Interview report and white paper for Liver package

Dialogue on the future of Ultrasound for Liver Disease led by ATI

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Canon Medical Systems' approach in the development of quantitative software applications for Diffuse Liver Diseases

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Introduction

Attenuation Imaging (ATI) is an invaluable method for measuring hepatic fat to identify high-risk patients with fatty liver. Dr. Takashi Kumada and Dr. Hiroko Iijima share their thoughts on ultrasound diagnostics.

Management of patients before they develop liver disease

Dr. Iijima: Back when I became a physician, hepatitis C virus (HCV) infection hadn't yet been discovered and large numbers of patients were found to have hepatic cancer. Although these cancers were often diagnosed and resected in the relatively early stages, with a tumor size of 3 cm or so, many of the patients died from hepatic cancer. My hope to be able to detect hepatic cancer in the earliest possible stages was one of the triggers that led me to the field of hepatology.

Dr. Kumada: Back when I was in medical school, I initially thought I'd become a pediatrician. But I later met an outstanding physician who was the director of the gastroenterology department at the hospital where I did my residency training. The instruction and guidance I received from this wonderful physician stimulated my young, inquisitive mind and caused me to switch to gastroenterology. Back in the days when we became physicians, there were hardly any interventional methods for the treatment of liver disease. My sad memory is that most patients who were hospitalized with ascites and jaundice died within a month or so. If we performed autopsy in these patients, we almost always found hepatic cancer. Back then, these patients had an extremely poor prognosis, with mortality rates comparable to those we see for pancreatic cancer today. I thought something had to be done to fight this problem. That's why I set my sights on hepatology.

Dr. Iijima: With regard to hepatic cancer, the situation changed dramatically with the introduction of the MRI contrast agent Gd-EOB-DTPA and the development of EOB-MRI. Dr. Kumada, as an expert in EOB-MRI, could you tell us a little more about it?

Dr. Kumada: EOB-MRI was introduced in the fall of 2007, and since 2008, I've performed many examinations using this imaging method. The introduction of EOB-MRI was truly revolutionary because it allowed us to visualize tumor masses that couldn't be clearly depicted by ultrasound. Based on the images obtained by EOB-MRI, we could go back and look at the ultrasound images again, identify tumor masses that were very difficult to detect by ultrasound alone, perform biopsy, and determine whether the tumors were malignant based on morphological findings. At first, the introduction of EOB-MRI led to some confusion in medical practice because interpretation was subjective and tended to vary between physicians. Nevertheless, it can't be denied that EOB-MRI brought about great changes in cancer diagnosis.

Dr. Iijima: For example, in patients with hepatitis B virus (HBV) infection, because the regenerative nodules seen in the liver may be very large, it can be difficult to determine whether they are hepatic tumors in B-mode images. The risk of such nodules developing into cancer may increase over time, and the introduction of EOB-MRI has made it easier to determine the appropriate timing for follow-up examination. This has all been made possible by your outstanding research and excellent papers, Dr. Kumada. Based on validated clinical evidence, I can determine the most suitable schedule for follow-up examination,

Takashi Kumada, MD (right) from Gifu Kyoritsu University and Hiroko Iijima, MD (left) from Hyogo College of Medicine Hospital

explaining to the patient, "If the tumor becomes this much bigger after a certain period of time, it means that the tumor is likely to be malignant, and to detect such changes at the proper time, the next follow-up should be around this date."

Dr. Kumada: The introduction of EOB-MRI has also led to some changes in the clinical role of ultrasound. The Fusion function has been developed to evaluate the nodules identified by EOB-MRI. This function allows ultrasound images and MRI images to be combined and viewed with real-time synchronization.

Dr. Iijima: As reflected in the latest guidelines for hepatic cancer treatment, EOB-MRI is the most effective modality for detecting hepatic cancer available today. However, ultrasound remains the most reliable modality for evaluating blood flow. As also reflected in the guidelines, contrast enhanced ultrasound is the best method for detecting tumors with high blood flow.

Dr. Kumada: Because only a certain amount of contrast agent can be administered in EOB-MRI, there are cases in which the target can't be fully enhanced if the timing isn't just right. If ultrasound is also performed in such patients, the findings often show the accumulated contrast. Based on the ultrasound findings, we can determine whether the tumor needs to be treated. To my mind, the clinical roles of ultrasound and EOB-MRI are complementary. The two modalities work well together, with each having its own strengths and weaknesses.

Dr. Iijima: Particularly in regions where motion artifacts tend to occur, ultrasound is truly essential.

Dr. Kumada: EOB-MRI isn't good for visualizing the left lobe, and artifacts are often seen. Ultrasound is sometimes the only option due to its high temporal resolution.

Establishment of diagnostic criteria for hepatic fibrosis

Dr. Iijima: Currently, my main focus is the evaluation of hepatic fibrosis. Dr. Kumada is also the Chairperson of the committee for developing new methods for the evaluation of fatty liver of the Japan Society of Ultrasonics in Medicine. This committee is focusing on the establishment of noninvasive diagnostic methods for diseases such as fatty liver and nonalcoholic steatohepatitis (NASH), which have recently been attracting a great deal of attention. But there are still many challenges to be overcome before the best method can be firmly established.

Dr. Kumada: At first, Transient Elastography (TE) was the only method available for measuring the degree of hepatic fibrosis. Later, Shear Wave Elastography (SWE) was developed and installed in ultrasound systems from various manufacturers, including Canon Medical Systems. What's so remarkable about your work, Dr. Iijima, is that you've installed a wide variety of ultrasound systems produced by almost every manufacturer in the examination rooms at the Hyogo College of Medicine Hospital, and you've conducted extensive comparison studies. You used these systems to examine patients and then performed analysis to compare the data obtained using

