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Editorial

Defect Reperfusion Imaging with Sonazoid®: A Breakthrough in Hepatocellular Carcinoma

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Editor *Liver Cancer*

The basic concept of contrast-enhanced ultrasonography (CEUS) has been confined to the hepatic nodule, which is detected by B-mode ultrasound (US). This is applicable to contrast agents such as SonoVue® [1, 2]. However, the use of Sonazoid® in combination with a technique termed defect reperfusion US imaging [3–5] has changed the management of hepatocellular carcinoma (HCC) drastically. Sonazoid® has three favorable properties: it allows real-time vascular imaging, stable Kupffer phase imaging lasting up to 60 minutes, and its use is tolerable for multiple scanning. Defect reperfusion US imaging, which is based on reinjection at the Kupffer phase, enables the detection of B-mode ill-defined nodules and locally recurring nodules. In addition, it facilitates the correct diagnosis of nodules detected on screening/surveillance or the detection of additional nodules for staging before treatment. This is a breakthrough technique that will change the clinical practice pattern of HCC management.

Background

Despite advances in diagnostic imaging techniques for HCC such as US, computed tomography (CT) and magnetic resonance imaging (MRI), many challenges remain unresolved, such as differential diagnosis, surveillance, staging, evaluation of treatment response, treatment guidance, identification of local recurring nodules after treatment, and the diagnosis of intrahepatic recurrence after treatment [6–11]. Among the techniques used to overcome these problems, Levovist®-enhanced US has contributed to diagnostic differentiation [12–14], evaluation of malignancy grade [15], evaluation of the therapeutic response to transarterial chemoembolization (TACE) [16–21], and needle insertion guidance [22, 23] to some extent. However, there are still significant limitations in the evaluation of the therapeutic response to radiofrequency ablation (RFA) [24–26], screening and staging.

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The main advantages of Sonazoid® are that it facilitates stable Kupffer phase imaging tolerable for repeated scanning from 10 to 60 minutes after its injection and the acquisition of real-time blood flow images at low acoustic power. Sonazoid® is more effective than Levovist® for real-time vascular imaging, it is easier to use, and it allows accurate imaging even with non high-end machines [27, 28]. This reduces the dependence on skills and machines, which may help facilitate the widespread use of CEUS.

Sonazoid®-enhanced US in combination with defect reperfusion imaging, which consists of Sonazoid® reinjection into areas showing defects in the Kupffer phase, is an innovative breakthrough technique that will change the clinical practice of HCC management [4, 5].

Defect Reperfusion Imaging with Sonazoid®

CEUS with Sonazoid® allows the acquisition of stable Kupffer images and real-time fine blood flow images. These features make it a useful technique for the diagnosis of typical HCC, which is depicted by CT but not by B-mode US scanning. Dynamic diagnostic imaging is based on enhancing patterns according to a time sequence or phase. However, by changing the basic idea, combined Kupffer and arterial phase images are obtained by Sonazoid® reinjection at the Kupffer phase.

After intravenous injection of Sonazoid® (0.01 ml/kg), early enhancement is observed in the vascular phase, and the presence or absence of defects is determined by an entire liver scan in the Kupffer phase 10–60 minutes after injection. Subsequently, the probe is applied to the area that shows a defect in the Kupffer phase. An additional injection of Sonazoid® (0.01 ml/kg) is used to determine the presence or absence of arterial blood flow in the defective area (defect reinjection test). A fast wash-in of arterial flow in the Kupffer defect area confirms the diagnosis of HCC [5]. The detection rate of HCC with Sonazoid®-enhanced US is superior to that of dynamic CT [29].

Detection of B-Mode US Undetectable HCC and Treatment Guidance

HCC nodules that cannot be visualized by B-mode US, but which are detected by dynamic CT, defects can be detected at the Kupffer phase by Sonazoid®-enhanced US. Reinjection of Sonazoid® allows the detection of a clear wash-in and staining in the Kupffer defect area (positive defect reperfusion sign). These defects can be treated by RFA. Kupffer phase Sonazoid®-enhanced US-guided RFA is possible in almost all cases of HCC that are not identified by B-mode US, with a sensitivity as high as 100% [30–34].

Response Evaluation after Locoregional Therapy

Treatment response after RFA or TACE is most accurately evaluated with Sonazoid®-enhanced US with a concurrent use of defect reperfusion imaging [35–39].

