J Med Ultrasonics (2013) 40:81–84
DOI 10.1007/s10396-012-0380-9

LETTER TO THE EDITOR

Contrast-enhanced ultrasonography using Sonazoid® is useful for diagnosis of malignant ovarian tumors: comparison with Doppler ultrasound

Shoko Kumazawa · Tomokazu Umezu · Yuko Kanayama · Naohisa Kamiyama · Shiro Suzuki · Mika Mizuno · Hiroaki Kajiyama · Kiyosumi Shibata · Fumitaka Kikkawa

Received: 15 February 2012 / Accepted: 18 May 2012 / Published online: 4 July 2012

Abstract
Purpose The purpose of this study was to assess the usefulness of Sonazoid®-enhanced ultrasonography (US) in the diagnosis of ovarian cancer in comparison with Doppler US.
Methods Twenty-five ovarian tumor patients who were scheduled to undergo surgery were recruited for this study. The day before the operation, each patient was evaluated with color and power Doppler and baseline US during intravenous infusion of Sonazoid. Each lesion was classified as "benign" or "malignant" on the basis of specific criteria for a Doppler signal or Sonazoid-enhanced pattern. The reference standard was the histology of surgically removed adnexal tumors.
Results Twenty patients were diagnosed with malignant tumors (invasive cancer, $n = 15$; metastatic cancer, $n = 1$; borderline tumor, $n = 4$), and the remaining five were diagnosed with benign tumors. Sonazoid-enhanced US correctly depicted the presence or absence of intratumoral blood flow in all patients with an accuracy of 92 %. Color Doppler ultrasound depicted the malignancies with an accuracy of 64 %, and power Doppler ultrasound depicted them with an accuracy of 76 %.
Conclusion Our study suggests that Sonazoid-enhanced US is superior to conventional color Doppler US for the diagnosis of malignant ovarian tumors, but not to power Doppler US. The data and their interpretation in our study should be taken with some degree of caution because of the small number of subjects. Further studies involving a larger sample size would be needed to confirm these findings.

Keywords Ovary · Cancer · Ultrasound · Enhance · Sonazoid

Epithelial ovarian cancer (EOC) has the poorest prognosis of gynecologic malignancies. The correct characterization of adnexal masses is important for optimal patient management. Imaging methods, particularly ultrasound (US) imaging, are almost always used to determine the nature of a mass [1]. The blood vessels that supply malignant tumors have morphologic and hemodynamic characteristics that differ from those observed in benign tumors.

Recently, in the case of hepatic tumors, contrast-enhanced US with an intravenous contrast agent has been demonstrated to depict tumor vascularity sensitively and accurately thanks to advances in US instruments and contrast agents [2–4]. The perfluorocarbon microbubble (Sonazoid®) is a second-generation contrast agent that contains perflubutane within a hard shell. The purpose of this study was to assess the usefulness of Sonazoid-enhanced harmonic US for the diagnosis of ovarian malignancies in comparison with Doppler US findings. Institutional review board approval was obtained for this study, and written informed consent was obtained from all patients.

Twenty-five patients strongly suspected of having an ovarian tumor after conventional US examinations were referred for enhanced transvaginal US examination using intravenous Sonazoid injection between February 2010 and

S. Kumazawa · T. Umezu (✉) · S. Suzuki · M. Mizuno · H. Kajiyama · K. Shibata · F. Kikkawa
Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8550, Japan
e-mail: t-ume@med.nagoya-u.ac.jp

Y. Kanayama · N. Kamiyama
Ultrasound Division, Toshiba Medical Systems Corporation, Ishigami 1385, Otawara, Tochigi, Japan

March 2011 at Nagoya University Hospital, Japan. The day before the operation, all patients were examined with Sonazoid-enhanced US as well as color and power Doppler US in this study. US was performed using the Aplio XG (Toshiba Medical Systems, Tokyo, Japan) and a vaginal probe (3.5–7 MHz). The machine setting for color Doppler was PRF, 4–10; wall motion filter, 3; FIO, on; CDI-MAP, 5; data no., 1; MAE, 2; CDI-Psel, 1; FrameInterplat, 2; CDI-TimeSmooth, 2; SpatialSmooth, 2; and Balance, 14. The machine setting for power Doppler was PRF, 4–10; wall motion filter, 3; FIO, on; CDI-MAP, 3; Data No., 1; MAE, 2; CDI-Psel, 1; FrameInterplat, 2; CDI-TimeSmooth, 3; SpatialSmooth, 2: and Power-DR, 20.