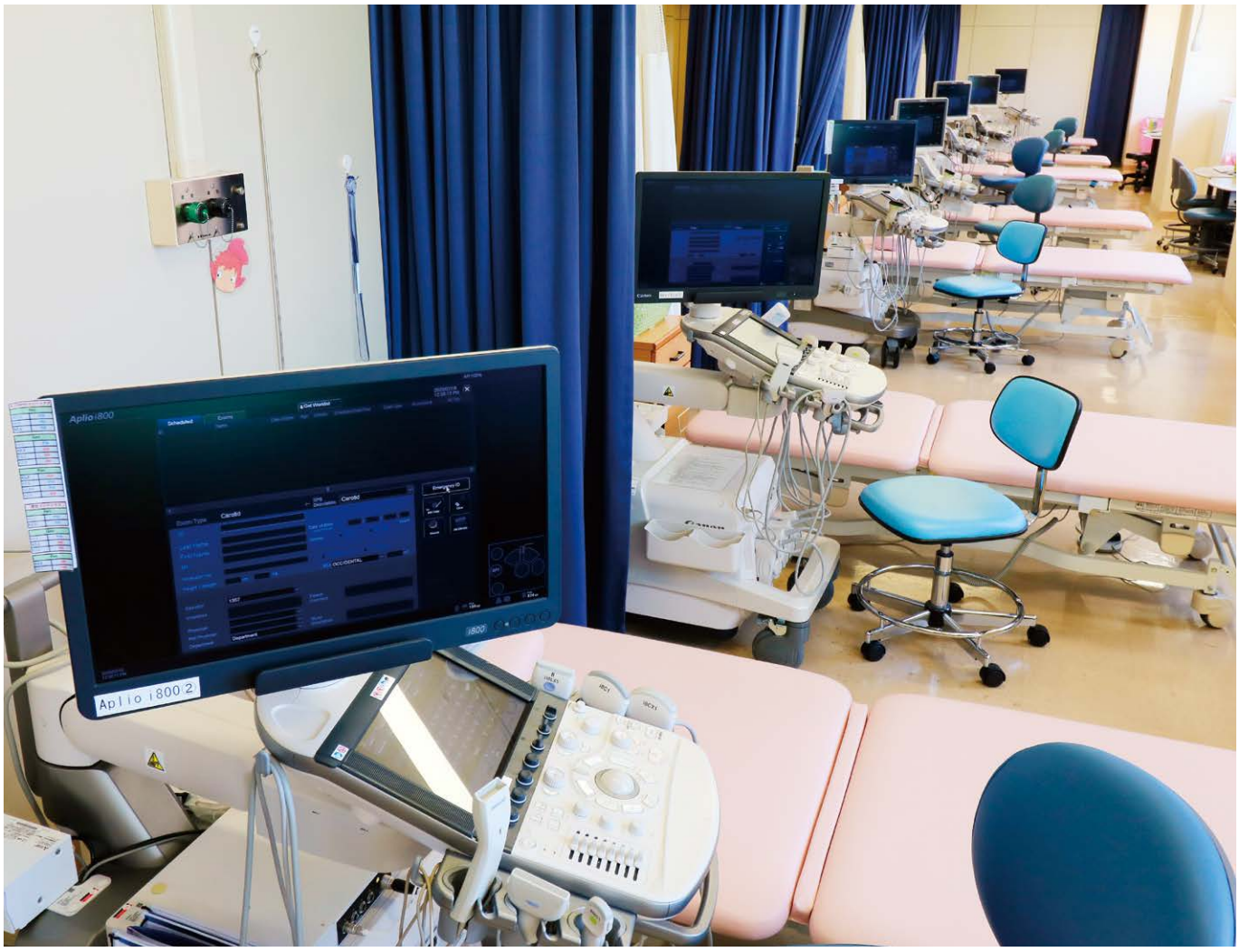
each system. The results showed that there was no significant variation between the systems in the quantitative evaluation of hepatic fibrosis. These findings were published in Hepatology Research, the official journal of the Japan Society of Hepatology. Thanks to your study, I can be confident in stating that the results obtained in such examinations show little variation between systems from different manufacturers. In addition, you've conducted joint research with Dr. Yamaguchi of Chiba University to validate the findings by comparing data obtained in human subjects and in phantoms. Basically, these studies also showed no significant variation in the values obtained using different systems, which is extremely useful evidence in actual clinical practice.

The development of hepatic fibrosis is the gateway to chronic liver disease.

Dr. Iijima: As has been observed in many patients, liver function declines in parallel with fibrotic changes before the development of hepatic cancer. That's why we previously focused on the progression of disease caused by HCV infection. Today, most HCV infections can be treated with Direct-Acting Antiviral (DAA) agents. But in some patients, hepatic cancer develops even after HCV infection has been treated. Further evaluation of such patients often shows fibrotic changes in the liver associated with increased tissue stiffness. This means that hepatic cancer can develop in a certain percentage of patients who have been successfully treated for HCV infection. Of course, there are a number of other considerations, such as genetic factors and so on. I'd be very interested to hear your thoughts, Dr. Kumada.

Dr. Kumada: I totally agree, Dr Iijima. Even though DAA therapy can eradicate HCV infection in patients with cirrhosis, this should never be taken to mean that the changes caused by HCV infection are reversed. Hepatic cancer can still develop in such patients and be found at a later time when the patient least expects it. Researchers often feel that hepatic cancer is most likely to develop in these patients if DAA therapy is administered after the disease has already progressed to a severe stage associated with cirrhosis.
In the past, the only way to evaluate hepatic fibrosis was liver biopsy, but this is an invasive procedure with a high risk of complications such as bleeding. In addition, the amount of tissue collected is quite small, and this can lead to sampling errors and inaccurate diagnostic findings. Interpretation of the results also varies between physicians, which can cause some confusion in clinical practice. The introduction of noninvasive ultrasound examination techniques to measure hepatic tissue stiffness was therefore quite revolutionary.

Dr. Iijima: For the measurement of fibrosis, TE was first introduced in 2000 or so, and it's now widely employed worldwide. I also had a chance to use TE around that time, but TE examination wasn't covered by the Japanese national health insurance system back then, so its application was limited. However, looking at the situation outside Japan, many studies were conducted using TE, and this prompted various manufacturers of ultrasound systems to begin developing functions for liver stiffness measurement.



Ultrasound center at the Hyogo College of Medicine Hospital with a lineup of Aplio ultrasound systems manufactured by Canon Medical Systems.

Liver stiffness measurement is now available in midrange ultrasound systems and can be used in a wide range of clinical settings.

Dr. Kumada: One weakness of TE is that the liver can't be observed in B-mode. For someone like me who's comfortable with ultrasound B-mode images, it's difficult to figure out which part of the ultrasound image is currently being displayed. For this reason, only a limited number of facilities in Japan are using TE. It's my impression that hospitals focusing on diagnostic ultrasound don't often employ TE. The introduction of SWE ultrasound technology, which shows the operator the region being examined while also displaying a conventional B-mode image, should prove to be more acceptable, in my opinion.

Dr. Iijima: Because TE doesn't provide images the operator can refer to, it's difficult for an inexperienced operator to be sure that scanning is being performed correctly. Operators need to gain experience, which is a gradual process.

Dr. Kumada: Today, TE is widely accepted as an alternative to liver biopsy. But, unfortunately, SWE hasn't yet established itself as another viable alternative.

Dr. Iijima: That's true. TE is designated as the gold standard in the clinical practice guidelines established in 2016 by the European Association for the Study of the Liver. However, SWE won't gain widespread acceptance until we've conducted more research and gathered more clinical data.

Dr. Kumada: SWE is now starting to become available in midrange systems, meaning that liver stiffness evaluation is no longer limited to high-end systems. As a result, this method will become more widely used in clinical practice. This will lead to the accumulation of more clinical data, and SWE will eventually gain acceptance as a standard diagnostic method in Japan.

