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TOPIC HIGHLIGHT

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Clinical oncology for pancreatic and biliary cancers: Advances and current limitations

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Abstract

In the early 2000s, the main stream of endoscopic ultrasonography (EUS) changed from a mechanical scanning method to electronic radial or linear scanning methods. Subsequently, useful applications in trans-abdominal ultrasonography came within reach of EUS. In particular, contrast-enhanced EUS (CE-EUS) and EUS-elastography became cutting-edge diagnostic modalities for pancreatic disorders. Each type of pancreatic disorder has characteristic hemodynamics. CE-EUS uses color Doppler flow imaging and harmonic imaging to classify pancreatic lesions. EUS-elastography can assess tissue hardness by measuring its elasticity. This parameter appears to correlate with the malignant potential of the lesions. Tissue elasticity studies can provide information on both its pattern and distribution. The former is the conventional method of morphological diagnosis, but it is restricted to observations made in a region of interest (ROI). The latter is an unbiased analysis that can be performed by image analysis software and is theoretically constant, regardless of the ROI. Though EUS-fine needle aspiration (FNA) is also a very useful diagnostic tool, there are several limitations. Diagnostic EUS-FNA of pancreatic cystic lesions has marginal utility mainly due to low sensitivity. Therefore, in particular, endoscopists should keep this limitation in mind.

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INTRODUCTION

Endoscopic ultrasonography (EUS) is thought to be one

of the most reliable and efficient diagnostic modalities for the pancreato-biliary diseases, especially when the diagnostic targets are limited to the locoregional area. Recently, electronic scanning EUS (both electronic radial and curved linear types) has been introduced in clinical settings and many applications in the field of transabdominal ultrasonography (US) are being used. Here, we review the current situation and limitations of EUS in the diagnosis of pancreatic diseases, mainly based on our experiences.

RECENT PROGRESS IN EUS

Recent progress in EUS is summarized in Figure 1. Mainstream EUS was a mechanical radial scanning method (MR-EUS) until the early 2000s. In the early 2000s, we first developed the endosonoscope with an electronic radial scanning method[1,2]. From that time, both electronic radial and linear (curved linear) type EUS was employed using the same utilities as those used with a high-end transabdominal ultrasound apparatus.

Despite many new emerging applications, the essence of ultrasonographic imaging still remains associated with B-mode image quality. In fact, conventional B-mode EUS images have been considered the most sensitive for diagnosing pancreatic tumors, permitting the detection of tumors smaller than 1 cm with the limitation of operator dependency[3-5]. Therefore, an important step in the development of new electronic radial scanning EUS (ER-EUS) was to keep the B-mode image quality at the same level as provided by EUS with a mechanical radial scanning method. A case of branch-duct type intraductal papillary mucinous neoplasm (IPMN; adenoma in this case) is shown in Figure 2. The leftmost image obtained by MR-EUS could not depict the mural nodule due to a near field artifact. A mural nodule is recognized as the most reliable predictor of diagnosing malignancy or benignancy[6]. From this standpoint, MR-EUS may not be useful for the diagnosis of IPMN. On the other hand, the right two images obtained by ER-EUS revealed the mural nodule, which was about 10 mm in diameter. The rightmost image was made more sophisticated by tissue harmonic imaging (THI) technology, which results in clearer ultrasonographic images by omitting acoustic artifacts. B-mode image quality, including that of THI modified images from ER-EUS, proved to be even better than the image quality from MR-EUS, which we considered as encouraging results.

On the basis of the above, a review of the efficacy and limitations of EUS with a variety of applications, listed in Figure 1, is offered here.

CONTRAST-ENHANCED EUS

Diagnostic modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), need the combination of non-contrast and contrast-enhanced images to provide an accurate diagnosis. EUS makes use of color/power Doppler flow imaging and harmonic imaging and, therefore, diagnosis with vascular information is possible.
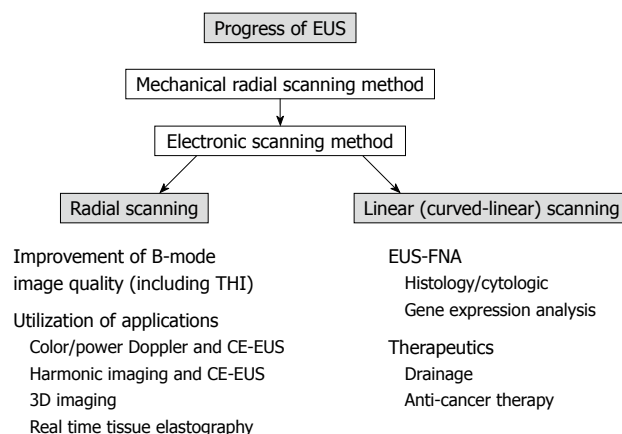
EUS is performed in the left lateral position under di-