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Detection of Local Progression after RFA

In cases of local progression or recurrence at a different region after RFA, that is not identified by B-mode US, the recurring nodules can be clearly identified in all cases (sensitivity: 100%) using CEUS with the Sonazoid® reinjection technique [40].

Surveillance and Confirmation of HCC

Surveillance of HCC is also possible by Kupffer phase of Sonazoid®-enhanced US [41]. A defect reperfusion US study is performed in cases in which a Kupffer defect is found. Sonazoid® (0.01 ml/kg) is intravenously injected into a patient at high risk of HCC (hepatitis B and C liver cirrhosis) in the outpatient setting. Subsequently, patients then undertake a US for the Kupffer phase imaging at between 10–60 minutes post-injection. When a defective area is identified at the Kupffer phase, reinjection of Sonazoid® is performed to determine the presence or absence of an arterial supply in the Kupffer-defect nodule. If an arterial supply is confirmed, a definitive diagnosis of HCC is also possible [41]. In this way, tiny HCC nodules smaller than 15 mm can be successfully depicted and confirmed.

Diagnosis of Pathologically Early HCC

Nodules showing a hypovascular pattern in the arterial phase on dynamic CT/MRI can show a hypervascular pattern with Sonazoid®-enhanced US, which is the most sensitive technique for the detection of arterial flow among all imaging modalities [29]. This indicates the presence of arterial flow in a well-to-moderately differentiated HCC nodule.

However, pathologically early HCC usually shows a hypovascular pattern at the early arterial phase and low intensity at the Kupffer phase. Also, it is well known that both dysplastic nodules and early HCC are both fed by portal blood flow, which can be also demonstrated by Sonazoid®-enhanced US [42]. This pattern provides an important clue for the diagnosis of pathologically early HCC, although a tumor biopsy is necessary for confirmation. In the diagnosis of pathologically early HCC, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI (Gd-DTPA EOB-MRI) is superior to CEUS with Sonazoid®, as stated in the Consensus-based HCC Practice Guidelines proposed by the Japan Society of Hepatology [8]. However, in the diagnosis of pathologically early HCC, Sonazoid®-enhanced US plays an important role to confirm it noninvasively [43, 44].

Intraoperative US

Intraoperative US is the most sensitive tool for the detection of additional liver nodules that are not detected by preoperative imaging. Kupffer defects detected in the Kupffer phase are not always intrahepatic HCC metastases, and defect reperfusion imaging is useful to distinguish true metastatic HCC lesions from the other types of tumors, such as cysts, hemangiomas or focal nodular hyperplasia [27, 45].

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Diagnosis of the Gross Pathological Type of HCC

Simple nodular with extra growth, and confluent multinodular type of HCC are biologically more malignant than simple nodular type of HCC [46, 47]. CEUS in the Kupffer phase is a useful technique for the identification of the gross pathological type of HCC, which is important to determine the optimal treatment strategy. Defect reperfusion imaging is used to confirm the gross pathological type of HCC, for which the diagnostic accuracy of Sonazoid®-enhanced US is superior to that of dynamic CT [48, 49].

Summary

The detection of small nodular lesions in coarse liver parenchyma is difficult by B-mode US alone, although dynamic CT or dynamic MRI can detect arterial enhancing nodules with venous washout. Approximately 10% of HCC nodules that are not detected by B-mode US can be clearly identified by defect reperfusion imaging with Sonazoid®. The false positive rate increases when the technique is confined to Kupffer phase scanning. In addition to the Kupffer defect, information on arterial vascularity, i.e., the reinjection method, increases the diagnostic accuracy to 100% even in deeply seated nodules.

This breakthrough method allows the detection of nodules that cannot be visualized by B-mode US, as defects on Kupffer images in the stable Kupffer phase. The presence of arterial blood flow in nodules with Kupffer defects is subsequently determined by the reinjection technique, making this method a breakthrough in diagnostic imaging [4, 5]. CEUS with Sonazoid® reinjection requires no special apparatus or analysis, and is the result of a change in the way of thinking regarding CEUS. For the typical CT image (so-called early enhancement with late washout nodules), defects are easily detected in the Kupffer phase, and arterial perfusion within the defect is subsequently demonstrated by the reinjection test (visualization of staining within the Kupffer defects, which is the reverse phenomenon of early enhancement with late washout). The introduction of this technique has allowed almost 100% accuracy in the detection of lesions observed on CT images that are not visualized on B-mode US images.