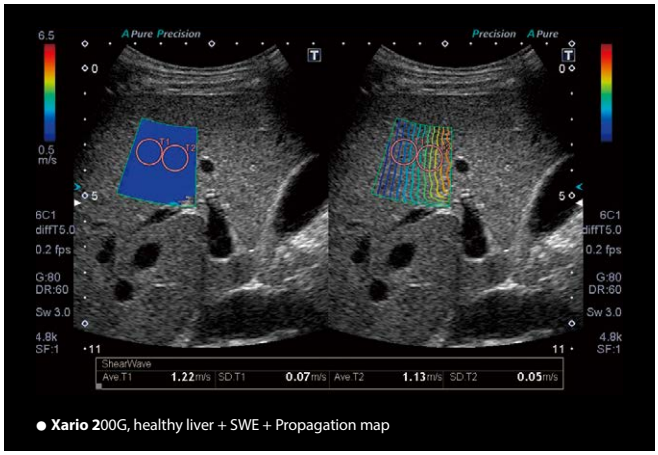


Figure 1 Xario 200G, healthy liver + SWE + Propagation map

Dr. Iijima: As I mentioned in a review article published in the Journal of the Japanese Society of Gastroenterology, with regard to the ultrasound systems manufactured by Canon Medical Systems, SWE is available not only in high-end models, but also in midrange models such as Xario 200. I've also heard that the image quality of the midrange models is nearly the same as that of the high-end models. A propagation map showing the shear wave propagation conditions can also be displayed, allowing the operator to clearly see where measurement should be performed. Because this function improves ease of use in small clinics, the situation is expected to improve greatly.

Dr. Kumada: With regard to the development and improvement of such functions, it's my hope that further studies will be conducted with the benefit of your expertise and support, Dr. Iijima.

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1977	Graduated from Nagoya University School of Medicine
2000	Chief, Department of Internal Medicine, Ogaki Municipal Hospital
2004	Associate Professor, Division of Clinical Medicine, Nagoya University School of Medicine
2011	Assistant Director, Manager of Medical Examination Center, Ogaki Municipal Hospital
2016	Professor, Division of Clinical Medicine, Nagoya University School of Medicine
2018	Professor, School of Nursing, Ogaki Women's College
2018	Visiting Professor, Suzuka University of Medical Science
2019	Professor, School of Nursing, Gifu Kyoritsu University

- Board certified by and supervising physician of the Japanese Society of Gastroenterology
- Board certified by and supervising physician of the Japan Society of Hepatology
- Member of Honor of, board certified by, and supervising physician of the Japan Society of Hepatology
- Chair of the committee for establishing diagnostic criteria in ultrasound for fatty liver of the Japan Society of Ultrasonics in Medicine

Seeing an improvement in the liver fat score can help increase a patient's motivation.

Advances in the treatment of liver disease made possible by ATI

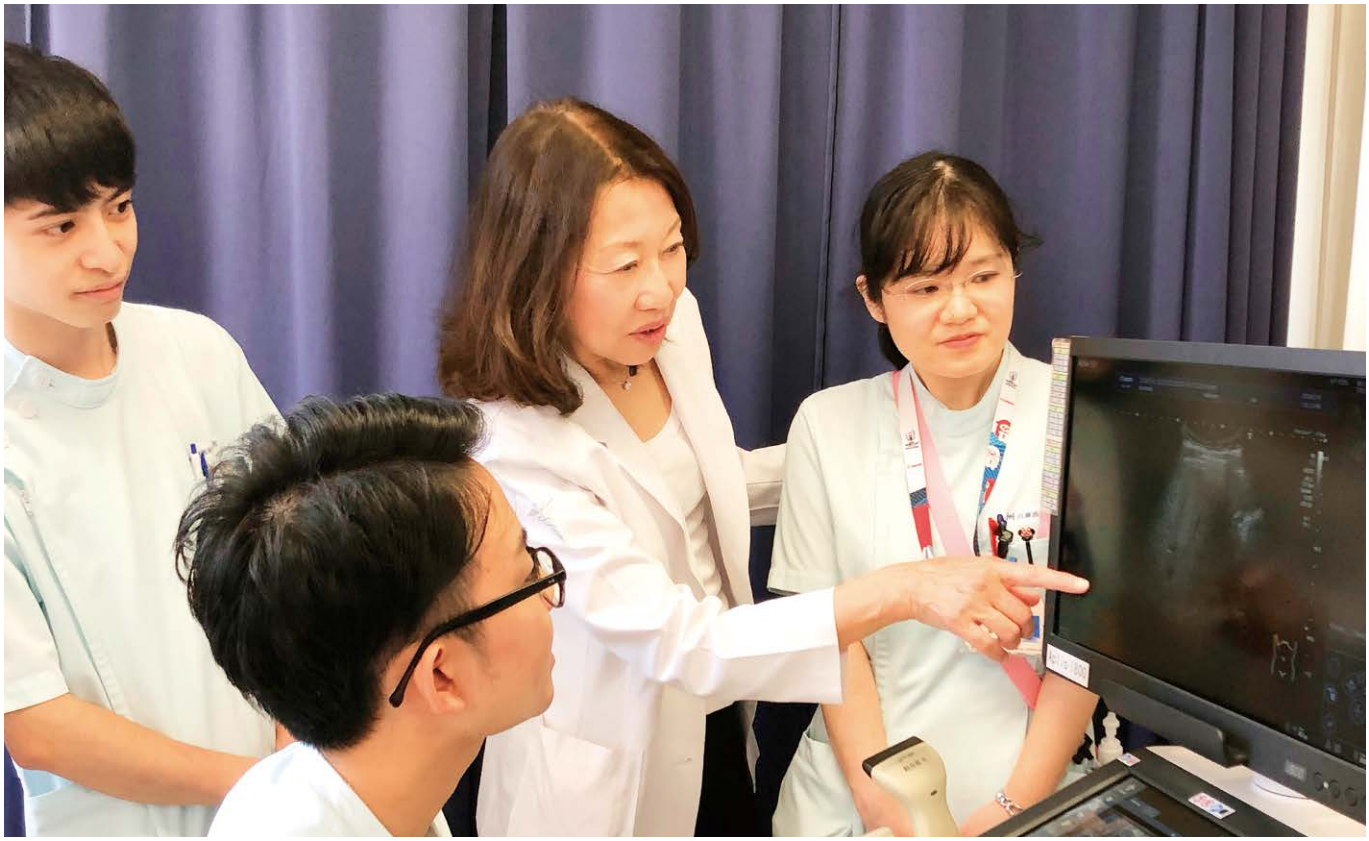
Dr. Kumada: It was around 2011 when I conducted a study on fatty liver, which is the stage before the development of fibrotic changes. A review of health checkup records showed that, in fact, the most common abnormal finding was fatty liver, not hyperlipidemia. Of those who underwent ultrasound examination, 30% to 40% were found to have fatty liver. I appreciated the importance of properly evaluating such patients, and that's why I became involved in organizing the committee for establishing diagnostic criteria in ultrasound for fatty liver of the Japan Society of Ultrasonics in Medicine back in 2011. Dr. Iijima also played an active role in this.
In our initial efforts to establish suitable diagnostic criteria, we tried to achieve quantification of B-mode images by focusing on four factors: liver brightness, liver-kidney contrast, deep attenuation, and vascular blurring. However, the interpretation of these factors was found to be quite subjective, and the committee members weren't able to reach a consensus.
For example, with regard to liver-kidney contrast, some may say that liver-kidney contrast is definitely present, while others may say that it's not so obvious. In addition, the results may also differ depending on the specific system settings, even when ultrasound systems of the same model are used. This also made it difficult for us to reach a conclusion.

