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【 ORIGINAL ARTICLE 】

The Efficacy of Sonazoid-enhanced Ultrasonography in Decision-making for Liver Abscess Treatment

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Abstract:

Objective The usefulness of contrast-enhanced ultrasonography (CEUS) for making decisions in the treatment of liver abscess is unknown.

Methods We evaluated the internal blood flow in the arterial-predominant phase by CEUS using Sonazoid® in 21 patients. The stain area rate was evaluated in maximum parting plane of abscess in CEUS. Patients were divided into two groups: the vascular phase enhancement (VE) group, in which ≥50% of the abscess cavity was enhanced (12 patients), and the vascular phase non-enhancement (VNE) group, in which <50% of the abscess cavity was enhanced (9 patients). The rate of patients who were cured by conservative treatment alone was examined in both groups. The defect rate of all liver abscesses in the post-vascular phase was also evaluated.

Results In the VE group, improvement by conservative treatment alone was obtained in 11 out of 12 patients (91.7%), while in the VNE group, improvement by conservative treatment alone was obtained in only 1 out of 9 patients (11.1%), a significant difference ($p<0.001$). In the VE group, one patient did not improve with conservative treatment alone because the abscess ruptured near the liver surface. In the VE group, the abscess size was smaller than in the VNE group. By examining the defect rate in the post-vascular phase, it was found that 16 out of 21 patients (76.2%) showed 71% or more defects.

Conclusion The enhancement rate in the arterial-predominant phase of CEUS was considered useful for determining the treatment approach for liver abscess.

Key words: liver abscess, treatment, sonazoid, contrast enhanced ultrasonography, arterial-predominant phase

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Introduction

Liver abscesses contain pus and develops due to bacteria or amoebae. In some cases, they can be fatal, so appropriate treatment is required to obtain a favorable prognosis. In the past, this disease had a high mortality rate. It was treated either conservatively by administering antibiotics and observing the course of the disease or by performing laparotomy drainage, and the mortality was 9-80% (1). However, in the last 40 years, the management of liver abscess has greatly changed.

With the progress of imaging techniques, in addition to laparotomy drainage, percutaneous transhepatic drainage or drainage by endoscopic retrograde cholangiopancreatography (ERCP) has been developed. Percutaneous transhepatic drainage can be performed safely under computed tomography (CT) or ultrasound guidance, but it is an invasive proce-

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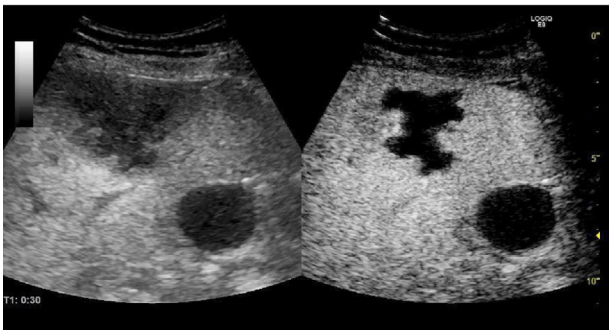

Figure 1. Results of an examination with conventional US (a) and CEUS in the arterial-predominant phase (b). CEUS revealed a clear boundary between the necrotic area and normal liver cells.

dure. In recent years, broader antibiotics have also been developed and are being used to treat bacterial liver abscess, but no criteria have been established for deciding whether it is possible to rely on conservative treatment with antibiotics alone or whether drainage is required.

In this study, we examined the efficacy of contrast-enhanced ultrasonography (CEUS) for deciding whether or not liver abscess can be treated conservatively with antibiotics only.

Materials and Methods

We performed a retrospective analysis of 21 patients who had been diagnosed with liver abscess via a biochemical examination of the blood, conventional ultrasonography (US), CEUS, and contrast-enhanced CT (CECT) in the gastroenterology department of our hospital from July 2011 to December 2015. The diagnostic criteria included hypoechoic to hyperechoic lesions and the detection of internal echoes reflecting debris or septation on US/CEUS and round lesions with central hypoattenuation, peripheral rim enhancement or surrounding edema on CECT. US/CEUS and CECT were performed for the initial diagnosis.