Figure 1 **Progress of endoscopic ultrasonography.** In the early 2000s, mainstream use of endoscopic ultrasonography (EUS) changed from a mechanical radial scanning method to an electronic radial or electronic linear scanning method, which enabled the endosonography to make use of many applications. FNA: Fine needle aspiration; THI: Tissue harmonic imaging; CE-EUS: Contrast-enhanced EUS; 3D: Three-dimensional.

azepam-induced sedation with heart rate monitoring. The electronic radial scanning mode is employed in all cases. An electronic radial-type endoscope and the ultrasound observation system EG-3670URK (Pentax Co., Ltd., Tokyo, Japan) with Hi Vision 900 (Hitachi Co., Ltd., Tokyo, Japan) are used in EUS (Figure 3), or a GF-UE260-AL5 (Olympus Co., Ltd., Tokyo, Japan) with Prosound α-10 (Aloka Co., Ltd., Tokyo, Japan, Figure 4). The former employs a wide-band pulse inversion method (WPI) with the mechanical index (MI) automatically set at 0.16-0.23 in accordance with the focal point. The latter employs the extended pure harmonic detection method (ExPHD) with the MI set at 0.25. A single focus is set on the distal side of the target lesion. WPI and ExPHD are essentially identical to each other in that both methods transmit the two reversal phased waves at the same time to cancel the fundamental wave, resulting in enhancement of the second harmonics. To perform contrast-enhanced EUS (CE-EUS) and study tissue hemodynamics, we first image the pancreas and targeted lesions with B-mode EUS and then administer Levovist® (Nihon Schering Co., Ltd., Tokyo, Japan) or Sonazoid® (Daiichi Sankyo Co., Ltd., Tokyo, Japan) through a peripheral vein[7]. The use of Sonazoid® for pancreatic diseases was approved by the Institutional Review Board of our institute, and was used after obtaining written informed consent from the patients.

In general, there are two main categories of CE-EUS, the first is contrast-enhanced color/power Doppler imaging and the second is contrast-enhanced harmonic imaging[7-9]. CE-EUS using a Doppler method provides the image that divides the target into vascular-rich areas and hypovascular areas clearly. CE-EUS using harmonic imaging methods presents a more detailed view of the vasculature of the target lesions. In addition, it gives quantitative information, such as a time-intensity curve showing the change of an echo-intensity over time. Those two methods should be selected in accordance with the intended use.

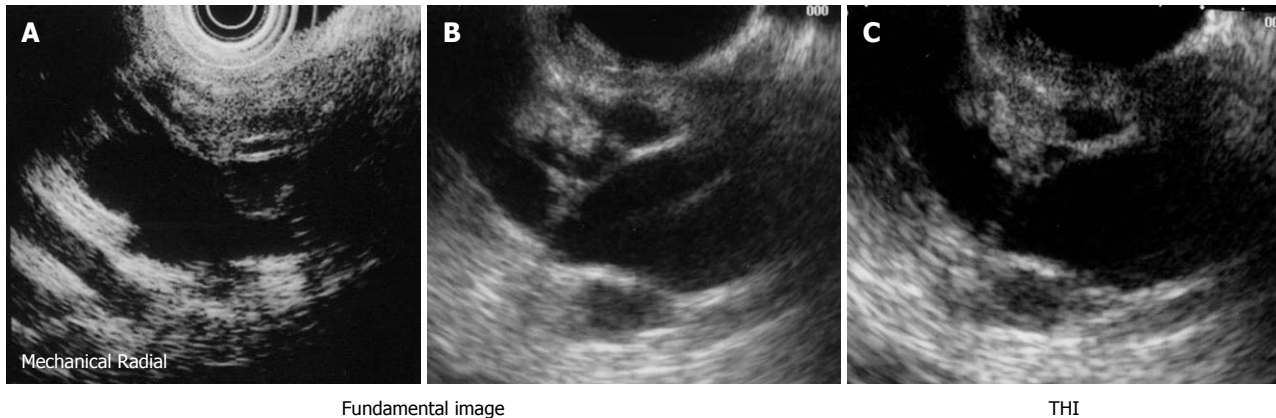Figure 5 shows images of a pancreatic endocrine tu-