Another consideration was whether it's actually useful to establish such diagnostic criteria in the first place, because patients with severe fatty liver don't always have a poor prognosis. For this reason, the activities of the committee gradually slowed down as the members lost enthusiasm due to uncertainty regarding the clinical relevance of fatty liver diagnosis. However, in 2015, a paper published in Gastroenterology (the most prestigious journal in the field) reported that the prognosis of patients with fatty liver isn't related to the amount of fat itself, but to the degree of fibrotic changes. This means that to assess the prognosis of these patients, we need to evaluate hepatic fibrosis. It also emphasizes the importance of screening for fatty liver, which is the stage prior to the development of fibrotic changes.

The recent introduction of Attenuation Imaging (ATI) has rekindled interest in the clinical application of ultrasound to evaluate patients with fatty liver. ATI is a new technology that allows us to quantitatively determine the degree of fatty degeneration by measuring ultrasound attenuation. Previously, the evaluation of fatty liver was based on subjective interpretation, and the fact that such evaluation can now be performed based on quantitative data is extremely exciting. Around 2018, with a new sense of enthusiasm, we stepped up our activities to establish diagnostic criteria for fatty liver. Thanks to the cooperative efforts of Dr. Iijima and other committee members, an outline of the diagnostic criteria was finally completed.

With regard to liver-kidney contrast in particular, interpretation tended to vary between physicians, but the new ability to obtain clear quantitative data is a big step forward in the diagnosis of fatty liver.

Dr. Iijima: You're right. It's also important to note that there was a change in the pathological criteria for the diagnosis of fatty liver, with the requirement that large lipid droplets should be observed in 5% or more of hepatocytes. Nowadays, patients often ask questions such as, "What's my liver fat score today?" And I can tell them something like, "Your liver fat score today is 230." Such conversations help the physician and the patient work together as a team. It makes a big difference when a patient can receive a clear explanation with numbers. It definitely helps to increase the patient's sense of involvement in their medical care, motivating them to try to achieve a better score in the next examination. This is such a great contribution to patient care!



The quantitative data provided by ATI makes it easier to set targets.

Dr. Kumada: In the past, we could only give our patients subjective descriptions like, "This is the condition of your liver today." But now, we can give them quantitative information such as, "This is the value from the previous examination, and this is the value from the latest examination." This allows patients to clearly understand whether they have been making enough effort. If the results are better, the patient can go home happy. This is a big change from how things were just a few years ago.

Dr. Iijima: Basically, some patients with fatty liver may progress to NASH. I feel it's important to perform screening examinations to identify patients with fatty liver in the earliest possible stages so we can treat these patients and prevent them from developing fibrosis.

Dr. Kumada: A major challenge is whether or not it's possible to detect the presence of lipid droplets in 5% of hepatocytes, which is the accepted diagnostic criterion for fatty liver. Many have expressed doubts that this can be detected by ultrasound, and others have even questioned the clinical relevance of detecting this 5% value. But the reason the 5% cutoff value is so important is that when fatty liver progresses to cirrhosis, the amount of fat actually decreases, which is sometimes referred to as "burn-out NASH." And if lower fat scores are cut off, we won't identify patients with far advanced and extremely severe fatty liver. It's my understanding that this is why a strict cutoff value of 5% is necessary.

To meet this requirement, ultrasound examination must be able to detect this 5% cutoff, but B-mode imaging isn't good enough for such measurement. With the introduction of ATI, it's now possible to perform ultrasound examination with a sufficient level of accuracy. This is truly great progress.

Dr. Iijima: Ultrasound still can't beat MRI. The advantage of MRI is that we can evaluate the entire liver. Among current ultrasound systems, Canon's ATI is more reliable because it allows us to examine a relatively wide range of the liver.

Dr. Kumada: Although MRI has excellent diagnostic capabilities, the use of MRI for the evaluation of fatty liver (which affects nearly 30% of Japanese population) is unrealistic if we consider the high cost and low throughput of MRI examinations. This means that gateway screening needs to be performed using ultrasound. Therefore, further improving the quality of diagnostic ultrasound systems is extremely important for accurately evaluating fatty liver.

Dr. Iijima: Dr. Kumada, not many facilities are as economically robust as your hospital, where MRI can be used to examine every patient who needs to be assessed for fatty liver. There are many patients with serious diseases who need MRI examinations, and they should be given priority over patients with less urgent diseases such as fatty liver. At our hospital, it would be quite a challenge to use MRI for fatty liver examinations.

Dr. Kumada: Actually, the situation is the same for us. The use of MRI for fatty liver examination is far from routine at our hospital. However, CT can't replace MRI, because it involves radiation exposure and is therefore unsuitable for repeated examination. In addition, its sensitivity isn't very good. In the end, ultrasound is really the only choice for examining patients with fatty liver in routine clinical practice. I should also point out that another advantage of ultrasound is that, in addition to obtaining the fatty liver score, it's also possible to measure tissue stiffness in the liver, which helps us to assess future progression to fibrosis. Ultrasound's soon-to-be achieved ability to detect the 5% fatty degeneration criterion is truly remarkable.

Dr. Iijima: Another issue is how to accurately identify this 5% cutoff value in livers with an uneven fat distribution.
Dr. Kumada: To address this issue, examinations must be performed by first identifying the target regions and then evaluating each region. One MRI study conducted using an isolated liver reported that the measurement results differed greatly in various regions. Therefore, my feeling is that we need to select a representative region and then calculate a value for the entire liver.

Dr. Iijima: Although I can try to guess the areas of the liver where fatty degeneration is more or less likely to be present, a big advantage of a system like Canon's is that Attenuation Imaging can be performed while observing B-mode images. This makes it possible to obtain images from regions with more fat while also identifying areas of relatively severe fatty degeneration as compared to surrounding areas.

Dr. Kumada: The measurement ROI in ATI is fairly large. Vessels and other structures are automatically subtracted, and the most suitable areas for performing measurement can be accurately selected. This isn't possible with TE and is one of the greatest advantages of ATI.

