博士学位論文

造影ハーモニックEUSにおける膵腫瘍の定量的血流解析による鑑別

近畿大学大学院
医学研究科医学系専攻

大　本　俊　介

Doctoral Dissertation

Characterization of pancreatic tumors with quantitative perfusion analysis in contrast-enhanced harmonic EUS

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November 2017

課博

同　意　書

平成 29年 11月 8日

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平成 29 年 11 月 8 日

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Characterization of pancreatic tumors with quantitative perfusion analysis in contrast-enhanced harmonic EUS

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Abstract

Objectives : This study evaluated whether quantitative perfusion analysis with contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) characterizes pancreatic tumors, and compared the hemodynamic parameters in diagnosing pancreatic carcinoma.

Methods : CH-EUS data from pancreatic tumors of 76 patients were retrospectively analyzed. Time-intensity curves (TIC) were generated to depict changes in signal intensity over time, and six parameters were assessed: baseline intensity, peak intensity, time to peak, intensity gain, intensity at 60 seconds (I_{60}), and reduction rate. These parameters were compared between pancreatic carcinomas (n=41), inflammatory pseudotumors (n=14), pancreatic neuroendocrine tumors (n=14), and other tumors (n=7). All six TIC parameters and subjective analysis: contrast imaging pattern for diagnosing pancreatic carcinoma were compared.

Results : Values of peak intensity and I_{60} were significantly lower and time to peak was significantly longer in pancreatic carcinoma than in the other three tumor groups ($P<0.05$). Reduction rate was significantly higher in pancreatic carcinomas than in pancreatic neuroendocrine tumors ($P<0.05$). Areas under the receiver operating characteristic curves, for the diagnosis of pancreatic carcinoma using subjective analysis, baseline intensity, peak intensity, intensity gain, I_{60}, time to peak and reduction rate, were 0.817, 0.664, 0.810, 0.751, 0.845, 0.777 and 0.725, respectively. I_{60} was the most accurate parameter for differentiating pancreatic carcinomas from the other groups, giving values of sensitivity/specificity 92.7%/68.6% when optimal cut-off was chosen.

Conclusions : Pancreatic carcinomas exhibited markedly different TIC patterns from the other tumor types, with I_{60} being the most accurate diagnostic parameter. Quantitative perfusion analysis is useful for differentiating pancreatic carcinomas from other pancreatic tumors.

Key words : quantitative perfusion analysis, pancreatic carcinoma, contrast-enhanced harmonic endoscopic ultrasonography, time-intensity curve

Introduction

The number of reports on the utility of contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) in the differential diagnosis of pancreatic masses has been increasing.[1-5] CH-EUS depicted the hypo-enhancement of pancreatic carcinomas with high sensitivity (89－96%) and specificity (64－94%).[1-5] Nonetheless, the visual evaluation of CH-EUS scans may be influenced by the endosonographers' subjective impressions.[6] In addition, there was no standardized method to analyze the images after the infusion of an ultrasound contrast agent, particularly regarding how to determine the enhancement pattern of the EUS-depicted pancreatic masses.

Recent studies have described the quantitative perfusion analysis of pancreatic diseases using a time-intensity curve (TIC), which graphs the changes in signal intensity over time within a region of interest (ROI) after infusion of an ultrasound contrast agent.[7-12] However, the scanning methods and evaluated parameters varied between these reports. Therefore, the primary aim of this study was to determine if quantitative perfusion analysis with CH-EUS characterizes pancreatic tumors. The secondary aim was to find the most accurate hemodynamic parameter of TIC for differentiating pancreatic carcinoma from other pancreatic tumors.

Methods

Patients and study design

This retrospective study considered to included patients who were suspected of having a pancreatic mass on the basis of results from computed tomography (CT), magnetic resonance imaging, or trans-abdominal ultrasonography (US) and who underwent both standard EUS and CH-EUS between February 2011 and February 2012 at the Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine. Patients were enrolled if the solid component of the mass was greater than 75% of the total volume and if, after the EUS examinations, they had undergone surgery or EUS-guided fine needle aspiration (EUS-FNA) leading to a histological or cytological diagnosis, with a follow-up of at least 12 months. Pancreatic cystic tumors with tumor solids content less than 25% were excluded. The histological or cytological outcome was considered the gold-standard diagnosis for the purposes of this study and was used to divide patients into four groups: pancreatic carcinomas, pancreatic neuroendocrine tumors, inflammatory pseudotumors, and other tumors.