Figure 2 Branch-duct type intraductal papillary mucinous neoplasm. A: An mechanical radial scanning endoscopic ultrasonography (EUS) image could not depict the mural nodule due to a near field artifact; B, C: Electronic radial scanning EUS images revealed a mural nodule about 10 mm in diameter; C: The image was made more sophisticated by tissue harmonic imaging (THI) technology, which brought a clearer ultrasonographic image by omitting acoustic artifacts.
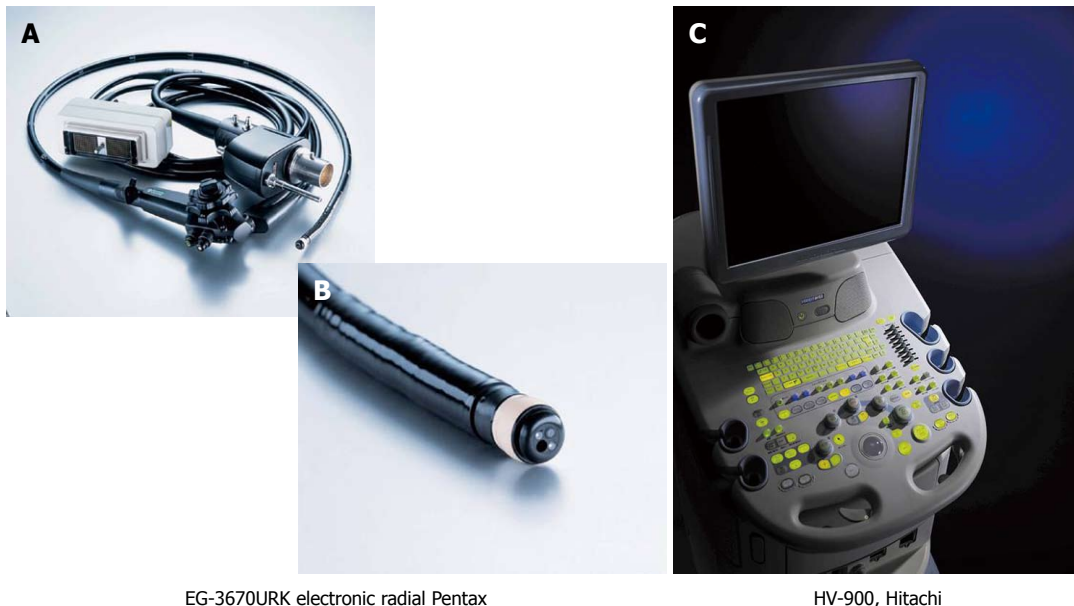

Figure 3 Endoscope and ultrasound machine (Setting-1). A, B: The images indicate the whole view of the Pentax endosonoscope (EG-3670URK) and the tip of the scope; C: The image shows the ultrasound machine (HV-900, Hitachi, Japan).

mor. Plain color Doppler EUS (non-enhanced color Doppler EUS) only showed few color signals inside the clearly delineated iso-echoic tumor (left image). In contrast, there were abundant color signals inside the tumor, indicating it was hypervascular. B-mode imaging combined with CE-EUS imaging provides an important clue to the diagnosis of pancreatic endocrine tumors. What is important to remember is that plain color Doppler EUS images give only limited information on color signals.

Figure 6 presents CE-EUS images using harmonic methods. There was a hypoechoic mass at the pancreatic body with an irregular margin (pre-enhanced). The leftmost image of the bottom indicated an increase in the echo-intensity close to that of the surrounding normal parenchyma. The center and rightmost images were those obtained 3 min and 5 min after injection of contrast-enhancing agents. The tumor became hypoechoic (i.e. hypovascular) compared with surrounding tissues. Moreover, the time-intensity curve showed

quantitative information on the changing echo-intensity in each region of interest (ROI, Figure 7). This case was, of course, one example of pancreatic ductal adenocarcinoma. Other types of enhanced pattern can be studied as well[10].

In summary, these two methods are both useful and efficient methods of diagnostic imaging. We must be careful to employ the appropriate method for each case.

THREE-DIMENSIONAL IMAGING

Electronic scanning brought three-dimensional (3D)-EUS imaging into reality. Figure 8 shows an IPMN with high-grade dysplasia case. There are numerous papillary growths in the IPMN. The volume-rendering images (Figure 8B) reflect the surface architecture with reality. Furthermore, the combination of volume-rendering imaging and color Doppler imaging may be more useful in the diagnosis of the malignancy potential of IPMN (Figure 8C). At this point,