Two physicians reviewed the clips of Doppler US and Sonazoid-enhanced US off-line in a consensus-based manner. The likelihood that a lesion represented a vascular finding was scored by each reader on a 2-point scale: score 1, no blood flow; score 2, positive blood flow. Figure 1 shows representative examples of Sonazoid-enhanced ultrasound images. To resolve discrepancies between the two observers, a third observer assessed all discrepant cases. However, there was no disagreement between the two observers.

On the basis of subjective evaluation of the Doppler and Sonazoid-enhanced ultrasound findings (pattern recognition), the examiner estimated the risk of malignancy. During scoring, the readers were aware that calculation of sensitivity would include those lesions assigned a score of point 2. The results were considered true positives only when the anatomic sites were matched between the imaging study and the histologic results. Statistical analysis was performed using the chi-squared test. A p value < 0.05 was considered significant. Data were analyzed using SPSS 19 software (SPSS, Chicago, IL, USA).

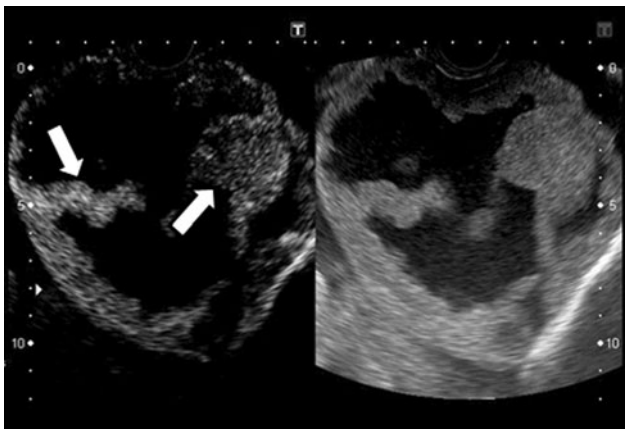

Fig. 1 Ultrasound characteristics on Sonazoid-enhanced examination of a solid projection (*right panel* B-mode image, *left panel* Sonazoid-enhanced image). Sonazoid-enhanced US showed diffuse vascularization in the solid projection (*white arrow*) (score 2). The final histopathologic diagnosis was endometrioid adenocarcinoma

Ovarian masses were surgically removed in all 25 patients; 20 of these patients had malignant tumors (three serous adenocarcinomas, four mucinous adenocarcinomas, two endometrioid adenocarcinomas, six clear cell carcinomas, one metastatic tumor, and four borderline tumors), and five had benign ovarian tumors (two serous cyst adenomas, one mucinous cyst adenoma, one mature cystic teratoma, and one chocolate cyst) (Table 1). In all cases, Doppler US and Sonazoid-enhanced US were performed without any side effect.

The results of color and power Doppler US and Sonazoid-enhanced US analysis are shown in Table 2. In discriminating between benign and malignant, the accuracies of color Doppler, power Doppler, and Sonazoid-enhanced US were 64, 76, and 92 %, respectively (Table 3). The accuracy of Sonazoid-enhanced US trended higher than that of color and power Doppler US, although it was not

Table 1 Patients, characteristics and pathologic diagnosis

Number	25
Age, years (mean)	15–74 (55)
Pathologic diagnosis	
Benign	
Serous cyst adenoma	2
Mucinous cyst adenoma	1
Mature cystic teratoma	1
Chocolate cyst	1
Malignant	
Borderline tumor	4
Serous adenocarcinoma	3
Mucinous adenocarcinoma	4
Endometrioid adenocarcinoma	2
Clear cell carcinoma	6
Metastatic tumor	1

Table 2

	Pathologic diagnosis	
	Benign	Malignant
Color Doppler US		
Score 1	6	9
Score 2	0	10
Power Doppler US		
Score 1	5	5
Score 2	1	14
Sonazoid-enhanced US		
Score 1	5	1
Score 2	1	18

Score 1 no blood flow, *Score 2* positive blood flow

Table 3

Validity parameters (%)	Color Doppler US	Power Doppler US	Enhanced US
Accuracy	64*	76	92
Sensitivity	53*	74	95
Specificity	100	83	83
PPV	100	93	95
NPV	40	50	83