Endoscopic ultrasonography

Conventional EUS of the pancreas without a contrast agent was performed first, with the special attention to pancreatic masses. When conventional EUS revealed a solid lesion, images of the ideal scanning plane were displayed to portray the whole area of the lesion. Thereafter, the imaging mode was changed to the Extended Pure Harmonic Detection (ExPHD) mode. This mode synthesizes the filtered second-harmonic components

with signals obtained from the phase shift, which is used for contrast-enhanced harmonic imaging. The transmitting frequency and mechanical index were 4.7 MHz and 0.3, respectively. The ultrasound contrast agent Sonazoid (Daiichi-Sankyo, Tokyo, Japan) was used. Immediately before CH-EUS, the contrast agent was reconstituted with 2 mL of sterile water for injection, and a dose of 15μL/kg body weight was prepared in a 1 mL syringe. A bolus injection of the contrast agent was administered. With a frame rate of about 10 images per second, all images and hemodynamic data were acquired using a Prosound Alpha-10 ultrasonography system (Aloka, Tokyo, Japan). All EUS procedures were performed by two endosonographers (M. K. and H. S.). One was responsible for endoscopic manipulation and scanning, and the other for operating the US scanner. Both endosonographers are certified by the Japan Gastroenterological Endoscopy Society and have more than 10 years of experience with CH-EUS; each has performed more than 1000 CH-EUS procedures. Subjective analysis was performed by these endosonograpfers for diagnosing pancreatic carcinoma. Hypo-enhancement pattern defined as pancreatic carcinoma.

TIC analysis

The acquired images were reviewed using a software "Time Intensity Curve" installed in processor, Prosound Alpha-10 ultrasonography system (Aloka, Tokyo, Japan). A ROI was placed over the pancreatic mass to cover as large as possible an area, and a TIC was generated to depict the changes in signal intensity over time within the ROI (Figure 1). From these data, the software calculated the baseline intensity (dB), and then, after the injection of contrast medium, the peak intensity (dB), the time to peak (seconds), the intensity gain (dB), the intensity at 60 seconds (I_{60}, dB), and the reduction rate at 60 seconds (reduction rate = $(1 - I_{60}/\text{ peak intensity}) \times 100$, %) (Figure 1).

Statistical analysis

All analyses were performed using the statistical software SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). Steel-Dwass test was applied to compare the TIC parameters among the four groups. When the *P*-value was <0.05, the difference was considered statistically significant. For the diagnosis of pancreatic carcinoma, receiver operating characteristic (ROC) analysis was performed for all TIC parameters to determine the sensitivity, specificity, and odds ratio using the optimal cut-off value.