GF-UE260-AL5 electronic radial Olympus   ProSound α-10, Aloka

Figure 4 Endoscope and ultrasound machine (Setting-2). A-C: The left three images indicate the whole view of the Olympus endosonoscope (GF-UE260-AL5) and the tip of the scope (both bare tip and tip with inflated balloon images are presented.); D: The image shows the ultrasound machine (ProSound α-10, Aloka, Japan).
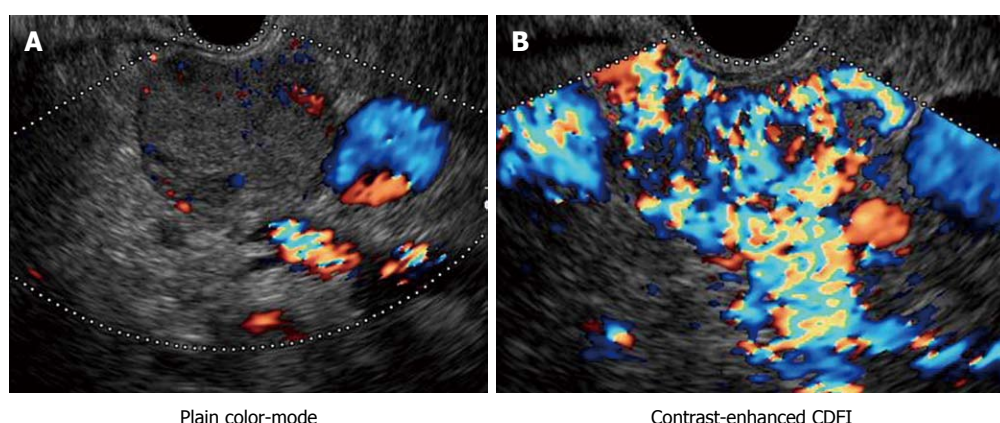

Plain color-mode   Contrast-enhanced CDFI

Figure 5 Endocrine tumor of the pancreas. A: Plain color (non-enhanced color) Doppler endoscopic ultrasonography (EUS) only showed few color signals inside the clearly delineated iso-echoic tumor; B: In contrast, there were abundant color signals inside the tumor, indicating it was hypervascular. B-mode image combined with contrast-enhanced EUS images provided an important clue for the diagnosis of pancreatic endocrine tumors. Levovist® was used in this case.

there is no positional information in the images obtained with our system. 3D-EUS may be more useful and informative with the addition of precise positional information.

EUS-ELASTOGRAPHY

In addition to B-mode observation, the diagnosis of pancreatic disorders can also be aided by evaluating tissue hemodynamics. Elastography has the potential to provide new information that differs from B-mode imaging or hemodynamic information, but without the need for contrast medium[11].

