Soft-tissue Tumor Differentiation Using 3D Power Doppler Ultrasonography With Echo-contrast Medium Injection

Hong-Jen Chiou[1,3,5]*, Yi-Hong Chou[1,3], Wei-Ming Chen[2,3], Winby Chen[4], Hsin-Kai Wang[1], Cheng-Yen Chang[1,3]

Departments of [1]Radiology and [2]Orthopedic Surgery, Taipei Veterans General Hospital, [3]National Yang-Ming University School of Medicine, [4]Taipei Institute of Pathology, and [5]National Defense Medical Center, Taipei, Taiwan, R.O.C.

Background: We aimed to evaluate the ability of 3-dimensional power Doppler ultrasonography to differentiate soft-tissue masses from blood flow and vascularization with contrast medium.

Methods: Twenty-five patients (mean age, 44.1 years; range, 12–77 years) with a palpable mass were enrolled in this study. Volume data were acquired using linear and convex 3-dimensional probes and contrast medium injected manually by bolus. Data were stored and traced slice by slice for 12 slices. All patients were scanned by the same senior sonologist. The vascular index (VI), flow index (FI), and vascular-flow index (VFI) were automatically calculated after the tumor was completely traced. All tumors were later confirmed by pathology.

Results: The study included 8 benign (mean, 36.5 mL; range, 2.4–124 mL) and 17 malignant (mean, 319.4 mL; range, 9.9–1,179.6 mL) tumors. Before contrast medium injection, mean VI, FI and VFI were, respectively, 3.22, 32.26 and 1.07 in benign tumors, and 1.97, 29.33 and 0.67 in malignant tumors. After contrast medium injection, they were, respectively, 20.85, 37.33 and 8.52 in benign tumors, and 40.12, 41.21 and 17.77 in malignant tumors. The mean differences between with and without contrast injection for VI, FI and VFI were, respectively, 17.63, 5.07 and 7.45 in benign tumors, and 38.15, 11.88 and 16.55 in malignant tumors. Tumor volume, VI, FI and VFI were not significantly different between benign and malignant tumors before and after echo-contrast medium injection. However, VI, FI and VFI under self-differentiation (differences between with and without contrast injection) were significantly different between malignant and benign tumors.

Conclusion: Three-dimensional power Doppler ultrasound is a valuable tool for differential diagnosis of soft-tissue tumors, especially with the injection of an echo-contrast medium. [*J Chin Med Assoc* 2010;73(12):628–633]

Key Words: echo-contrast medium, soft-tissue tumor, 3D power Doppler ultrasonography, vascular-flow index

Introduction

Soft-tissue tumors are not uncommon and most are benign. In the USA, the annual incidence of soft-tissue tumors is approximately 3 cases per 1,000 people, approximately 1 in 150 of which are malignant.[1] Soft-tissue malignancy accounts for 0.64% of all malignant tumors in Taiwan.[2] These tumors include soft-tissue sarcomas, the outcomes of which vary with prompt management. As with small tumors, prognosis is better for low-grade than for high-grade sarcoma.[3,4]

Several imaging modalities are used to assess soft-tissue tumors, including plain radiography, nuclear medicine study, high-resolution ultrasonography (US), computed tomography (CT), magnetic resonance imaging, angiography, and positron emission tomography. However, none of them reliably distinguish benign from malignant lesions,[5,6] including high-resolution

*Correspondence to: Dr Hong-Jen Chiou, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: hjchiou@vghtpe.gov.tw • Received: January 22, 2010 • Accepted: August 4, 2010

US, despite its high sensitivity in detecting tumors.[7,8] Power Doppler US (PDUS) or color Doppler US (CDUS) with spectral analysis can show vascular irregularities in malignant tumors, but the reported criteria for malignancy vary widely,[9] and some investigators have questioned their usefulness in distinguishing benign from malignant lesions.[10,11] PDUS is generally superior to CDUS, especially in situations of low-velocity blood flow.[12] Three-dimensional (3D) US has shown promising results in the obstetric, gynecologic, prostate, and cardiovascular fields.[13–15] Three-dimensional PDUS (3D-PDUS) is used in gynecologic and neck lymph node differentiation,[16,17] and in adnexa masses to quantify blood flow and vascularization.[18]