The ultrasonic devices used for conventional US/CEUS were a Aplio500, Xario (Toshiba, Tokyo, Japan), LOGIQ E9, LOGIQ E9 XD Clear 2.0 (GE Healthcare, Chicago, USA), and Ascendus (Hitachi, Tokyo, Japan). The contrast agent was Sonazoid® [common name perfluorobutane; Dai-Ichi Sankyo Seiyaku (Tokyo, Japan)]. Sonazoid® was administered intravenously at 0.01 mL/kg, and after flushing with 10 mL of saline, an evaluation was made in the arterial-predominant phase (10-30 seconds following administration of the contrast agent) and the post-vascular phase (10 min after injection and lasting for 1 hour or more) (2). In the conventional US and CEUS examinations, videos were recorded, and the abscess size, stain area rate relative to the whole abscess area in the arterial-predominant phase and defect rate of the whole abscess in the post-vascular phase were calculated (Fig. 1). In cases with multiple liver abscess, we evaluated the largest abscess using CEUS. The stain area rate was evaluated in the maximum parting plane of the abscess. CEUS was performed for the initial diagnosis by a skilled Ultrasound Physician who was a supervisor of the Japan Society of Ultrasonics in Medicine with 20 years of experiences (C.O.). The diagnosis and analysis were performed by two doctors who are board-certified hepatologists of the Japan Society of Hepatology. The strategy in our hospital is to start antibiotics at the time of the diagnosis of hepatic abscess, with drainage treatment added at the judgment of the attending physician if exacerbation was observed in the clinical course.

Patients were evaluated for their age, gender, presence of dementia, diabetes mellitus, cancer, outcome, hospitalization, period, whether or not drainage was performed (including catheter drainage, needle aspiration and surgical operation) and whether or not antithrombotic drugs were being taken. They were divided into two groups: the vascular phase enhancement (VE) group, in which ≥50% or more of the whole abscess was enhanced in the arterial-predominant phase, and the vascular phase non-enhancement (VNE) group, in which <50% of the whole abscess was enhanced in the arterial-predominant phase (Fig. 2), and the proportion of improvement by the use of antibiotics only and patient characteristics were recorded (Table 1). We compared the stain rate in the arterial-predominant phase with the improvement with antibiotics only. We also compared the defect rate in the post-vascular phase with the improvement with antibiotics only.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. The chi-square or Fisher' s exact tests were applied to evaluate the differences in the categorical variables. Continuous data were presented as the mean, and Student' s *t*-test was used to evaluate the difference in continuous variables. The statistical analyses were performed with a two-tailed significance level of 0.05.

Results

The 21 patients were 10 men and 11 women, the mean age was 70.6±13.0 years old (mean ± standard deviation).

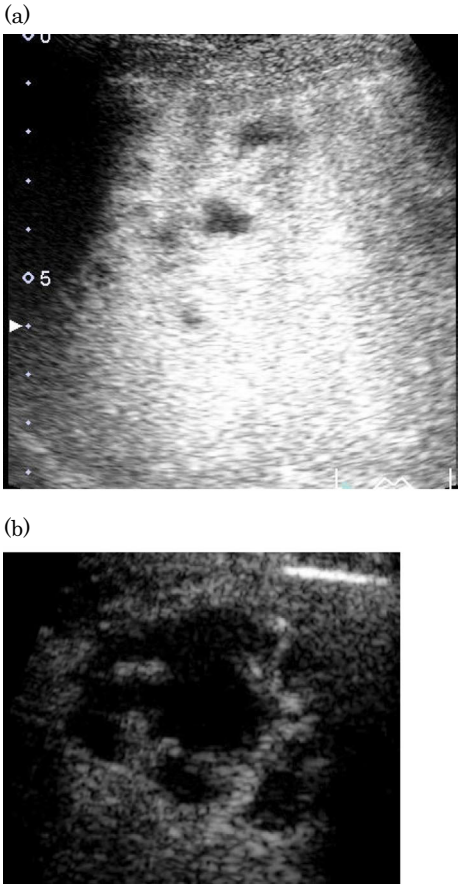

Figure 2. Images of the VE and VEN groups. (a) ≥50% of the whole abscess was enhanced in the arterial-predominant phase. (b) <50% of the whole abscess was enhanced in the arterial-predominant phase.