Generally, tissue hardness is thought to correlate with malignant potential; malignant tumors are harder than those that are benign. Changes in tissue elasticity are generally correlated with pathological phenomena. Many cancers, such as scirrhous carcinoma of the breast, appear as extremely hard nodules that are a result of increased stromal density. Other diseases involve fatty and/or collagenous deposits that increase or decrease tissue elasticity[12]. On the basis of this concept, several techniques to evaluate tissue hardness, also called tissue elastic imaging, have been developed[13,14]. Tissue elastic imaging with MRI or CT has been introduced for clinical use but, in this review, we will focus on tissue elastic imaging with an ultrasonographic approach that is named real-time tissue elastography (Hitachi Co., Ltd.) and is combined with EUS. The principles of elastography can be explained by using a spring model[11,12]. Thus, when a one-dimensionally connected hard spring and soft spring are compressed, the hard spring is negligibly deformed, but the soft spring is compressed. This difference in deformation results in differences in displace-
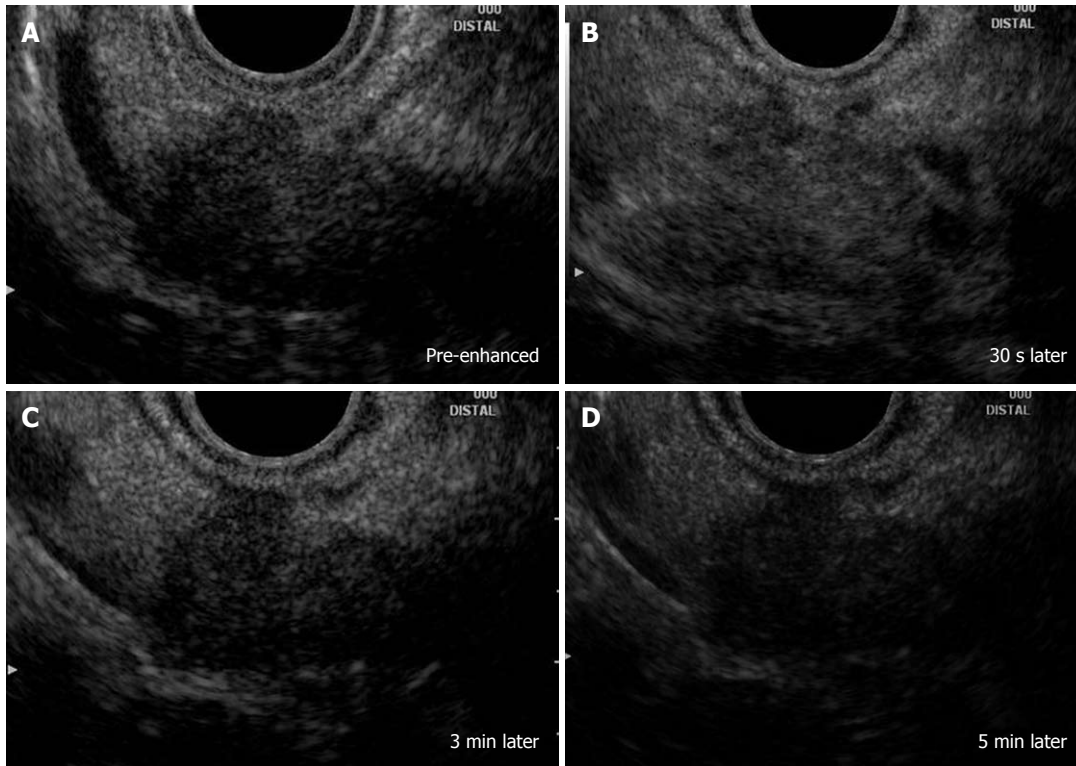
Figure 6 Pancreatic ductal adenocarcinoma. A: There was a hypoechoic mass at the pancreatic body with an irregular margin (pre-enhanced); B: The image indicated an increase in echo-intensity close to that of the surrounding normal parenchyma (30 s later after injection of Sonazoid); C, D: The center and the rightmost images were obtained 3 min and 5 min after injection. The tumor became hypoechoic (i.e. hypovascular) compared with surrounding tissues.
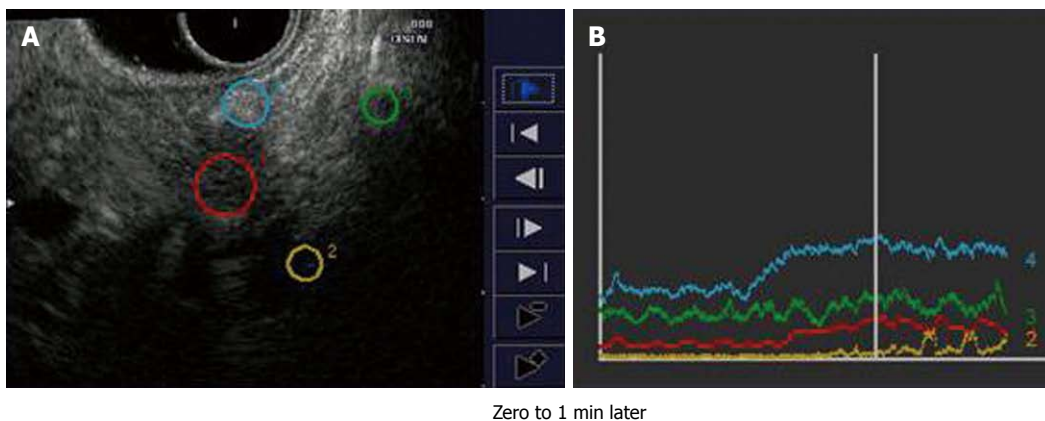

Zero to 1 min later

Figure 7 Time intensity curve for pancreatic ductal adenocarcinoma. A, B: Both settings (settings 1 and 2) can provide a quantitative analysis graphic curve of the changing echo-intensity named the "time intensity curve".

ment among various areas, and the amount of distortion obtained by spatial differentiation of this displacement distribution provides elasticity information.

One should appreciate that real-time tissue elastography provides information about the distributed pattern of tissue hardness as well as hardness at a specific point. The information regarding hardness at a specific point is classified further into 2 categories: (1) pattern recognition; and (2) quantitative assessment (strain ratio) (Table 1).

Figure 9 shows a case of pancreatic ductal adenocarcinoma. The EUS-elastographic image (left side) shows a markedly hard area at the site of the low-echo tumor area (right side) and distribution of slightly soft spots in the

Table 1 Interpretation of real time tissue elastography

Hardness at the specific point
Pattern recognition
Quantitative assessment: strain ratio
Distributed pattern of tissue hardness

interior. Histopathologic examination confirmed that the hard area contained a large amount of fibrous tissue, and the internal soft spots were aggregations of atypical ducts (of various sizes).