Contrast medium injection US may provide more detailed information on tumor vascularity,[19,20] and it has greatly increased sensitivity to slow flow, compared with Doppler US. A liver study showed that contrast-enhanced US improves the accuracy and confidence of diagnosis of focal liver lesions and reduces the need for further studies.[21] We previously found that when applying 3D-PDUS in soft-tissue neoplasm, there seemed to be no significant difference in the differential diagnosis between benign and malignant.[22] The purpose of this study was to evaluate the ability of 3D-PDUS to differentiate soft-tissue masses from blood flow and vascularization of the neoplasm, with and without contrast medium injection.

Methods

A total of 25 patients (13 females, 12 males; mean age, 44.1 years; age range, 12–77 years) were enrolled in this study. They were consecutively referred from the orthopedics and oncology departments at Taipei Veterans General Hospital to radiology for assessment. This study was approved by the institutional review board of Taipei Veterans General Hospital, and each patient provided written informed consent before examination.

The procedures were performed using a GE-Kretz Voluson 730 Expert 3D-PDUS machine (GE Medical Systems/Kretztechnik, Zipf, Austria), equipped with an RSP 6–12 MHz linear-array or RAB 2–5 MHz curve linear-array mechanically-driven transducer. Volume data acquisition was performed using linear and convex 3D probes. Tumor size influenced the duration of the scanning procedure. The scanning angle depended on the size and color of the tumor. Instrument settings for pulse repetition frequency, signal power, wall motion filter, persistence and color gain were adjusted for optimal signal quality in each nodule and condition before and after contrast medium injection. The contrast medium used was Levovist (Schering AG, Berlin, Germany), prepared with 300 mg/mL medium in a total of 2 g solution and injected through the antecubital vein manually via bolus injection within 10 seconds. All patients were scanned by the same senior sonologist (H.J. Chiou), an ultrasound radiologist with more than 15 years' experience. The volume data were stored on the hard disk of the US machine with a CD backup. The tumor was traced slice by slice for >12 slices by the same physician on the US machine. To avoid bias, the 36 nodules, all of which had 3D-PDUS data stored in the ultrasound machine, were traced manually by 2 senior sonographers, who had 7 years and 12 years of ultrasound scanning experience, respectively. The vascular index (VI) or vessels in the tumor, flow index (FI) or intensity of flow at the time of the 3D sweep, and vascular-flow index (VFI) or blood flow and vascularization, were then automatically calculated after the tumor was completely traced. VI was calculated as the number of color voxels (total voxels minus background voxels), FI was defined as the number of weighted color voxels (color voxels minus border voxels), and VFI was calculated as the number of weighted total voxels (total voxels minus background voxels).[18] All tumors were verified by US-guided biopsy or surgical pathology.

SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis, including the interobserver reliability test (paired *t* test to test the agreement commitment) and nonparametric *t* test (Mann-Whitney test).

Results

There were 8 benign and 17 malignant tumors. The benign tumors included neurogenic tumors in 3 patients, inflammatory processes in 3 patients, leiomyoma in 1 patient and tumoral calcinosis in 1 patient. The malignant tumors included osteogenic sarcoma in 7 patients (1 post chemotherapy), liposarcoma in 4 patients, lymphoma in 2 patients, carcinoma metastasis in 2 patients, malignant fibrous histiocytoma in 1 patient and breast carcinoma in 1 patient.