If the reinjection test shows no enhancement of a Kupffer defect, this defect differs from the nodule detected by CT. This method then serves to guide needle insertion.

In surveillance, this procedure facilitates screening because Sonazoid® US can be performed in the setting of a routine examination. In addition, operators only need to concentrate on the delineation of Kupffer defects in the Kupffer phase in contrast to routine B-mode US, in which regenerative nodules or dysplastic nodules may mimic malignant ones. If defects are detected, HCC can be confirmed by Sonazoid® reinjection, which provides information on both Kupffer cell function and arterial blood flow on the same cross-sectional image. This dual phase fusion imaging allows detection and definitive diagnosis of HCC with 100% confidence. As a result, Sonazoid® has markedly improved the efficiency of HCC detection.

In the past, CEUS was considered only for nodules previously depicted by B-mode US and was not used as a screening tool. However, this concept changed with the introduction of defect reperfusion imaging using Sonazoid®.

Defect reperfusion imaging is also useful for the localization of recurrent lesions at a previously ablated area, which is difficult by B-mode US because of the inhomogeneous echo pattern mixed with viable lesions, the ablated area, and ablated surrounding liver. In this setting, even skilled operators have difficulties determining the viable area on B-mode US images alone, which corresponds to the enhancing area on CT because of numerous US

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cross-sections [50]. This problem has been readily overcome by defect reperfusion imaging with Sonazoid®.

Defect reperfusion imaging is particularly useful for needle insertion guidance in the treatment of HCC. For invisible nodules on B-mode US, needle insertion can be performed under the guidance of either fusion imaging [51, 52] or SonoVue®-enhanced US. However, fusion imaging requires CT/MRI volume data and special apparatus. In addition, complete concordance of synchronized images from B-mode US that correspond to the cross-sectional plane of CT/MRI volume data is sometimes difficult. Similarly, under SonoVue®-enhanced US, puncture should be performed in a very short time in the early arterial phase.

Conversely, in Sonazoid®-enhanced US, Kupffer defects are detected easily, and whether blood flow is present in defective areas can be determined by the reinjection technique (defect reperfusion imaging) in all cases. Therefore, needle insertion can be easily performed during a stable period in the Kupffer phase, and accurate needle placement followed by sufficient treatment is possible with Sonazoid®-enhanced US.

Conclusions

CEUS with Sonazoid® is useful in the characterization of hepatic tumors when compared with multidetector raw CT. Sonazoid®-enhanced US with defect reperfusion imaging is a breakthrough technique in the diagnosis and treatment of HCC. This innovative technique was developed based on the two major favorable properties of Sonazoid®, namely, the demonstration of real-time blood flow images with low acoustic power, and stable Kupffer phase images tolerable for repeated scanning in the Kupffer phase. Among them, especially the presence of a Kupffer phase is the key of defect reperfusion imaging. This technique will markedly change the clinical practice of HCC management. The method is not possible with SonoVue® or Definity®, which do not have Kupffer phase imaging properties. Although these contrast agents are approved in most parts of the world, the Kuppfer phase imaging technique is only possible using Sonazoid®, which is so far only approved in Japan, Korea, China and Norway. In this respect, Sonazoid® should be made more available worldwide.

References

1 Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX, World Federation for Ultrasound in Medicine European Federation of Societies for Ultrasound: Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultrasound Med Biol 2013;39:187–210.
2 Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX: Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver—update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultraschall Med 2013;34:11–29.
3 Kudo M, Hatanaka K, Chung H, Minami Y, Maekawa K: A proposal of novel treatment-assist technique for hepatocellular carcinoma in the sonazoid-enhanced ultrasonography: Value of defect re-perfusion imaging. Kanzo 2007;48:299–301 (in Japanese).
4 Kudo M: Defect reperfusion imaging, a newly developed novel technology using sonazoid in the treatment of hepatocellular carcinoma. J Med Ultrasound 2008;16:169–176.
5 Kudo M, Hatanaka K, Maekawa K: Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78(Suppl 1):40–45.