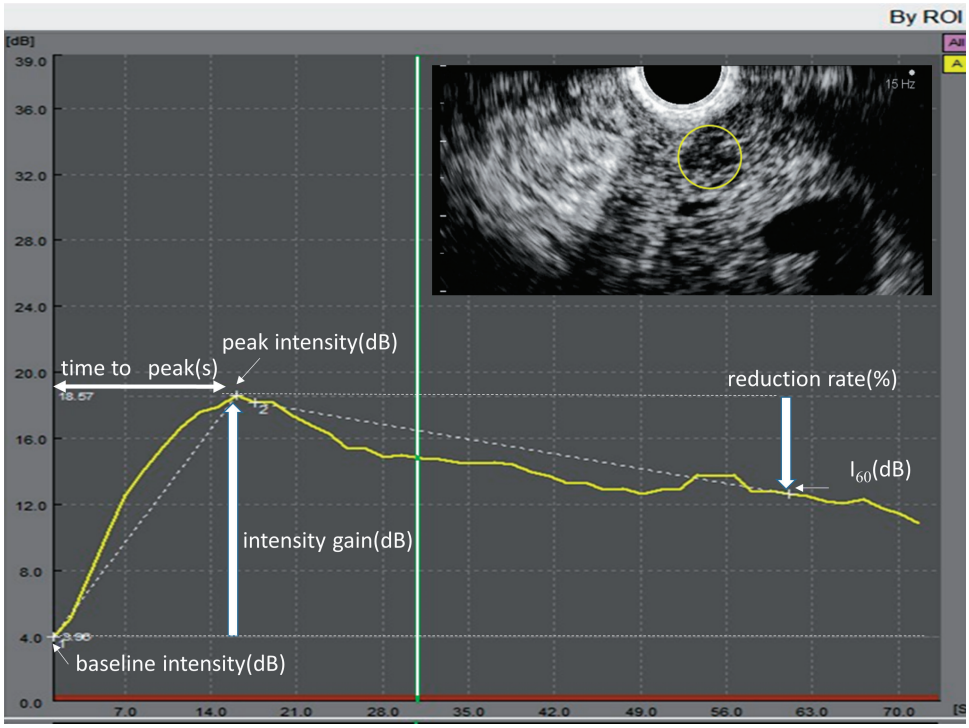

Figure 1. Quantitative perfusion analysis of contrast-enhanced harmonic EUS of a pancreatic carcinoma
A ROI (*yellow circle*) is placed over the pancreatic mass. baseline intensity (dB) : echo intensity before injection of contrast agent. peak intensity (dB) : echo intensity at the peak. time to peak (seconds) : time from injection of contrast medium to peak intensity. intensity gain: echo intensity gain from base intensity to the peak intensity. I_{60} intensity at 60 seconds: echo intensity at 60 seconds after injection of contrast medium. reduction rate (%) : the rate of reduction intensity from the peak to 60 seconds (reduction rate = $(1 - I_{60} / \text{peak intensity}) \times 100$).

Results

During the study period, 76 consecutive patients with suspected pancreatic masses were enrolled. Of the enrolled patients, 44 were men and 32 were women, the mean age was 68.3±10.2 years. Table 1 shows the final diagnoses of the 76 lesions. There were 41 patients with pancreatic carcinoma, which was diagnosed histologically after surgical resection in 13 cases and EUS-FNA in 28. Six patients with pancreatic neuroendocrine tumor were diagnosed by histological analysis of resected specimens. In the remaining 8 patients with neuroendocrine tumor, which was diagnosed by EUS-FNA. In all patients with inflammatory pseudotumor, which was diagnosed histologically after EUS-FNA, periodic follow-up with computed tomography and/or EUS revealed reduction or no change in size. In 10 patients who were suspected of having autoimmune pancreatitis based on the 2011 International Clinical Diagnostic Criteria, tumor reduction was observed after steroid therapy.[13] The seven remaining other tumors were four pancreatic metastases from renal cell carcinoma, two pancreatic metastases from ductal carcinoma of breast, and one solid pseudopapillary neoplasm.

Table 1. Patient characteristics

Age (mean ± SD)	68.3 ± 10.2
Gender, men / women	44/32
Maximum tumor diameter (mm, mean ±SD)	25.9 ± 16.5
Final diagnosis n, total (n, surgically resected)	
Pancreatic carcinoma	41 (13)
Inflammatory pseudotumors	14 (0)
Pancreatic neuroendocrine tumor	14 (6)
Other tumors	7 (1)
Pancreatic metastasis from renal cell carcinoma	4 (0)
Pancreatic metastasis from breast carcinoma	2 (0)
Solid pseudopapillary neoplasm	1 (1)

There was no significant difference in baseline intensity among the four groups (Figure 2a). After the injection of contrast medium, values of peak intensity and I_{60} for the pancreatic carcinoma group were significantly lower than those of the other groups ($P<0.05$) (Figures 2b, 2d). Values of intensity gain for the pancreatic carcinoma group were significantly lower than those of pancreatic neuroendocrine tumor and other tumor groups ($P<0.05$) although there was no significant difference in intensity gain between pancreatic carcinoma and inflammatory pseudotumor groups (Figure 2c). Instead, time to peak was significantly longer in pancreatic carcinoma than in the other groups ($P<0.05$) (Figure 2e). Finally, reduction rate for pancreatic carcinoma was significantly higher than for pancreatic neuroendocrine tumor ($P<0.01$) (Figure 2f).

In ROC analysis for the diagnosis of pancreatic carcinoma (Figure 3), the areas under the curve for subjective analysis, baseline intensity, peak intensity, intensity gain, I_{60}, time to peak and reduction rate were 0.817, 0.664, 0.810, 0.751, 0.845, 0.777, and 0.725, respectively. According to the ROC data, the optimal cut-off values for these parameters without subjective analysis were 3.2 dB, 15.1 dB, 13.7 dB, 12.4 dB, 12.0 s, and 31.4 %, respectively. These cut-offs correspond to the values of sensitivity, specificity and odds ratio are shown in Table 2. In addition, Subjective analysis for the diagnosis of pancreatic carcinoma are shown in Table2. The sensitivity and specificity of subjective analysis were 80.4% and 82.9%. The I_{60} (cut-off value = 12.4 dB) was the most accurate parameter by ROC analysis for diagnosis of pancreatic carcinoma with 92.7 % of sensitivity, 68.6% of specificity and 27.636 of odds ratio.