The average abscess diameter was 55.2 mm, and in all 21 cases, the cause was bacterial. Amoeba cases were not included in this study. Regarding the outcomes, 12 patients improved with antibiotics only, while 9 did not. Of the 21 patients, the VE group consisted of 12 patients (average diameter 41.1 mm), and the VNE group consisted of 9 patients (average diameter 73.9 mm). In the VE group, 11 of 12 patients (91.7%) improved with antibiotics only, whereas in the VNE group, only 1 of 9 (11.1%) improved with antibiotics only, showing a significantly higher proportion of improvement with antibiotics only in the VE group ($p< 0.001$). The patient in the VE group who did not improve with antibiotics only had a rupture on the liver surface (Table 2).

The mean hospitalization period in the VE group was 47 days when drainage was performed and 28 days without drainage, whereas that in the VNE group was 41.3 days when drainage was required and 14.5 days when drainage was not required (including 1 case who died of other causes). All seven patients with a stain rate of ≥71% improved with antibiotics only (7 out of 7 patients, 100%). In contrast, patients with a stain rate of ≤ 30% did not improve with antibiotics only [6 out of 7 (85.7%) underwent drainage, and 1 patient had no drainage but died from other causes] (Fig. 3).

Considering the defect rate in the post-vascular phase and improvement rate with antibiotics only, 16 out of 21 patients (76.2%) showed a defect rate of ≥71%. Both groups of patients who demonstrated an improvement whether they took antibiotics or not, showed a high defect rate in the post-vascular phase. As a result, it was considered to be difficult to determine the optimal treatment approach base on the post-vascular phase (Fig. 4).

Of the 21 cases, 33.3% (7 of 21) were receiving antithrombotic drugs, 23.8% (5 of 21) had dementia, and 4.8% had both (1 of 21). The presence of either antithrombotic drug treatment or dementia was noted in 52.4% (11 of 21).

Table 1. Characteristics of the Patients with Improvement with Antibiotics Only and Those with No Improvement by Conservative Therapy.

	Improvement by antibiotics only 12 cases	No improvement by conservative therapy 9 cases
Sex (male/ female)	7/5	3/6
Age	74.4 (57-92)	65.6 (53-83)
Comorbidities		
Dementia	4	1
Diabetes mellitus	4	5
Cancer (colon cancer)	9 (1)	4 (2)
Biliary infection	5	3
Antithrombotic drugs	5	2
Laboratory test		
White blood cell count (/μL)	9,903 (4,300-18,800)	13,951 (5,940-37,700)
CRP	12.7 (3.53-21.25)	22.6 (8.7-35.38)
Platelet count ($\times 10^4$/μL)	19.8 (10.4-48.9)	20.4 (8-42.2)
DIC	0	5

Table 2. Demographics and Abscess Characteristics in the Patients with Improvement with Antibiotics Only and Those with No Improvement by Conservative Therapy.

	Improvement by antibiotics only 12 cases	No improvement by conservative therapy 9 cases
Abscess size (mm)	39.5 (8-64.7)	76.1 (45-132)
Diameter ≤5cm	8	2
Abscess location(right/left lobe)	9/5	6/4
Single / Multiple	7/5	8/1
Unilocular / Multilocular	10/2	5/4
Stain rate in the arterial-predominant phase <50% (VNE group) / ≥50% (VE group)	1/11	8/1
Hospitalization	25.6 (13-50)	37.6 (2-57)