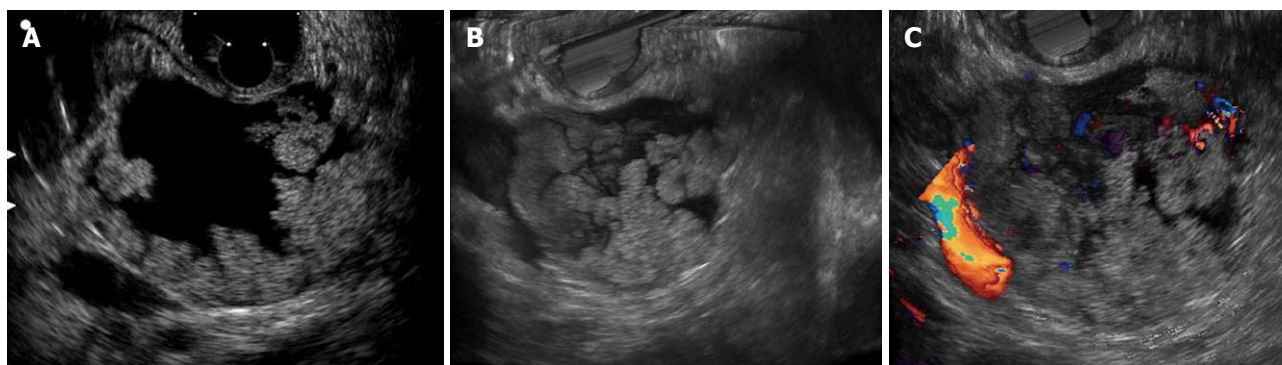EUS-elastography provides additional important infor-

Figure 8 Image of a intraductal papillary mucinous neoplasm with high-grade dysplasia. A: There are numerous papillary growths in the intraductal papillary mucinous neoplasm (IPMN) maximum intensity projection image; B: The volume-rendering images reflect the surface architecture with reality; C: The combination of volume-rendering imaging and color Doppler imaging may be more useful in the diagnosis of the malignant potential of the IPMN.
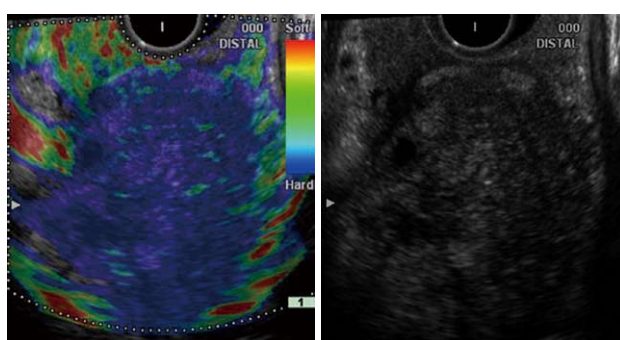

Figure 9 Pancreatic ductal adenocarcinoma. Endoscopic ultrasonography-elastographic image (left side) shows a markedly hard area at the site of the low-echo tumor area (right side) and distribution of slightly soft spots in its interior. Histopathologic examination confirmed that the hard area contained a large amount of fibrous tissue, and the internal soft spots were aggregations of ducts atypical (of various sizes).

mation relating to hardness; that is, the distributed pattern (Table 1). Regardless of ROIs, the distributed pattern is theoretically a constant. The distributed pattern of hardness in a case of chronic pancreatitis is analyzed in Figure 10. The prototype image analysis software used here extracted various features from real-time tissue elastography images. It converted the red-green-blue value inside the ROI of the elastography image into relative strain value and calculated other features of the elastography image, such as the mean of relative strain value, the standard deviation of the relative strain value, and the proportion of blue (low strain) region in the analysis region, and determined the complexity of the blue (low strain) region in the analysis region [(Perimeter of blue region)2/(Area of blue region)]. With this software (produced in cooperation with Hitachi Co., Ltd.), we can demonstrate the uniformity, or lack thereof, of a target lesion and quantify a number of objective parameters of the distribution of hardness described above.

The fourth tissue characterization, following B-mode imaging, color/power Doppler imaging and CE-EUS, must be EUS-elastography. Nevertheless, what we must keep in mind is that represented colors in this system are relative in each ROI. We cannot compare the images among individuals precisely. An absolute value or image with elastic information is eagerly awaited.