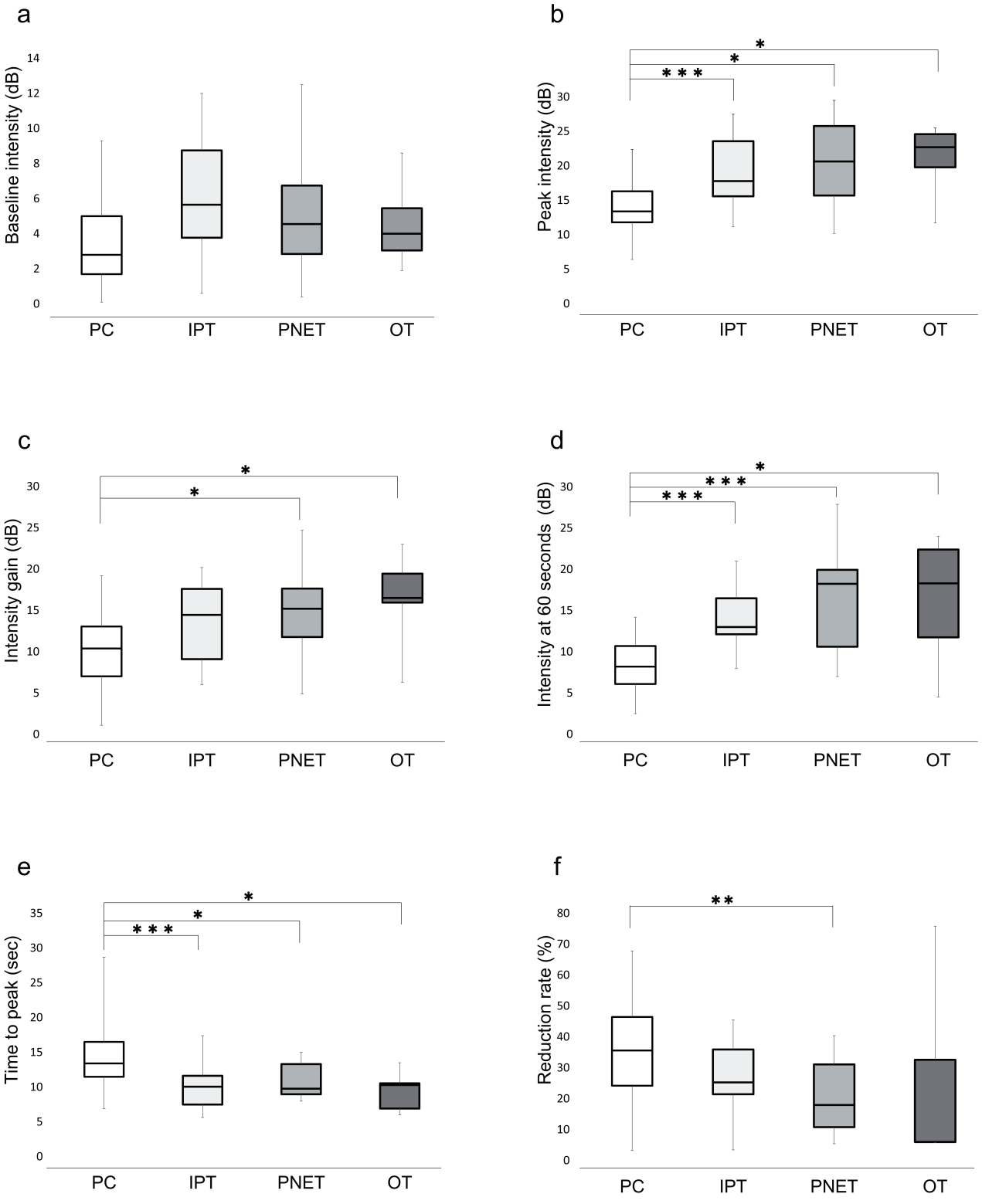

Figure 2. Comparison of TIC parameters among four types of pancreatic tumors.
TIC parameters include baseline intensity (a), peak intensity (b), intensity gain (c), intensity gain at 60 seconds (d), time to peak (e) and reduction rate (f). PC: pancreatic carcinoma (n=41). IPT: inflammatory pseudotumor (n=14). PNET: pancreatic neuroendocrine tumor (n=14). OT: other tumors (n=7). Values shown are median (horizontal line), 25th and 75th percentiles (box) and range (vertical lines). *: $P<0.05$, **: $P<0.01$, ***: $P<0.005$ (Steel-Dwass test).