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2000	Lecturer, 4th Department of Internal Medicine, Tokyo Medical University
2003	Visiting Professor, University of Toronto, Toronto General Hospital
2005	Assistant Professor, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine
2008	Director, Department of Ultrasound Imaging Center, Hyogo College of Medicine Hospital Professor, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine
2020	Director, Ultrasound Imaging Center, Hyogo College of Medicine Hospital Professor, Department of Gastroenterology, Hyogo College of Medicine Assistant President (in charge of promoting diversity), Hyogo College of Medicine Hepatobiliary Disease Center, Hyogo College of Medicine Hospital • Supervising physician of the Japanese Society of Gastroenterology • Supervising physician of the Japan Society of Hepatology • Supervising physician of the Japan Society of Ultrasonics in Medicine • Member of the committee for establishing guidelines for the treatment of hepatic cancer of the Japan Society of Hepatology • Member of the Japan Society of Ultrasonics in Medicine • Member of the committee for formulating guidelines for elastography in the treatment of the liver and the committee for formulating guidelines for the treatment of fatty liver of the Japan Society of Ultrasonics in Medicine

The ability to evaluate the degree of both fatty degeneration and fibrosis is important in assessing the prognosis of high-risk patients.

Diabetes and fatty liver are closely related diseases.

Dr. Iijima: Based on the findings of our study, the prevalence rate of hepatic cancer is higher in patients with diabetes, particularly when the blood sugar is elevated in patients with chronic liver disease.

Dr. Kumada: I've been conducting joint studies with clinical departments specializing in outpatient diabetes care. In my experience, patients with diabetes very often have fatty liver. Of all the liver-related problems in these patients, hepatic fibrosis is the most important. Recently, we collected data covering a 10-year period for about 4000 patients diagnosed with fatty liver at our hospital. We were surprised to find that, in this patient population, the percentage of patients in whom the cause of death was directly related to liver disease was only 5%. The most common cause of death was cardiovascular disease, which accounted for 20% to 30%. It was also surprising to find that the second most common cause of death was tumors in regions other than the liver. Cancers of the digestive tract, including pancreatic cancer, accounted for a large percentage, but taken together, they were the second leading cause of death, but still unrelated to liver disease. This was followed by cerebrovascular disease and then by liver disease.
The most common cause of death in patients with diabetes is also cardiovascular disease, so in this sense, fatty liver and diabetes are as closely related as siblings. And the cause of death in patients with fatty liver isn't always directly related to liver disease either.

But what I'd like to emphasize is that fibrosis was found to be more of a problem. This was also true for the patients who died of cardiovascular disease. There was no direct correlation with the amount of fat. The mortality rate was higher in patients with advanced fibrosis. This may also be true for patients with cancer. Some clinical data indicate that advanced fibrosis is associated with a higher mortality rate. This strengthens my belief that the ability to evaluate the severity of both fatty degeneration and fibrosis is extremely important when I assess the prognosis of high-risk patients. Regarding these points, the ultrasound systems manufactured by Canon Medical Systems are very useful because they allow us to measure both liver stiffness and fatty degeneration in a single scan and display the results in a single image. The fact that the leading causes of death in patients with fatty liver are diseases other than liver disease might lead me to say that fatty liver is not really a liver disease. For this reason, the ability to evaluate the severity of both fatty degeneration and fibrosis may also be useful for the treatment of regions other than the liver.

Dr. Iijima: Our clinical data also show that fatty liver is frequently associated with hypertension, diabetes, and hyperlipemia and that (as Dr. Kumada mentioned) cancers of the digestive tract, such as gastric cancer, bowel cancer, and pancreatic cancer, are likely to be associated with fatty liver, while liver diseases are often not associated with fatty liver. Is that right, Dr. Kumada?

Dr. Kumada: Yes, that's about right. If we look at various liver diseases, they don't show clear relationships with fatty liver. However, it should be pointed out that the population of patients with liver disease is likely to be at high risk for developing other diseases. That's why hepatologists also need to have a thorough understanding of other organ systems.

Similar findings have also been reported in papers published outside Japan. A study published in 2018 in which about 100 patients diagnosed with fatty liver were followed over 20 years also showed that the cause of death in many of these patients was cardiovascular disease or cancer in organs other than the liver, with only a few of the patients ultimately developing cirrhosis. In addition, the data also showed that liver disease was the cause of death in only one or two of the patients. This means we must keep in mind that when we evaluate patients with fatty liver, we always need to consider the entire body. Since we know that fatty liver is also related to a variety of diseases, we should always be aware that the presence of advanced hepatic fibrosis may indicate the presence of diseases elsewhere in the body.

With regard to the liver, the key requirement for a modern diagnostic ultrasound system is, of course, the ability to evaluate the severity of fatty degeneration and fibrosis. But it's also important for the ultrasound system to be suitable for evaluating other organ systems, such as the cardiovascular system.

Advantages of ultrasound in a wide range of applications in Japan

Dr. Iijima: Due to our modern lifestyle and dietary habits, about 30% to 40% of the Japanese population is reported to have fatty liver. It's extremely important to identify high-risk patients who require further treatment from among those who require only lifestyle guidance to lose weight. Given this situation, I think that Canon's ultrasound systems are outstanding because they allow us to quantify not only fatty changes but also fibrotic changes.

Dr. Kumada: Nowadays, many patients are visiting our hospital for the treatment of fatty liver after they're found to have abnormal screening results. When it comes to identifying high-risk patients, we first detect fatty liver, and we then screen for cirrhotic changes by measuring tissue stiffness. These are the two essential steps. Without them, it's impossible to select the patients who require treatment. Ultrasound systems that are able to evaluate such patient are extremely useful. Clinical flowcharts are also starting to be introduced by academic societies outside Japan.

Dr. Iijima: I think that the guidelines of the European Association for the Study of the Liver (EASL) are very well designed. The key point is that the flowchart starts with whether or not the patient has metabolic syndrome. Next is the presence of fatty liver. I've always thought that the reason flowcharts start with metabolic syndrome in guidelines issued outside Japan may be because hospitals in other countries don't have as many ultrasound systems as hospitals in Japan. In other words, we have more ultrasound systems here in Japan than anywhere else in the world. Taking advantage of this fact, we can design our flowchart so it starts with the quantitative evaluation of the presence of fatty liver using ultrasound. This should prove to be very useful for the treatment of patients.

Dr. Kumada: The development of diagnostic methods based on blood markers of fibrosis is currently attracting a great deal of interest. But here in Japan, I believe that ultrasound is still the most suitable method due to its noninvasiveness and high throughput. Of course, it's difficult to cover everything with ultrasound alone, but I still feel that it's better to screen for fatty changes and fibrotic changes using ultrasound as much as possible.

Dr. Iijima: Ultrasound has a lot of advantages and, above all, it's patient friendly. There's no need for needle puncture. Examination is performed by simply applying the probe, and there's no discomfort.

Dr. Kumada: With regard to liver disease, because viral hepatitis will be conquered at some point in the future, the focus will shift to fatty liver. How we screen for fatty degeneration among the large number of patients with liver disease will become crucial. Ultrasound will be capable of identifying liver diseases with or without fatty degeneration or fibrotic changes, so I believe that ultrasound is going to be an extremely useful tool.

When SWE and ATI are installed in all ultrasound systems, it will become possible to conduct mass screening for fatty liver, allowing the early identification of high-risk patients with fatty liver. I have high expectations for Canon Medical Systems because they are the first manufacturer to have developed a method for the quantitative evaluation of fatty liver.