Liver Cancer 2016;5:1–7
DOI: 10.1159/000367760
Published online: December 15, 2015

6 Murakami T, Tsurusaki M: Hypervascular benign and malignant liver tumors that require differentiation from hepatocellular carcinoma: key points of imaging diagnosis. Liver Cancer 2014;3:85–96.
7 Ichikawa T, Sano K, Morisaka H: Diagnosis of pathologically early HCC with eob-mri: Experiences and current consensus. Liver Cancer 2014;3:97–107.
8 Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K, Liver Cancer Study Group of Japan: JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer 2014;3:458–468.
9 Kudo M: Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. Liver Cancer 2015;4:39–50.
10 Minami Y, Kudo M: Imaging modalities for assessment of treatment response to nonsurgical hepatocellular carcinoma therapy: Contrast-enhanced US, CT, and MRI. Liver Cancer 2015;4:106–114.
11 Ichikawa S, Ichikawa T, Motosugi U, Sano K, Morisaka H, Enomoto N: Was hypervascular hepatocellular carcinoma visible on previous gadoxetic acid-enhanced magnetic resonance images? Liver Cancer 2015;4:154–162.
12 Kudo. M: Contrast harmonic imaging in the diagnosis and treatment of hepatic tumors.; Springer Verlag. Tokyo, 2003, pp p1-253.
13 Wen YL, Kudo M, Zheng RQ, Ding H, Zhou P, Minami Y, Chung H, Kitano M, Kawasaki T, Maekawa K: Characterization of hepatic tumors: value of contrast-enhanced coded phase-inversion harmonic angio. AJR Am J Roentgenol 2004;182:1019–1026.
14 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K: Hepatocellular carcinoma: depiction of tumor parenchymal flow with intermittent harmonic power Doppler US during the early arterial phase in dual-display mode. Radiology 2001;220:349–356.
15 Inoue T, Kudo M, Watai R, Pei Z, Kawasaki T, Minami Y, Chung H, Fukunaga T, Awai K, Maenishi O: Differential diagnosis of nodular lesions in cirrhotic liver by post-vascular phase contrast-enhanced US with Levovist: comparison with superparamagnetic iron oxide magnetic resonance images. J Gastroenterol 2005;40:1139–1147.
16 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K: Contrast-enhanced subtraction harmonic sonography for evaluating treatment response in patients with hepatocellular carcinoma. AJR Am J Roentgenol 2001;176:661–666.
17 Minami Y, Kudo M, Kawasaki T, Kitano M, Chung H, Maekawa K, Shiozaki H: Transcatheter arterial chemoembolization of hepatocellular carcinoma: usefulness of coded phase-inversion harmonic sonography. AJR Am J Roentgenol 2003;180:703–708.
18 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Chung H, Kawasaki T, Maekawa K: Evaluation of posttreatment response of hepatocellular carcinoma with contrast-enhanced coded phase-inversion harmonic US: comparison with dynamic CT. Radiology 2001;221:721–730.