EUS-FINE NEEDLE ASPIRATION RELATED PROCEDURES (SPECIAL FOCUS ON THE DIAGNOSIS OF CYSTIC NEOPLASMS)

The usefulness of EUS-fine needle aspiration (FNA) has been well recognized in the diagnosis of intramural lesions (e.g. gastrointestinal stromal tumor: GIST, leiomyoma) and extramural lesions, such as pancreatic tumors, lymph nodes and mediastinal masses. In 1995, Hammel *et al*[15] reported its usefulness for the differential diagnosis of cystic lesions of the pancreas by analyzing cyst fluid collection obtained by transabdominal US guided FNA. In the early 2000s, enthusiasm for preoperative fluid collection analysis reported positive results. Recently, however, there have been reports[16,17] that preoperative analysis of the pancreatic cyst fluid obtained by EUS-FNA has marginal utility. Moreover, dissemination due to EUS-FNA was reported[18].

According to ASGE guidelines (on the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas)[19], it was recommended that aspirated cyst contents may be submitted for cytologic, chemical and/or tumor marker analysis.

As to cytology, ASGE guidelines indicated that FNA can provide material for a cytologic diagnosis in up to 80% of cases of pancreatic cystic lesions, and the accuracy for diagnosing various cystic lesions by EUS-FNA was 54% to 97%. In addition, ASGE guidelines stated that malignancy within a cystic neoplasm can be identified by cytology with 83% to nearly 100% specificity, despite marginal sensitivity varying from 25% to 88%. Moreover, ASGE guidelines pointed out that low sensitivities, combined with the reported results of chemistry analysis and tumor markers, had broad ranges, which made interpretation difficult. There have been several reports[16,17] related to this issue with negative tones. Furthermore, concern for potential dissemination caused by EUS-FNA of pancreatic cystic neoplasms[18] still remains unresolved. Enthusiastic exploration may be important, but the attempts in this field cannot be fully encouraged at this time.

DISCUSSION

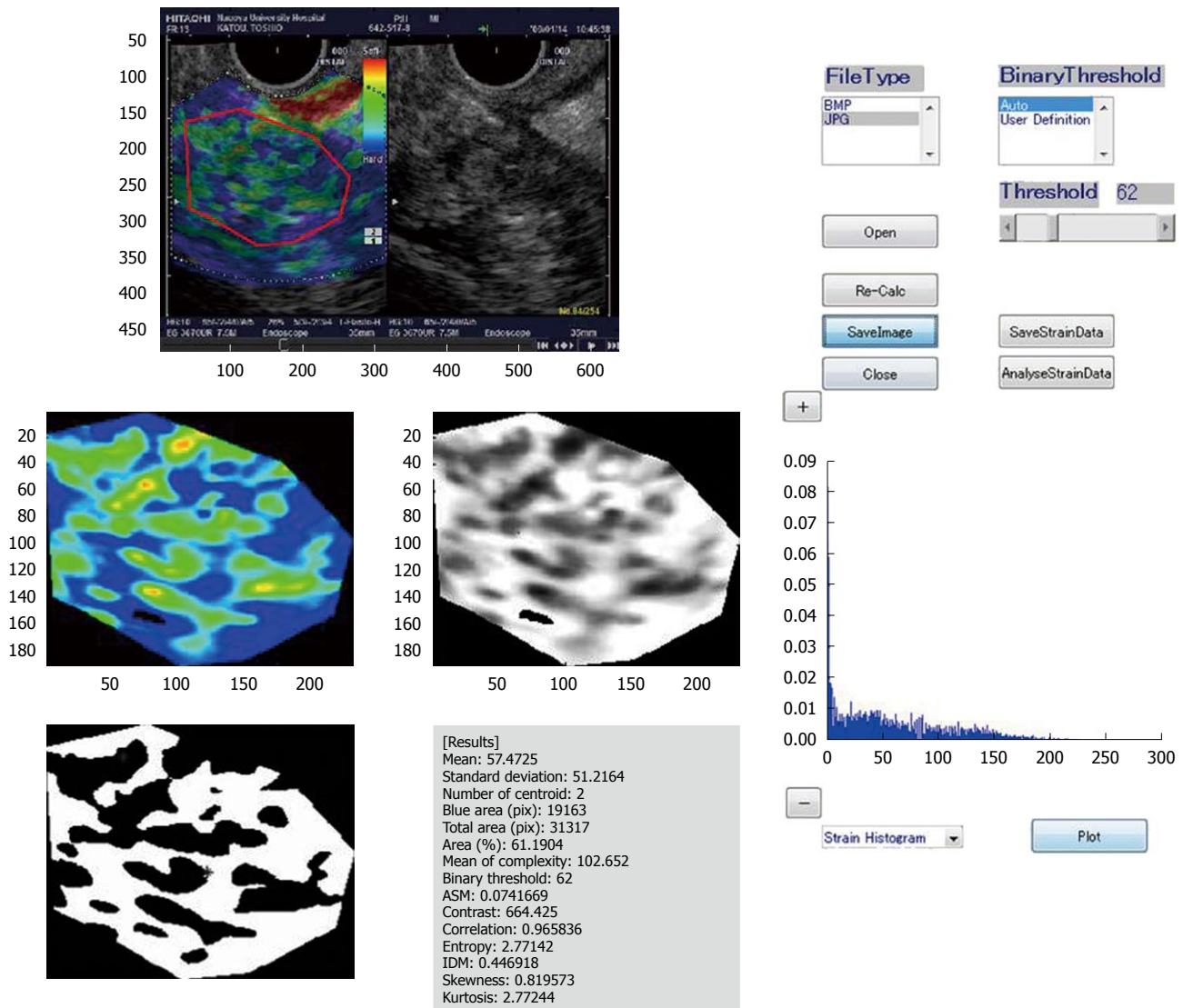In this review, we have described the potential of CE-