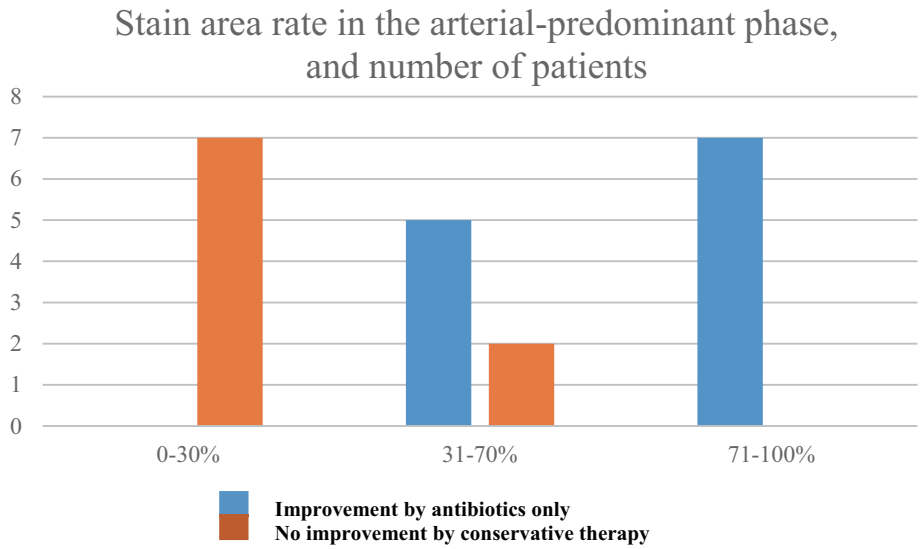

Figure 3. The number of patients that showed an improvement by antibiotics alone, and those that showed no improvement by conservative therapy were analyzed regarding the stain area rate in the arterial-predominant phase. All patients who obtained an enhancement of ≥71% for the whole abscess in the arterial-predominant phase were treated by conservative therapy, but those who obtained an enhancement of ≦30% for the whole abscess in the arterial-predominant phase did not demonstrate any improvement by conservative therapy.

A total of 61.9% (13 of 21) of patients had malignant disease, so a substantial proportion of patients required special care when performing drainage.

The relationship between the abscess size and improvement rate with antibiotics only was also examined. Eight of 10 patients (80.0%) with an abscess size of ≤ 50 mm and 11 of 13 patients with an abscess size of ≤ 60 mm improved with antibiotics only (Fig. 5).

Discussion

Liver abscesses are usually composed of a viscous fluid in an intrahepatic partition caused by inflammation as a defense reaction against infection.

Conventional US is used to assess the condition of the normal liver, perform an accurate diagnosis in real time, and perform repeated evaluations at a low cost, and this modality is well tolerated without radiation exposure. However, for the diagnosis of liver abscesses, it is limited. Although CECT is extremely useful for evaluating the extent of abscesses and necrosis, it carries a risk of radiation exposure and contrast agent allergy, and it is difficult to perform in patients with renal dysfunction. It also cannot be used repeatedly to evaluate the treatment effect.

CEUS solves the above problems, since it can be used without the risk of affecting the kidney function and can be used in real time without a risk of radiation exposure. The utility of CEUS for examining liver abscesses has been reported to be comparable to that of CECT and magnetic resonance imaging (MRI) (3-5). The European Federation for Ultrasound in Medicine and Biology (EFSUMB) and World Federation for Ultrasound in Medicine and Biology (WFUMB) guidelines specify ultrasonic patterns for liver abscesses. Conventional US findings of liver abscess are a low-echoic mass with a thick irregular wall and interior partitions, sometimes including gas (presenting as a bright dot-

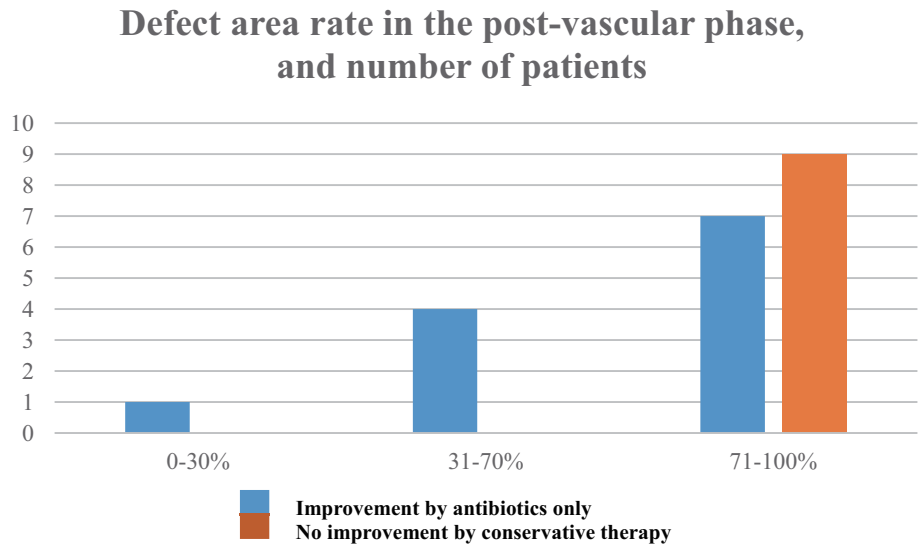

Figure 4. **The number of patients who showed an improvement by antibiotics alone, and those who demonstrated no improvement by conservative therapy were analyzed regarding the defect area rate in the post-vascular phase. Both groups who improved by antibiotics or not, showed high defect rate in the post-vascular phase. As a result, evaluations using the defect area rate in the post-vascular phase are therefore not considered to be useful.**