19 Raoul JL, Gilabert M, Piana G: How to define transarterial chemoembolization failure or refractoriness: a European perspective. Liver Cancer 2014;3:119–124.
20 Kudo M: Locoregional therapy for hepatocellular carcinoma. Liver Cancer 2015;4:163–164.
21 Tsurusaki M, Murakami T: Surgical and locoregional therapy of HCC. Tace Liver Cancer 2015;4:165–175.
22 Minami Y, Kudo M, Kawasaki T, Chung H, Ogawa C, Shiozaki H: Treatment of hepatocellular carcinoma with percutaneous radiofrequency ablation: usefulness of contrast harmonic sonography for lesions poorly defined with B-mode sonography. AJR Am J Roentgenol 2004;183:153–156.
23 Minami Y, Kudo M, Chung H, Kawasaki T, Yagyu Y, Shimono T, Shiozaki H: Contrast harmonic sonography-guided radiofrequency ablation therapy versus B-mode sonography in hepatocellular carcinoma: prospective randomized controlled trial. AJR Am J Roentgenol 2007;188:489–494.
24 Wen YL, Kudo M, Zheng RQ, Minami Y, Chung H, Suetomi Y, Onda H, Kitano M, Kawasaki T, Maekawa K: Radiofrequency ablation of hepatocellular carcinoma: therapeutic response using contrast-enhanced coded phase-inversion harmonic sonography. AJR Am J Roentgenol 2003;181:57–63.
25 Teng W, Liu KW, Lin CC, Jeng WJ, Chen WT, Sheen IS, Lin CY, Lin SM: Insufficient ablative margin determined by early computed tomography may predict the recurrence of hepatocellular carcinoma after radiofrequency ablation. Liver Cancer 2015;4:26–38.
26 Kang TW: Recent advances in tumor ablation for hepatocellular carcinoma. Liver Cancer 2015;4:176–187.
27 Hatanaka K, Kudo M, Minami Y, Ueda T, Tatsumi C, Kitai S, Takahashi S, Inoue T, Hagiwara S, Chung H, Ueshima K, Maekawa K: Differential diagnosis of hepatic tumors: value of contrast-enhanced harmonic sonography using the newly developed contrast agent, Sonazoid. Intervirology 2008;51(Suppl 1):61–69.
28 Kudo M, Hatanaka K, Maekawa K: Sonazoid-enhanced ultrasound in the diagnosis and treatment of hepatic tumors. J Med Ultrasound 2008;16:130–139.
29 Hatanaka K, Kudo M, Minami Y, Maekawa K: Sonazoid-enhanced ultrasonography for diagnosis of hepatic malignancies: comparison with contrast-enhanced CT. Oncology 2008;75(Suppl 1):42–47.
30 Kudo M: The 2008 Okuda lecture: Management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. J Gastroenterol Hepatol 2010;25:439–452.
31 Minami Y, Kudo M, Hatanaka K, Kitai S, Inoue T, Hagiwara S, Chung H, Ueshima K: Radiofrequency ablation guided by contrast harmonic sonography using perfluorocarbon microbubbles (Sonazoid) for hepatic malignancies: an initial experience. Liver Int 2010;30:759–764.
32 Inoue T, Minami Y, Chung H, Hayaishi S, Ueda T, Tatsumi C, Takita M, Kitai S, Hatanaka K, Ishikawa E, Yada N, Hagiwara S, Ueshima K, Kudo M: Radiofrequency ablation for hepatocellular carcinoma: assistant techniques for difficult cases. Oncology 2010;78(Suppl 1):94–101.