Hyogo College of Medicine Hospital

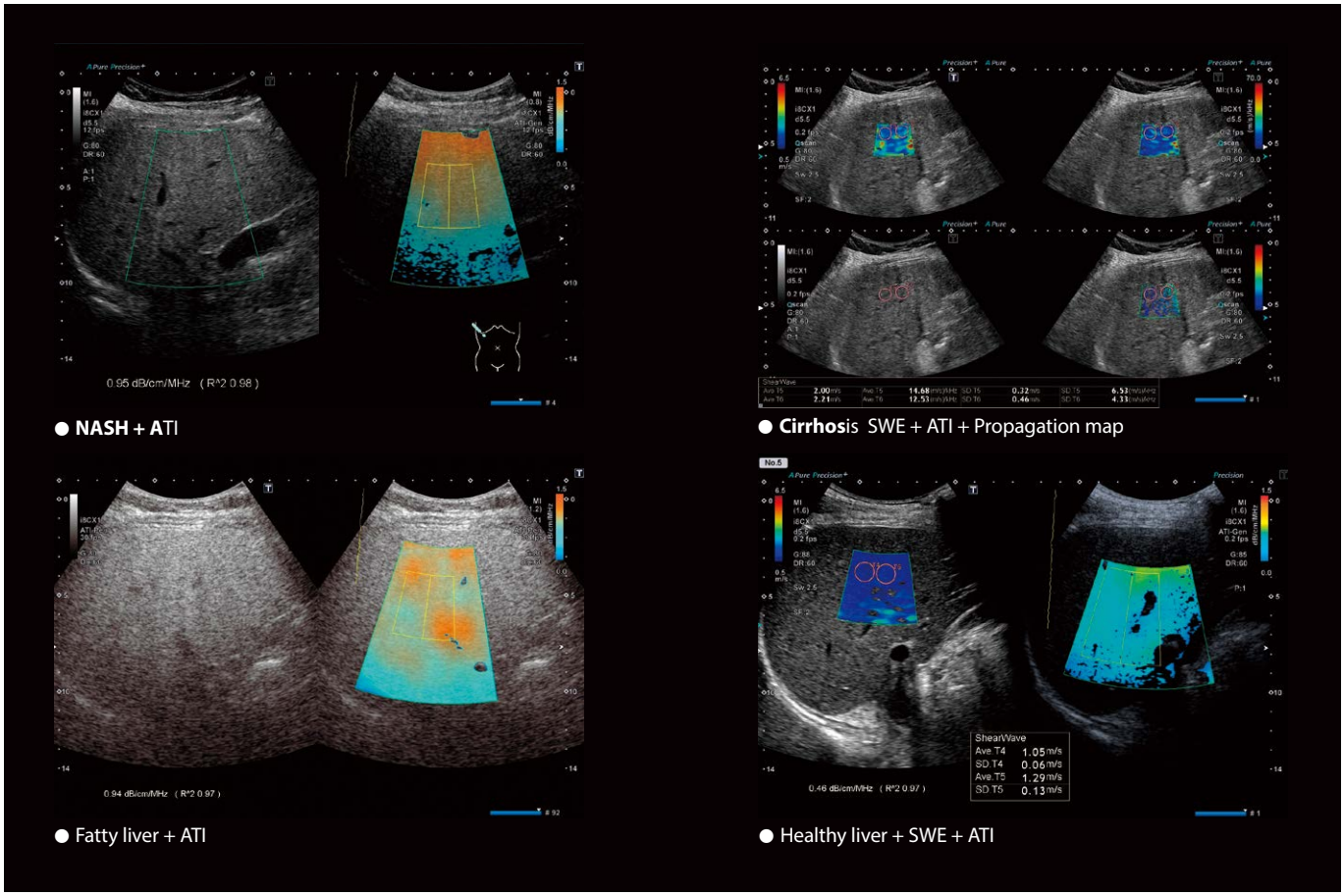


Figure 2 NASH + ATI (top left), Cirrhosis SWE + ATI + Propagation map (top right), Fatty liver + ATI (bottom left), Healthy liver + SWE + ATI (bottom right)

SWE and ATI are most valuable when they are installed in midrange systems.

Dr. Kumada: In order to quantify the severity of fatty changes using ATI and use it as a guideline, I think that the obtained data should be compared against the MRI Proton Density Fat Fraction (PDFF).

Dr. Iijima: Do you think it's reasonable to compare ATI against PDFF rather than the tissue diagnosis?

Dr. Kumada: Nowadays, it's becoming standard practice to use PDFF rather than the tissue diagnosis when evaluating the severity of fatty changes. Therefore, facilities that employ both PDFF and ultrasound first need to collect data from as many patients as possible and then validate the data. If such verification could be conducted by clinicians such as yourself, Dr. Iijima, it would be a great help in collecting data on a nationwide scale for establishing suitable diagnostic criteria. In addition, I'd like to make a request to the manufacturers of ultrasound systems. It's completely understandable that advanced technologies such as SWE and ATI are initially available only in high-end systems. However, the facilities that truly need these technologies are those which provide routine health checks and primary care services. I strongly urge you to make these technologies available in ultrasound systems that are suitable for use in such facilities.

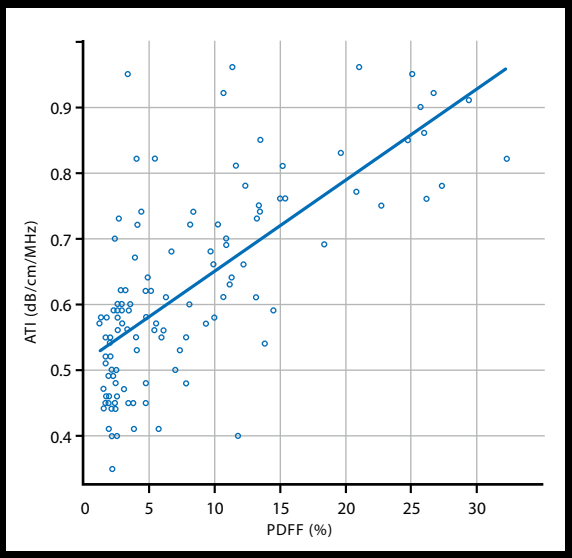
Dr. Iijima, you mentioned earlier that SWE is installed in the midrange ultrasound system Xario 200, which I think is great. Also, ATI can easily be installed by upgrading the software, which isn't too difficult.

If SWE and ATI were available in all systems and could be used to accurately screen patients with fatty liver at the time of routine health checks, it would be more than we could ask for. It would make it possible to quickly identify high-risk patients with fatty liver. I have high expectations for Canon Medical Systems because they are the first manufacturer to have developed a method for the quantitative evaluation of fatty liver.