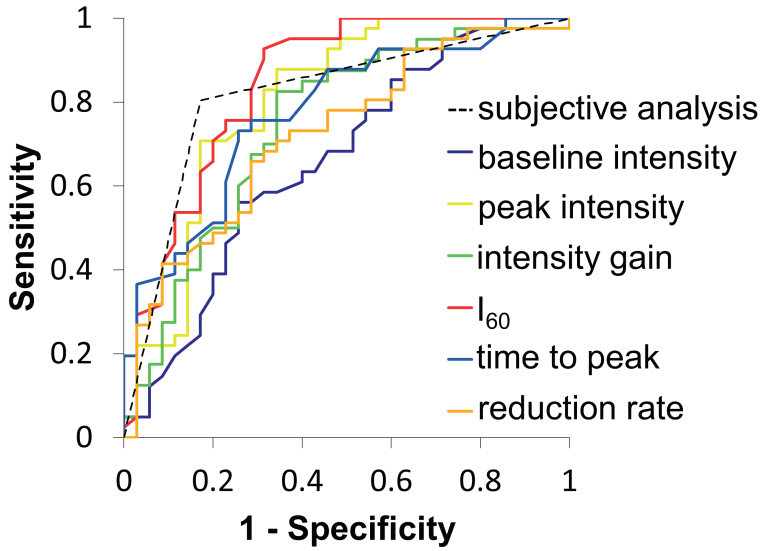

Figure 3. Receiver operating characteristic curves for the diagnostic ability of TIC parameters of CH-EUS for pancreatic carcinoma.
The areas under the curve for subjective analysis, baseline intensity, peak intensity, intensity gain, I_{60} (intensity gain at 60 seconds), time to peak and reduction rate were 0.817, 0.664, 0.810, 0.751, 0.845, 0.777 and 0.725, respectively.

Table 2. ROC analysis of quantitative perfusion data from CH-EUS for the diagnosis of pancreatic carcinoma

Parameter	AUC	Cut-off	Sensitivity	Specificity	Odds ratio
subjective analysis	0.817	–	80.4%	82.9%	19.938
baseline intensity	0.664	3.2 dB	56.1%	74.3%	3.691
peak intensity	0.810	15.1 dB	70.7%	82.9%	11.681
intensity gain	0.751	13.7 dB	82.5%	65.7%	9.036
I_{60}	0.845	12.4 dB	92.7%	68.6%	27.636
time to peak	0.777	12.0 s	73.2%	74.3%	7.879
reduction rate	0.725	31.4 %	65.9%	71.4%	4.821

I_{60} : intensity gain at 60 seconds. AUC : area under the curve.

