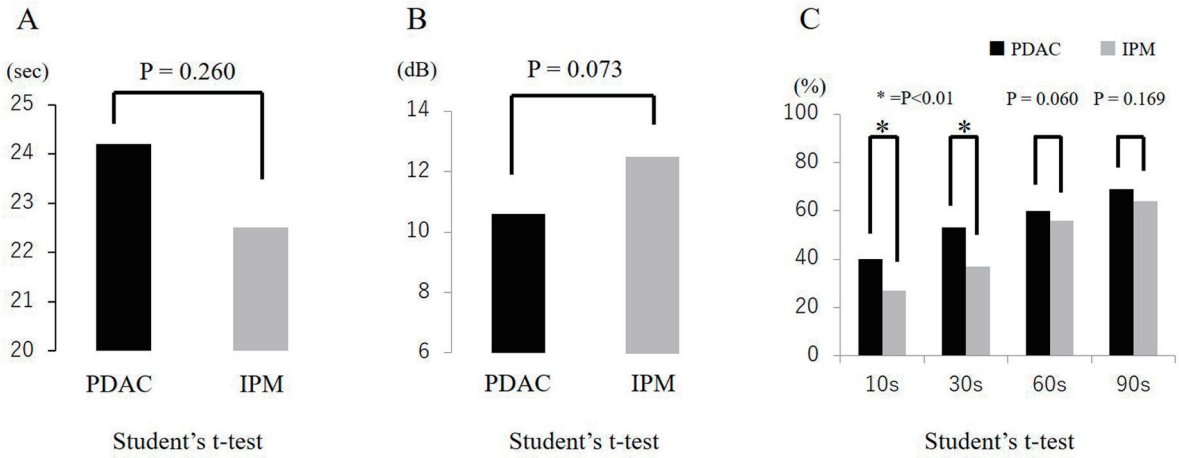

Fig. 4 Comparison of TIC analysis results for pancreatic ductal adenocarcinoma and inflammatory pancreatic masses

A. Time to peak intensity

There is no significant difference in time to peak intensity between pancreatic ductal adenocarcinoma and inflammatory pancreatic masses.

B. Peak intensity value

The peak intensity values are higher in inflammatory pancreatic masses vs. pancreatic ductal adenocarcinoma, but the difference is not statistically significant.

C. Intensity reduction rate

The intensity reduction rates for pancreatic ductal adenocarcinoma in seconds after peak intensity. The intensity reduction rates after 10 and 30 seconds are significantly higher in pancreatic ductal adenocarcinoma.

PDAC: pancreatic ductal adenocarcinoma, IPM: inflammatory pancreatic mass, TIC: time intensity curve.

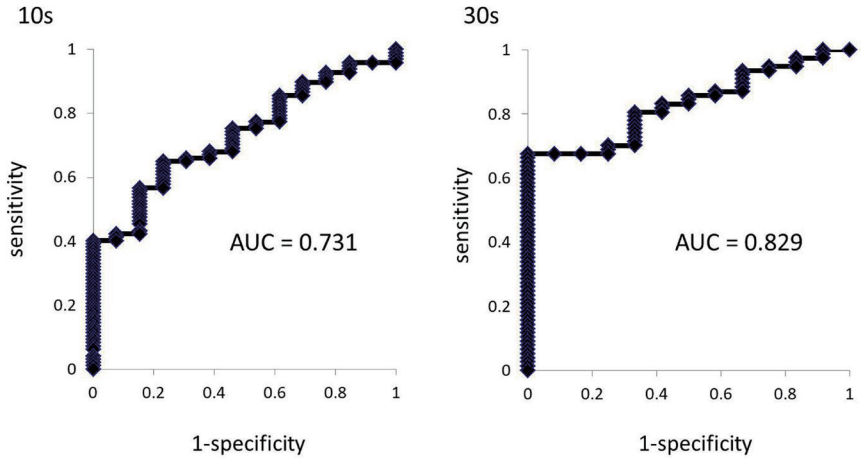

Fig. 5 Receiver operating characteristic curve analysis

The receiver operating characteristic (ROC) curves were prepared with data of the intensity reduction rate at 10 and 30 seconds after peak intensity. The area under the curve of the ROC analysis of the intensity reduction rate at 10 and 30 seconds after peak intensity was 0.731 and 0.829, respectively.

ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

Previously, it was reported that differences in intratumor vessels and vascular diameter, the degree of fibrosis, and tumor differentiation affected values in CE-EUS. In addition, it was reported that the degree of inflammation affected intensity value in CE-EUS, in cases of IPM.[2,5,11-14]

It was reported that arterial components are seen about 15 - 25 seconds after Sonazoid® injection, which increases the intensity in TIC, and venous components are observed decreasing in TIC.[5,6] Herlinger and Finlay reported that angiography for pancreatic cancer cases showed wall irregularities and stenosis of arteries, and avascular areas in capillaries.[15] These findings suggest that the effect of contrast is not delayed, and the intensity steeply decreased from the peak in TIC analysis. In contrast, it was reported that mass-forming pancreatitis does not cause arterial obstruction and showed development of capillaries and arteries in the pancreas.[16] These findings are consistent with high peak values and the delayed contrast effect in CE-EUS. Moreover, these findings demonstrate that the attenuation of intensity from the peak in TIC is subtle. Therefore, the existence of arterial obstruction and development of capillaries in the pancreatic lesion contribute to the TIC in pancreatic cancer and mass-forming pancreatitis.

Yamashita et al. investigated the relationship between CE-EUS images and histopathological findings.[12] They revealed that hypovascular areas of early phase images had heterogeneous tumor cells with fibrous tissue, necrosis, and few vessels.

Many studies have reported the efficacy of EUS and CE-EUS in diagnosing pancreatic cancers.[2-11] We have previously reported a comparison of 49 cases that underwent CE-EUS, comparing the B-mode alone to the early phase (30-50 sec) and late phase (70-90 sec) of CE-EUS, which showed that evaluation with CE-EUS contributed to improving diagnostic accuracy.[3] However, the major limitation of our previous study was that objective evaluation of CE-EUS was difficult to assess the changes in the short term. Recently, some studies have investigated quantitative evaluation of CE-EUS by adding TIC analysis.[2] Matsubara et al. reported that CE-EUS with dynamic quantitative analysis preparing TIC increased the diagnostic accuracy for pancreatic diseases.[2] They evaluated intensity reduction rates in the TIC analysis comparing rates 1, 3, and 5 minutes after the injection of Sonazoid®. They indicated that the echo intensity significantly decreased 1 minute after the peak in pancreatic cancer compared with those of autoimmune pancreatitis and mass-forming pancreatitis. Saftoius et al. performed TIC analysis and compared factors including peak intensity, intensity rise rates, and mean time to peak.[4] They observed significant differences in peak intensity and intensity rise rates between pancreatic cancer and inflammatory masses. On the TIC, Kersting et al. reported that significant differences in the contrast agent inflow start time and time to peak intensity were observed.[5]

However, there have been no reports on changes in hemodynamics within 1 minute. We studied detailed changes in contrast behavior after peak intensity in order to understand how hemodynamics change in each phase and to determine the most useful phase for diagnosis. We used differences in intensity compared to baseline before contrast agent injection. On the diagnostic evaluation of CE-EUS images, the enhanced pattern of PDAC was most often hypovascular and heterogeneous, which was similar to previous studies.[2,3,6,10,17] Although a significant difference in peak intensity has been observed in some previous reports, we found that peak intensity tended to be higher in IPM, but not significantly different.

Focusing on hemodynamics, it was indicated that intensity reduction rates at 10 and 30 seconds was significantly difference between PDAC and IPM, and the echo signal of blood flow in PDAC significantly reduced after only 10 seconds from the peak intensity. A ROC curve of the intensity reduction rate at 30 seconds after peak showed the largest differences between PDAC and IPM. This result indicated that comparison of intensity after 30 seconds after peak was most suitable for differential diagnosis of PDAC from IPM. We also evaluated the diagnostic accuracy by combining CE-EUS images and TIC analysis.

When cases that were detected as hypovascular and heterogeneous by CE-EUS or had an intensity reduction rate of 49% or more at 30 seconds after peak intensity were diagnosed as PDAC, sensitivity was 90.9%, specificity was 83.3%, and accuracy was 89.9%. These results were improved compared to diagnosis by CE-EUS images only (sensitivity: 77.9%, specificity: 83.3%, and accuracy: 78.7%). Diagnosis by EUS including contrast enhancement has the inherent problem that objective evaluation is not possible. Using TIC analysis, it may be possible to perform objective diagnosis. Combining diagnosis by CE-EUS images and TIC analysis, which has objectivity, may contribute to improving diagnostic ability.

A major limitation of this study was the small number of IPM cases enrolled. More substantive analyses should be performed using a larger number of cases.

In conclusion, we showed TIC analysis of CE-EUS to be useful in objectively differentiating PDAC from IPM. In particular, the intensity reduction rate 30 seconds after peak intensity was the most useful for differentiation.

Conflict of Interest

The authors declare no conflict of interest.

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