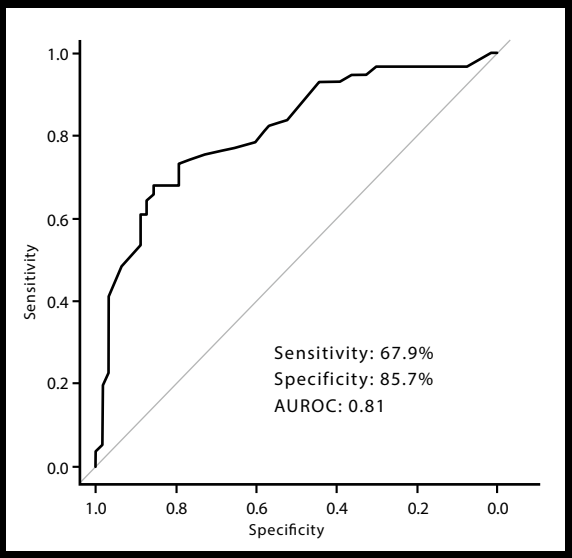
Diagnostic performance of ATI and PDFF and fatty liver S1 (5% or more)

● Spearman's rank correlation coefficient

r=0.70, 95%CI：0.59-0.78, p<0001



Cutoff value: 0.63 dB/cm/MHz



Data courtesy of Toshifumi Tada, Takashi Kumada, et al.

About the ultrasound systems featured in this article

Aplio i-series is a range of premium high-end ultrasound systems manufactured by Canon Medical Systems Corporation. Incorporating advanced technologies to transmit and receive narrow, uniform ultrasound beams at high density in both superficial and deep regions, Aplio i-series provides clear images with excellent uniformity and continuity. In addition, Superb Micro-vascular Imaging (SMI), which is an original technology developed by Canon, allows low-velocity flow and small blood vessels to be clearly visualized.

Micro-convex transducers can be used to reduce the variation in image quality when a convex transducer intended for routine examinations or a transducer intended for biopsy procedures is used. The use of micro-convex transducers also minimizes blind spots.

Disposable biopsy adapters designed to avoid blind spots along the biopsy line can easily be mounted.

Canon Medical Systems' approach in the Development of Quantitative Software Applications for Diffuse Liver Diseases

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Aplio i-series integrates a variety of software applications for quantitative analysis into a single suite. This software suite, called the "Liver Package", includes Shear Wave Elastography (SWE), Shear Wave Dispersion maps for SWE (SWD), and Attenuation Imaging (ATI) (Fig. 1). These applications have been developed for the evaluation of diffuse liver diseases based on multiple parameters. Another function that has been introduced as a part of this development is the Multi Parametric Report (Fig. 2), which is a comprehensive report function for displaying the values obtained using each application as a single Multi Parametric Worksheet. Ultimately, by permitting the comparative evaluation of results as trend graphs that can be created for each user (Fig. 3) based on various indices, the goal of the system is to improve the differential diagnosis of liver diseases. This report presents a brief technical introduction to SWE, SWD, and ATI.

• Attenuation Imaging (ATI) (Fig. 1, top right)

In patients with fatty liver, it is well known that the attenuation of ultrasound signal intensity in deeper parts of the liver can interfere with imaging. The amount of attenuation varies depending on the tissue structure and acoustic characteristics of the hepatic parenchyma. We have therefore focused on the amount of attenuation and have developed a function for estimating the attenuation coefficient.

Because the signals obtained in B-mode imaging are affected by the changes in intensity caused by gain correction and the beam profile, it is difficult to obtain the attenuation coefficient by simply calculating the amount of change in the signals. To address this issue, in addition to eliminating these gain effects from the signals obtained in B-mode imaging, the specific effects of various acoustic field characteristics are also eliminated based on measurements obtained using a reference phantom. This approach converts the obtained signals into a signal intensity distribution that reflects only the attenuation caused by dispersion or absorption in the tissues. The main technological feature of this function is that it can effectively estimate representative values while minimizing variation. We initially considered employing a method in which the attenuation coefficient is estimated by using two different frequencies and calculating the ratio between the measured values, but we ultimately decided to employ a different method because it was found to be superior in minimizing variation due to other tissue characteristics.

Also, as mentioned above, if the amount of change (i.e., the slope) is simply removed from the signal intensity distribution after correction, it becomes difficult to accurately calculate the attenuation coefficient when the target region includes strongly reflective structures or very weakly reflective structures such as vessel lumens. To overcome this problem, we have developed a special filtering technology in which the target regions for calculating the attenuation coefficient are divided into smaller regions and the local dispersion values of signal intensity are then calculated to determine whether or not each region includes such structures. If a region is found to include such structures, the values in that region are excluded from the calculation.

In this function, special filtering technology to exclude unnecessary structures plays an important role in ensuring that attenuation coefficients are calculated accurately. This provides information related to the determination coefficient when the slope is linearly fitted and serves as an index of the reliability of the measurement results. The determination coefficient is displayed as a value in white when the reliability