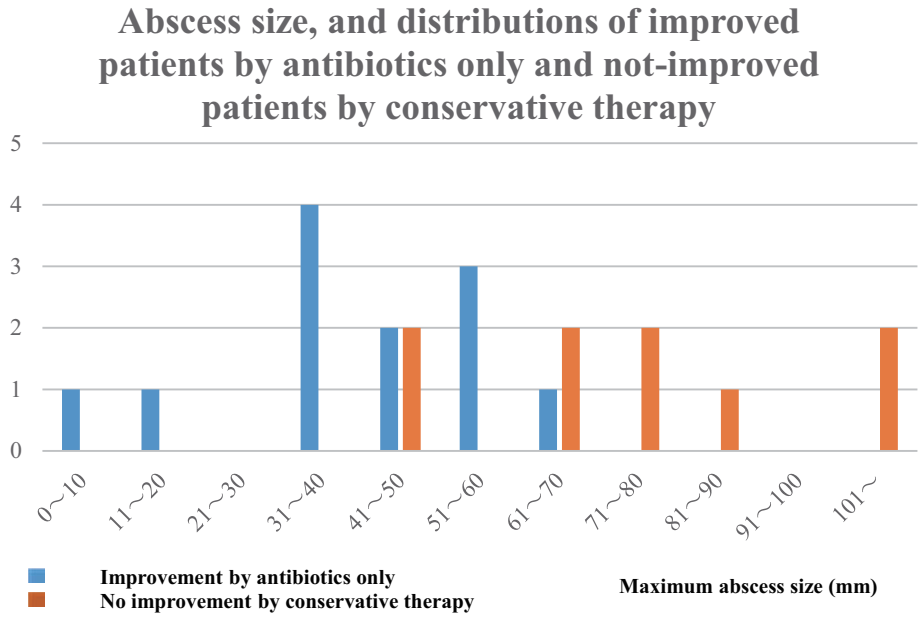

Figure 5. **Relationship between the abscess size and improvement rate with conservative treatment. The rate of improvement in abscesses measuring ≥61 mm in size was not good.**

ted echo with a shadow behind). These are the most frequently observed findings, but they are not specific. Regarding the findings of CEUS, mature abscesses typically show marginal enhancement in the arterial-predominant phase, occasionally with enhancement of septae followed by venous hypoenhancement (2, 6, 7).

In the present study, the evaluation of the defect rate in the post-vascular phase was not recognized as a useful marker for deciding whether conservative treatment of liver abscess was possible or whether drainage treatment was necessary. However, even if only a few normal liver cells remain, they are likely to be stained in the arterial-predominant phase, so the evaluation of the arterial-predominant phase, where there is a clear boundary from the necrotic area, where normal liver cells are not present, would be a useful marker for deciding whether conservative treatment is possible or whether drainage treatment is required.

Several types of ultrasound contrast agents are currently in use, but Sonazoid®, a second-generation contrast ultrasonic agent, can evaluate the blood flow dynamics of the post-vascular phase as well as that of the arterial-

predominant phase, so a more precise diagnosis has become possible (8). Sonazoid® is used clinically in Japan (9) and in recent years has come to be used in China, South Korea, Norway and other countries as well; however, in countries where Sonazoid® is not approved for use, the evaluation in the post-vascular phase is impossible.

Thus far, the treatment approach for liver abscess was determined by the number and size of the abscesses. In cases of a single lesion with a diameter of ≤ 5 cm, percutaneous catheter drainage or needle aspiration is often performed. Drainage catheters should remain in place until drainage is minimal (usually up to seven days). Repeat needle aspiration may be required in up to half of cases if a catheter is not left *in situ*. If the lesion is ≤ 5 cm, the prognosis is expected to be good, regardless of a puncture or catheter being used (10-13).