Mean tumor volume was 36.5 mL (range, 2.4–124 mL) in benign tumors, and 319.4 mL (range, 9.9–1,179.6 mL) in malignant tumors. The VI, FI and VFI before contrast medium injection are shown in Table 1 (see also Figures 1A and 2A), while those after contrast medium injection are shown in Table 2 (see also Figures 1B and 2B). There were no significant differences between benign and malignant tumors

Table 1. VI, FI and VFI in benign and malignant tumors without contrast medium*

	VI (%)	FI	VFI
Benign	3.22 ± 2.04 (0.02–5.48)	32.26 ± 5.51 (20.24–38.78)	1.07 ± 0.65 (0.004–1.82)
Malignant	1.97 ± 3.29 (0.04–12.12)	29.33 ± 4.86 (21.59–38.02)	0.67 ± 1.13 (0.01–1.52)
T	–0.333	–0.160	–0.128
p	NS	NS	NS

**Data presented as mean ± standard deviation (range). VI = vascular index; FI = flow index; VFI = vascular-flow index; T = according to the results of a t test; NS = not significant.*

in tumor volume, VI, FI and VFI before and after echo-contrast medium injection ($p > 0.05$). Agreement between the 2 sonographers showed high reliability, with an intraclass correlation of 0.999 (Figure 3).

The differences in VI, FI and VFI between before and after contrast medium injection are shown in Table 3. Malignant tumors had significantly higher differences for VI ($p = 0.03$), FI ($p = 0.01$) and VFI ($p = 0.03$) under self-differentiation. The cutoff values for VI, FI and VFI under self-differentiation after and before echo-contrast injection were 13.6, 6.0, and 5.1, respectively, with a sensitivity of 88.9% and a specificity of 57%.

Discussion

The 3D volume was generated from stacked 2D images by automatic mechanical driving of the transducer in the study machine. The tumor margin could not be well identified automatically by the machine because of insufficient contrast between the normal and abnormal interface. As reproducibility of tumor margin definition was very important, the tumor margin was therefore drawn manually by the operator and then reconstructed by the US machine, i.e. the measure of tumor volume was semiautomatic. Our study showed that the reproducibility of manually drawn tumors was very high, even accounting for differences between experienced sonographers, which allowed for the easy definition of tumor margins.

The current study showed that the average tumor volume was larger in malignant tumors than in benign tumors, but this result did not reach statistical significance. However, our previous larger-size study with more patients had already confirmed these results.[23]

There was a large variation of tumor volume in this study, with almost more than a 50-fold difference from small to large tumors. Our previous report[24] showed that 2D-CDUS and 3D-PDUS were not significant indicators for differentiation of soft-tissue tumors. Therefore, the volume effect was not a significant factor for influencing outcome. VI, FI and VFI were measured in the whole volume of the tumor in this study, and we found that there was no significant difference between benign and malignant soft-tissue tumors.