Figure 10 Prototype image analysis software (chronic pancreatitis in this case). The prototype image analysis software used here extracts various features from real-time tissue elastography images. It converts the red-green-blue value inside the region of interest of the elastography image into a relative strain value and calculates other features of the elastography image, such as the mean of the relative strain value, the standard deviation of the relative strain value, and the proportion of the blue (low strain) region in the analysis region, and determines the complexity of the blue (low strain) region in the analysis region [(Perimeter of blue region)2/(Area of blue region)].

EUS (both Doppler and harmonic methods), 3D-EUS, EUS-elastography and EUS-FNA to be used as cutting-edge diagnostic modalities. In addition, we summarized our experience with these technologies. The performance of EUS depends on both the efficiency of an endoscope and ultrasonographic technologies.

In 2003, we first developed the endosonoscope with electronic radial scanning in cooperation with PENTAX (PENTAX Co., Ltd., Tokyo, Japan) to combine ultrasound techniques that were being used for transabdominal US. An electronic scanning method made it possible for us to perform CE-EUS, 3D-EUS and EUS-elastography. Tissue characterization by EUS was only made by B-mode imaging before the advent of CE-EUS, 3D-EUS and EUS-elastography. CE-EUS can now provide hemodynamic analysis of pancreatic disorders at the same level as CT or MRI.

EUS-elastography has introduced a new form of pathologic analysis; that is, tissue elasticity. Tissue elasticity as detected by this system can be divided into 2 major categories. One is pattern recognition, which has been the conventional method of morphologic diagnosis. Importantly, the image of EUS elastography indicates the relative value in a ROI, so the same lesion might display different colors in a different ROI. This is a limitation of EUS-elastography. The other is the distribution of tissue elasticity. With the prototype image analysis software, we can now capture and analyze features of real-time tissue elastography by using computer software. Theoretically, this will limit interpretation bias and provide a measure of pattern distribution that is constant and independent, regardless of ROIs.

CE-EUS and EUS-elastography, as well as other methods, have the potential to provide clinical utility for the diagnosis of pancreatic disorders, however, additional studies and greater experience are needed before their place in our diagnostic armamentarium can be fully understood.

TECHNICAL TERMS FOR BETTER UNDERSTANDING

Near field artifact (Otherwise known as reverberation artifact): Reverberation is the persistence of sound in a particular space after the original sound is removed. Reverberation artifact is created when a sound is produced in an enclosed space causing a large number of echoes to build up and then slowly decay as the sound is absorbed by the walls and air.

THI: Imaging method produced by tissue harmonic component which is generated during the propagation of ultrasound in the media such as a body tissue.

WPI® (wideband pulse inversion: Hitachi Medico, Tokyo, Japan) and ExPHD® (extended pure harmonic detection: Aloka, Tokyo, Japan): Most of the same technique of ultrasound imaging. They work by sending two trains of pulses out of phase to each other, and summing the returning echoes. The signal from tissue cancels, whereas the signal from the collapsing or vibrating microbubbles is recorded.

MI: MI is used as an estimate for the degree of bioeffects which a given set of ultrasound parameters will induce. A higher mechanical index means a larger bioeffect. Currently the FDA stipulates that diagnostic ultrasound scanners cannot exceed a mechanical index of 1.9.

Volume-rendering image: Volume rendering is a technique used to display a 2D projection of a 3D discretely sampled data set.

Relative strain value: Real-time tissue elastography® represents 256-stepwise colors corresponding to the relative strain values in the ROI.

MIP: A MIP is a computer visualization method for 3D data that projects in the visualization plane the voxels with maximum intensity that fall in the way of parallel rays traced from the viewpoint to the plane of projection.

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