For a single, large abscess >5 cm in diameter, catheter drainage is preferred over needle aspiration. According to Zerem et al., in 60 cases of antibiotics + catheter drainage vs. antibiotic + needle aspiration, in abscesses of ≤ 5 cm, treatment was successful in all patients, irrespective of catheter drainage or needle aspiration. However, in cases with an abscess diameter >5 cm, catheter drainage was successful in all cases, whereas needle aspiration succeeded in only 50% of cases (13). Even very large abscesses (>10 cm) can be successfully managed with catheter drainage, although the risk of treatment failure and other complications is substantial (14, 15).

According to Ahmed et al., in Singapore, in 44 cases of hepatic abscesses exceeding 10 cm, 25% of 39 patients who underwent drainage therapy suffered complications such as death, sepsis, and pleural infiltration, and frequent drainage therapy was necessary (15). However, some reports have claimed that percutaneous transhepatic drainage therapy does not work with abscesses >5 cm in size (16). In a retrospective analysis of 80 liver abscesses exceeding 5 cm, the failure rate of percutaneous transhepatic drainage was greater than that of surgical drainage (28% vs. 7%). However, there was no significant difference in the mortality, morbidity, fever period, or incidence of complications. Surgical drainage is usually preferred in the following circumstances: multiple abscesses, loculated abscesses, abscesses with viscous contents obstructing the drainage catheter, underlying disease requiring primary surgical management, and inadequate response to percutaneous drainage within seven days (10, 11, 17, 18).

In our study, 13 of 21 patient had malignant disease. In some reports, liver abscess has been described as occasionally complicated with colon cancer (19). General screening, especially that of the colon tract, should be performed in hepatic abscess patients. A considerable proportion of pyogenic liver abscesses follow one or more episodes of portal vein pyemia, usually related to bowel leakage and peritonitis. Another important route is the direct spread from biliary infection. Underlying biliary tract disease, such as gallstones or malignant obstruction, is present in 40% to 60% of cases (20-22). Occasionally, abscesses arise from surgical or penetrating wounds, including injury from migration of an ingested foreign body (23, 24).

Recently, in aging societies, cases with various complications have increased, and patients taking antithrombotic drugs at the diagnosis cannot be punctured. In the present study as well, five patients were taking antiplatelet agents, and two were taking anticoagulants. In the future, the proportion of high-risk patients in whom puncture is difficult will increase. For this reason, it was considered very useful to identify a predictor of conservative treatment based on noninvasive contrast echography at an early stage. In the present study, we found that the stain rate of the abscess in the arterial-predominant phase of contrast ultrasound was useful as a marker for conservative treatment. If the arterial-predominant phase has a high stain rate, there is a strong likelihood that risky drainage treatment can be avoided without prolonging the hospital stay.

Although the identification of pathogenic bacteria was not possible partially due to the fact that drainage was not performed, it may nevertheless be possible to successfully detect pathogenic bacteria in blood cultures and thereby choose the optimal sensitive antibiotics. If pathogenic bacteria are not detected in a blood culture and the patient' s medical condition is getting worse, then drainage treatment should be carefully considered, including the identification of the causative bacteria and the selection of appropriate antibiotics. In addition, regarding the abscess size, 8 of 10 cases with an abscess size of ≤ 50 mm, and 11 of 13 cases with an abscess size of ≤ 60 mm improved with antibiotics only. Since it becomes difficult to form an abscess cavity as the abscess diameter shrinks, this is thought to be correlated with the stain rate in the arterial-predominant phase.

Although the diameter of the abscess is useful as a marker, it is thought that the stain rate may be more useful, as in this study, 11 of the 12 patients in the VE group improved with antibiotics only. In the VE group, the hospitalization period was not extended, even when drainage was not performed. Due to the fact that the non-necrotic area was deemed to be indicated for conservative treatment and the area had still not liquefied, the benefits obtainable by drainage were therefore thought to be negligible. In the VE group, one patient who did not improve with conservative therapy had an abscess that burst near the liver surface. When an abscess is near the liver surface, the risk of rupture should always be considered.

Our study was limited by the small sample size and the use of only a single contrast agent that is not available in many countries.

Conclusion

Although decision-making in cases of liver abscess is difficult based on the post-vascular phase of CEUS, the enhancement rate in the arterial-predominant phase can predict the response to conservative treatment.

The authors state that they have no Conflict of Interest (COI).

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