PPV positive predictive value, *NPV* negative predictive value

* $p < 0.05$

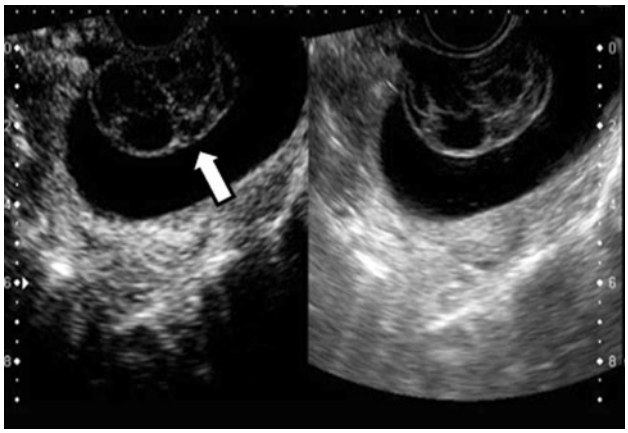

Fig. 2 Sonazoid-enhanced US detected vascularization of the tumoral capsule (*white arrow*) (score 2). The final histopathologic diagnosis was mucinous cyst adenoma

statistically significant. However, there was one false-positive case using Sonazoid (Fig. 2). In that case, the ovarian tumor had multiple cysts. Intratumoral capsule vascularity was detected using Sonazoid, so observers detected a positive blood flow. The pathologic result was mucinous cyst adenoma.

Diagnosis of a malignant ovarian tumor requires assessment of morphologic characteristics as well as vascularity and enhancement patterns within the lesion. In the case of ultrasound, the standard approach for the diagnosis of a malignant ovarian tumor includes only the use of color and power Doppler US, which is not able to demonstrate the microvasculature. Thus, in our study, the accuracy using color and power Doppler US was low. With the introduction of ultrasound contrast agents like Sonazoid, assessment of the intratumoral vascularity pattern became possible. In this study, the malignant imaging pattern of contrast-enhanced US using Sonazoid had a higher accuracy for the diagnosis of ovarian malignancies compared with color and power Doppler US, although it was not statistically significant. The lack of a statistically significant difference might have been due to the small sample size.

A recent study reported that Doppler US was inferior to magnetic resonance imaging (MRI) and computed tomography (CT) in the identification of malignancy [5]. A recent prospective study conducted by the Radiology Diagnostic Oncology Group (RDOG) showed that CT and MRI were equally accurate for diagnosing and staging advanced ovarian cancer [6]. Studies of contrast CT and MRI have shown sensitivities of almost 90 % in the diagnosis of ovarian cancer [7]. However, MRI and CT have some disadvantages. MRI involves a long acquisition time, burdening patients. CT involves the patients being exposed to ionizing radiation and iodinated contrast material. CT and MRI involve waiting times, which can be stressful for patients. Sonazoid-enhanced US can be performed immediately after standard abdominal ultrasound, and thus a confident diagnosis can be obtained in approximately 3 min. Further, Sonazoid-enhanced US requires no exposure to radiation or use of nephrotoxic contrast agents, and the machines are widely available. Sonazoid is a well-tolerated drug owing to its low rate of mild side effects. Sonazoid-enhanced US showed a sensitivity of 95 % in the diagnosis of ovarian cancer. This was superior to the sensitivity for diagnosing ovarian cancer using MRI or CT. However, this study involved a small number of subjects. Thus, further studies with larger series of patients are necessary to clarify the usefulness of Sonazoid-enhanced US for the diagnosis of benign and malignant ovarian tumors.

In conclusion, Sonazoid-enhanced US may assist in the diagnosis of malignant ovarian tumors and offer potential advantages relative to conventional Doppler US. However, the data and their interpretation in our study should be taken with some degree of caution because of the small number of subjects. Further studies involving a larger sample size would be needed to confirm these findings.

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Valentin L. Imaging in gynecology. Best Pract Res Clin Obstet Gynaecol. 2006;20:881.
2. Fujimoto M, Moriyasu F, Nishikawa K, et al. Color Doppler sonography of hepatic tumors with a galactose-based contrast agent: correlation with angiographic findings. AJR Am J Roentgenol. 1994;163:1099.
3. Ding H, Kudo M, Onda H, et al. 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.
4. Kudo M, Tomita S, Tochio H, et al. Sonography with intraarterial infusion of carbon dioxide microbubbles (sonographic angiography):

value in differential diagnosis of hepatic tumors. AJR Am J Roentgenol. 1992;158:65.
5. Kinkel K, Lu Y, Mehdizade A, et al. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization—meta-analysis and Bayesian analysis. Radiology. 2005; 236:85.
6. Tempany CM, Zou KH, Silverman SG, et al. Staging of advanced ovarian cancer: comparison of imaging modalities—report from the Radiological Diagnostic Oncology Group. Radiology. 2000;215:761.
7. Liu J, Xu Y, Wang J. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma. Eur J Radiol. 2007;62:328.