Liver Cancer 2016;5:1–7
DOI: 10.1159/000367760
Published online: December 15, 2015

33 Minami Y, Kudo M: Review of dynamic contrast-enhanced ultrasound guidance in ablation therapy for hepatocellular carcinoma. World J Gastroenterol 2011;17:4952–4959.
34 Minami Y, Okumura N, Yamamoto N, Tsuji N, Kono Y, Kudo M: Quantification of tumor vascularity with contrast-enhanced ultrasound for early response of transcatheter arterial chemoembolization for hepatocellular carcinoma: A report of three cases. J Med Ultrasound 2012;39:15–19.
35 Xia Y, Kudo M, Minami Y, Hatanaka K, Ueshima K, Chung H, Hagiwara S, Inoue T, Ishikawa E, Kitai S, Takahashi S, Tatsumi C, Ueda T, Hayaishi S, Maekawa K: Response evaluation of transcatheter arterial chemoembolization in hepatocellular carcinomas: the usefulness of sonazoid-enhanced harmonic sonography. Oncology 2008;75(Suppl 1):99–105.
36 Andreana L, Kudo M, Hatanaka K, Chung H, Minami Y, Maekawa K, Ruggiero G: Contrast-enhanced ultrasound techniques for guiding and assessing response to locoregional treatments for hepatocellular carcinoma. Oncology 2010;78(Suppl 1):68–77.
37 Inoue T, Kudo M, Hatanaka K, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, Minami Y, Sakurai T, Ueshima K, Nishida N: Usefulness of contrast-enhanced ultrasonography to evaluate the post-treatment responses of radiofrequency ablation for hepatocellular carcinoma: comparison with dynamic CT. Oncology 2013;84(Suppl 1):51–57.
38 Minami Y, Kudo M: Therapeutic response assessment of transcatheter arterial chemoembolization for hepatocellular carcinoma: ultrasonography, CT and MR imaging. Oncology 2013;84(Suppl 1):58–63.
39 Minami Y, Nishida N, Kudo M: Therapeutic response assessment of RFA for HCC: contrast-enhanced US, CT and MRI. World J Gastroenterol 2014;20:4160–4166.
40 Inoue T, Kudo M, Hatanaka K, Takahashi S, Kitai S, Ueda T, Ishikawa E, Hagiwara S, Minami Y, Chung H, Ueshima K, Maekawa K: Imaging of hepatocellular carcinoma: qualitative and quantitative analysis of postvascular phase contrast-enhanced ultrasonography with sonazoid. Comparison with superparamagnetic iron oxide magnetic resonance images. Oncology 2008;75(Suppl 1):48–54.
41 Kudo M, Hatanaka K, Kumada T, Toyoda H, Tada T: Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. Am J Gastroenterol 2011;106:368–370.
42 Kudo M, Hatanaka K, Inoue T, Maekawa K: Depiction of portal supply in early hepatocellular carcinoma and dysplastic nodule: value of pure arterial ultrasound imaging in hepatocellular carcinoma. Oncology 2010;78(Suppl 1):60–67.
43 Inoue T, Kudo M, Maenishi O, Komuta M, Nakashima O, Kojiro M, Maekawa K: Value of liver parenchymal phase contrast-enhanced sonography to diagnose premalignant and borderline lesions and overt hepatocellular carcinoma. AJR Am J Roentgenol 2009;192:698–705.
44 Inoue T, Hyodo T, Korenaga K, Murakami T, Imai Y, Higaki A, Suda T, Takano T, Miyoshi K, Koda M, Tanaka H, Iijima H, Ochi H, Hirooka M, Numata K, Kudo M: Kupffer phase image of Sonazoid-enhanced US is useful in predicting a hypervascularization of non-hypervascular hypointense hepatic lesions detected on Gd-EOB-DTPA-enhanced MRI: a multicenter retrospective study. J Gastroenterol 2015; Epub ahead of print.
45 Mitsunori Y, Tanaka S, Nakamura N, Ban D, Irie T, Noguchi N, Kudo A, Iijima H, Arii S: Contrast-enhanced intraoperative ultrasound for hepatocellular carcinoma: High sensitivity of diagnosis and therapeutic impact. Journal of hepatobiliary-pancreatic sciences 2013;20:234–242.
46 Hui AM, Takayama T, Sano K, Kubota K, Akahane M, Ohtomo K, Makuuchi M: Predictive value of gross classification of hepatocellular carcinoma on recurrence and survival after hepatectomy. J Hepatol 2000;33:975–979.
47 Shirabe K, Aishima S, Taketomi A, Soejima Y, Uchiyama H, Kayashima H, Ninomiya M, Mano Y, Maehara Y: Prognostic importance of the gross classification of hepatocellular carcinoma in living donor-related liver transplantation. Br J Surg 2011;98:261–267.
48 Hatanaka K, Chung H, Kudo M, Haji S, Minami Y, Maekawa K, Hayaishi S, Nagai T, Takita M, Kudo K, Ueda T, Tatsumi C, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Ueshima K: Usefulness of the post-vascular phase of contrast-enhanced ultrasonography with sonazoid in the evaluation of gross types of hepatocellular carcinoma. Oncology 2010;78(Suppl 1):53–59.
49 Hatanaka K, Minami Y, Kudo M, Inoue T, Chung H, Haji S: The gross classification of hepatocellular carcinoma: usefulness of contrast-enhanced US. J Clin Ultrasound 2014;42:1–8.
50 Kudo M: Local ablation therapy for hepatocellular carcinoma: current status and future perspectives. J Gastroenterol 2004;39:205–214.
51 Minami Y, Kudo M, Chung H, Inoue T, Takahashi S, Hatanaka K, Ueda T, Hagiwara H, Kitai S, Ueshima K, Fukunaga T, Shiozaki H: Percutaneous radiofrequency ablation of sonographically unidentifiable liver tumors. Feasibility and usefulness of a novel guiding technique with an integrated system of computed tomography and sonographic images. Oncology 2007;72(Suppl 1):111–116.
52 Minami T, Minami Y, Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Inoue T, Hagiwara S, Ueshima K, Nishida N, Kudo M: Combination guidance of contrast-enhanced US and fusion imaging in radiofrequency ablation for hepatocellular carcinoma with poor conspicuity on contrast-enhanced US/fusion imaging. Oncology 2014;87(Suppl 1):55–62.