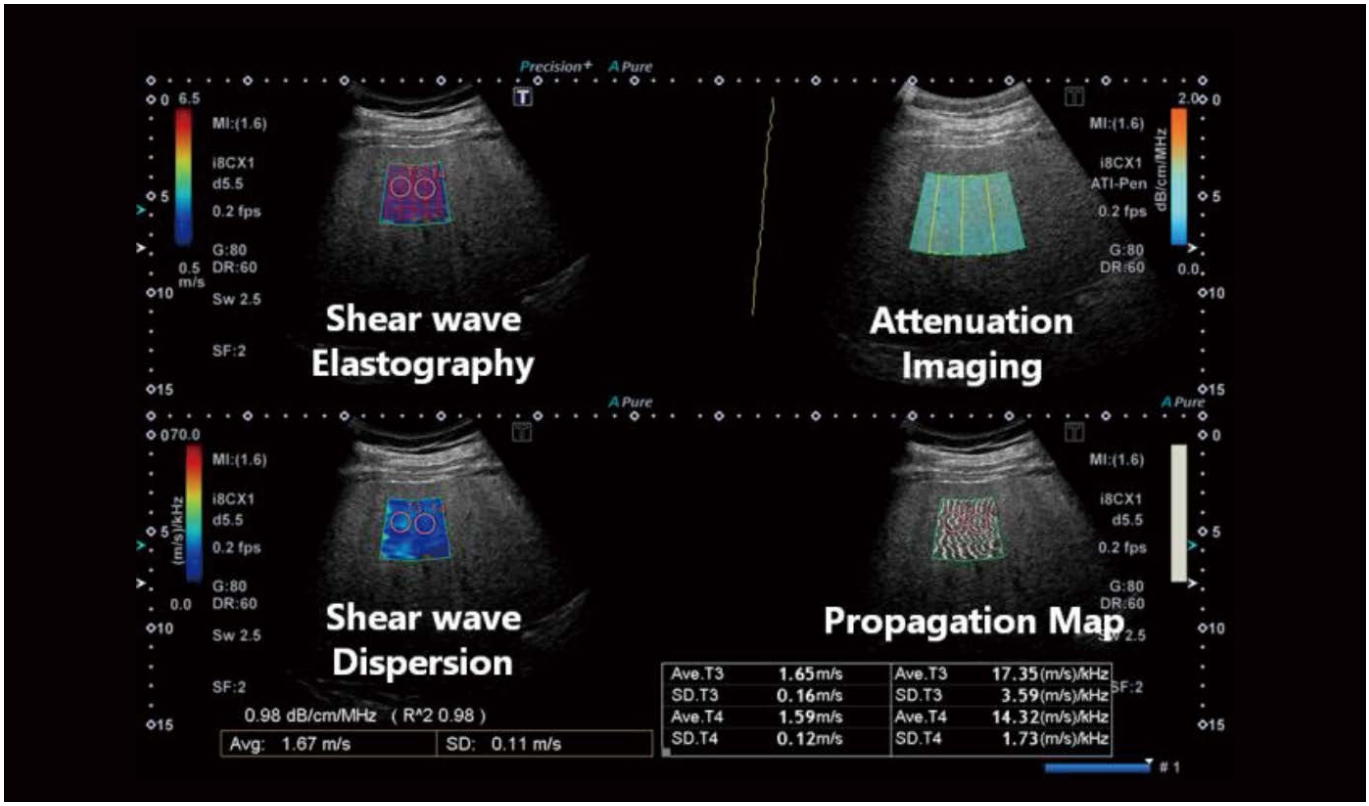

Figure 1 Example of SWE, SWD, and ATI display

is high, while it is displayed as "***" in red when the reliability is low. In ATI, it is assumed that the attenuation coefficient is measured based on large and relatively uniform regions. This determination coefficient is useful for ensuring that the signal distribution in the target region for linear fitting is suitable for calculating the attenuation coefficient. Both SWE and ATI information can be obtained in a single scan.

The top left image shows Shear Wave Elastography, the top right image shows Attenuation Imaging, the bottom left image shows Shear Wave Dispersion, and the bottom right image shows a propagation map for SWE. The red frame in the color ROI in the top left image is the measurement area detection display, and the measurement results in the measurement area are displayed in the yellow frame in the bottom left image. The value displayed above the yellow frame in the bottom left image is the estimated attenuation coefficient. The values displayed at the lower right are the measurement results for Shear Wave Elastography and the Shear Wave Dispersion map for SWE.

• Shear Wave Dispersion map for SWE (SWD) (Fig. 1, bottom left)

Basically, frequency dispersion which varies with the propagation velocity is observed when shear waves propagate through a viscous medium with high shear viscosity. Details of the actual dynamics related to viscosity are not yet clearly understood, and a number of physical parameters remain difficult to analyze or interpret.

However, most tissues in the human body exhibit some degree of viscosity, and it will therefore be necessary to identify clinically useful viscosity measurements and viscosity-related parameters in the future. For this reason, based on the understanding that shear wave arrival times are presented as dispersion values relative to frequency, the propagation velocity of the shear waves is calculated for each frequency in this function. By performing fitting for the relationships between the frequency components after subtraction of the phase velocity (propagation velocity) according to the Voigt model or Maxwell model, the shear elasticity coefficient and the shear viscosity coefficient can be calculated. However, it should be noted that these models are only theoretical models which have not yet been verified in large numbers of clinical cases.

For this reason, keeping in mind the fact that frequency dispersion occurs due to shear viscosity, the amount of dispersion is presented as a primary approximation and the value is displayed in color in the image as the Dispersion Slope (DS) value. It must be emphasized that the DS value does not represent the actual viscosity coefficient. It is only an index of the amount of change in velocity relative to frequency. Nevertheless, although it may be affected by factors other than the tissue viscosity, the DS value can still be considered a useful index of the relationship between viscosity and shear wave frequency.

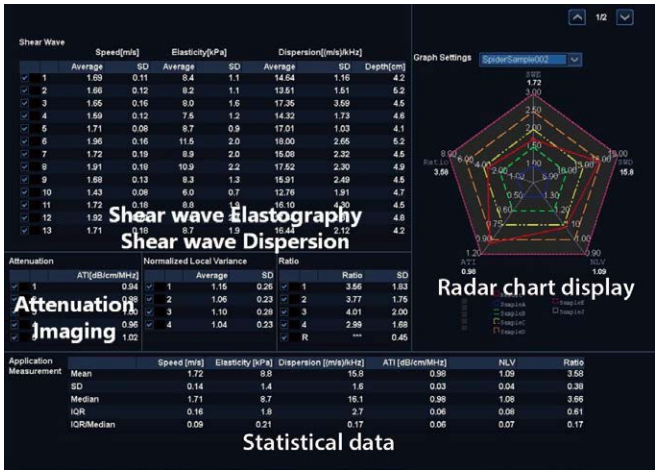

Figure 2 Example of Multi Parametric Worksheet display*
The indices obtained using Shear Wave Elastography and Attenuation Imaging in batch measurement mode can be displayed. The radar chart display can be customized by the user.

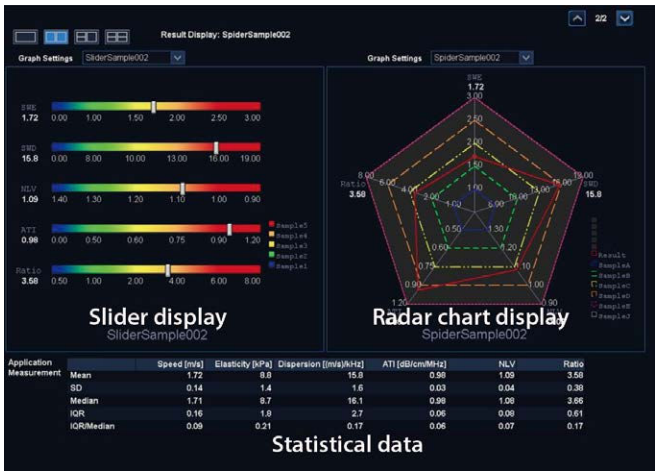

Figure 3 Example of Multi Parametric Worksheet graph display*
Sliders (left) and a radar chart can be generated and displayed. * NLV (Normalized Local Variance) and Ratio are W.I.P. functions. The values shown in the figure are only examples.

• Shear Wave Elastography (SWE) (Fig. 1, top left)

Shear Wave Elastography is an imaging method in which acoustic power is emitted in order to vibrate the target tissues and the propagation of the generated shear waves is then monitored to measure the propagation velocity. The propagation velocity can be used to calculate the elasticity, which is an index of tissue stiffness. In the conventional method, it is necessary to obtain SWE and ATI information separately, but we have developed a new function known as batch measurement mode (Fig. 1) in which SWE, SWD, and ATI information can be obtained in a single scan. This allows examinations to be performed more quickly and efficiently. In addition, the waiting time for the operator is minimized by allowing display setting and data processing to be performed during the cooling time while the system is being prepared for the next scan.

Acknowledgement:

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