Discussion

In this study, various TIC parameters were assessed in pancreatic masses and compared in terms of ability to diagnose pancreatic carcinoma. Pancreatic carcinoma exhibited markedly different TIC patterns from the other tumor types. This clinical observation suggests quantitative analysis with contrast-enhanced harmonic EUS is useful for differential diagnosis of pancreatic masses. There have been some reports on the usefulness of a quantitative analysis of CH-EUS data, using TICs, in the diagnosis of pancreatic tumors. Seicean *et al.* compared pancreatic carcinomas and mass-forming chronic pancreatitis in terms of contrast medium uptake and concluded that the uptake ratio (tumor / surrounding tissue) was significantly lower in adenocarcinoma than in pancreatitis, although they analyzed data from only 30 patients.[10] Gheonea *et al.* measured various parameters including AUC, time to peak, maximum intensity and median intensity; in their report, the sensitivity and specificity were remarkably high (93.75% and 89.47%), although it was unclear which parameter was used for diagnostic analysis and the cut-off values for each parameter were not reported.[11] Imazu *et al.* found that autoimmune pancreatitis (n=8) and pancreatic carcinoma (n=18) had markedly different TICs.[8] Intensity gain of pancreatic mass lesions in patients with autoimmune pancreatitis was significantly higher than in patients with pancreatic carcinoma (accuracy, 100%). Saftoiu *et al.* reported usefulness of TIC and automated computer-aided diagnostic system based on their TIC data.[12] Matsubara *et al.* compared the reduction rate from the peak at 1 minute between pancreatic carcinomas (n=48), inflammatory pseudotumors (n=27) and pancreatic neuroendocrine tumors (n=16).[9] In their report, the reduction rate was the greatest in pancreatic carcinoma followed by mass-forming pancreatitis, autoimmune pancreatitis, and pancreatic neuroendocrine tumor ($P<0.05$). However, it is difficult to determine the diagnostic accuracy with quantitative analysis because these previous reports enrolled patients with different kinds of diseases, and employed different kinds of parameters. Therefore, our study included all solid tumors and assessed various parameters. There are several parameters for diagnosing pancreatic tumors. From these previous reports, [7-12] we chose baseline intensity, peak intensity, intensity gain, I_{60}, time to peak, and reduction rate as parameters for the TIC analysis. Peak intensity, intensity gain and I_{60} were significantly lower in the pancreatic carcinoma group than in the other groups, while time to peak and reduction rate were higher. These results suggest that pancreatic carcinomas have a slower blood inflow velocity and faster blood outflow velocity, and may reflect the fact that most of these carcinomas have a rich fibrous stroma that usually accounts for the observed hypo-vascularity.[14-16] However, there are no reports on which TIC parameter represents vessel volume or fibrosis. Further CH-EUS studies on tumors that are then all surgically resected are needed to clarify the histological meaning of the six TIC parameters used in the present study.

The current study first compared diagnostic ability of different kinds of TIC parameters using ROC analysis and determined the most reliable TIC parameter. ROC analysis revealed that the best parameter for diagnosing pancreatic carcinoma was I_{60}. When the cut-off for I_{60} was set at 12.4 dB, the sensitivity, specificity

were 92.7%, 68.6%, respectively. I_{60} showed higher sensitivity than subjective analysis. Eight out of 38 (21%) correctly diagnosed as pancreatic carcinoma by I_{60} showed iso-enhancement pattern by subjective analysis. Despite evaluation by experts, subjective analysis can be difficult to distinguish from iso-enhancement pattern or hypo-enhancement pattern. Therefore, the case of iso-enhancement pattern might be a good adaptation of TIC analysis.

Although, I_{60} was lower than Subjective analysis in specificity, I_{60} was higher than Subjective analysis in ROC-AUC. ROC analysis can change cut off value in all parameters. When the patient cannot receive EUS-FNA because of anticoagulation therapy or intervening vessel, higher specificity is required.

In the present study, a single ROI was placed over the pancreatic tumor. Some reports used a second, parenchymal ROI in the surrounding tissue, and measured the value in the tumor relative to surrounding tissue. [10, 11] However, when the tumor is large, it is not possible to set two ROIs (the tumor and the surrounding tissue) on a fixed single image. Moreover, setting two ROIs may lead to selection bias. Therefore, we chose a single ROI and placed it so as to cover as large as possible an area of the tumor, because the intensity in the tumor is heterogeneous.

Our study has several limitations. A fixed single image without sweep scan technique has to be used in order to obtain the time intensity curve. If subjective observation is employed, sweep scanning of the whole lesion with the transducer allows comparison of the tumor and the surrounding tissue in relatively large tumors. It was a retrospective study at a single center, and the sample number was relatively small. Also, some tumors were diagnosed only from samples obtained by EUS-FNA and follow-up with imaging. A multicenter, prospective study using more cases, diagnosed only with surgical resection, is needed to clarify the diagnostic utility of quantitative perfusion analysis with CH-EUS.

In conclusion, pancreatic carcinoma exhibited markedly different TIC patterns from inflammatory pseudotumors, pancreatic neuroendocrine tumors and other pancreatic tumors. Thus, quantitative perfusion analysis is useful to differentiate pancreatic carcinomas from other pancreatic masses. Intensity at 60 seconds is the most accurate parameter.

ACKNOWLEDGMENTS

The authors have no conflicts of interest or financial ties to disclose. This study was supported by grants from the Japan Society for Pro1motion of Science (No. 22590764 and 25461035).

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