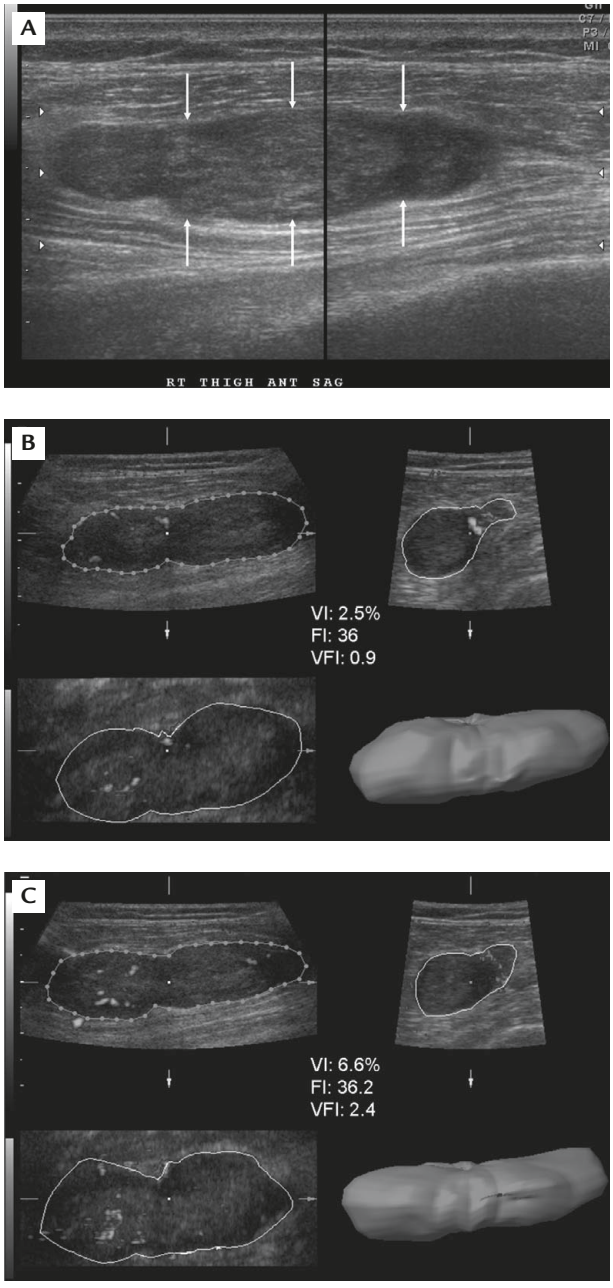
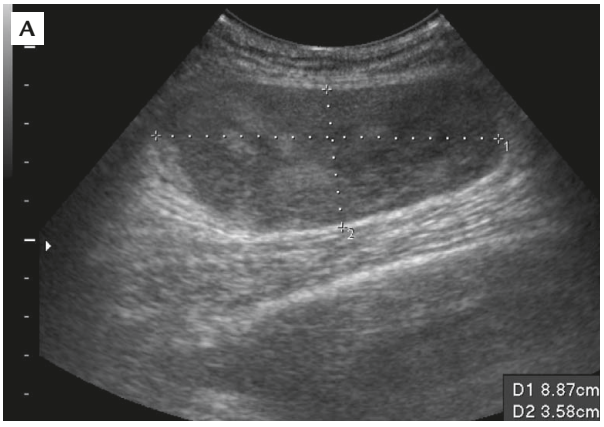
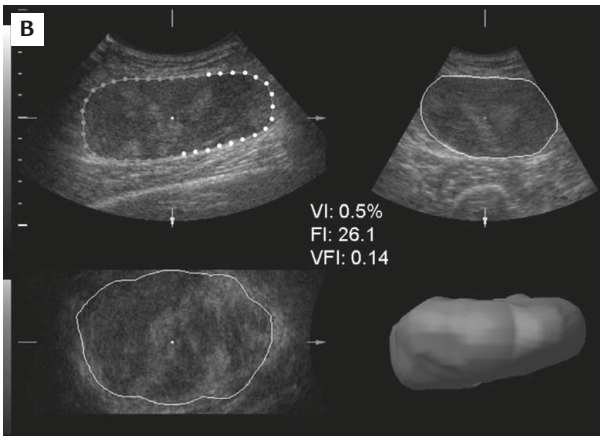


Figure 1. A 63-year-old male patient with the complaint of a right thigh mass. (A) 3D power Doppler ultrasonography shows an ovoid-shaped hypoechoic nodule with mild vascularity (VI, 2.5%; FI, 36; VFI, 0.9). (B) 3D power Doppler ultrasonography shows an ovoid-shaped hypoechoic nodule with mild vascularity (VI, 2.5%; FI, 36; VFI, 0.9). (C) After contrast injection, 3D power Doppler ultrasonography shows relatively increased vascularity (VI, 6.6%; FI, 36.2; VFI, 2.4). This tumor was determined to be a schwannoma.





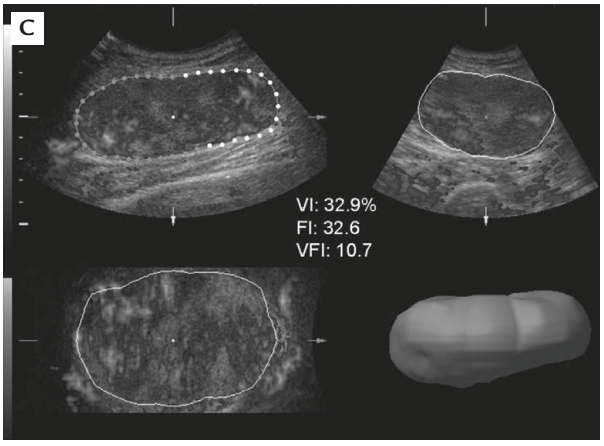


Figure 2. A 43-year-old female patient with the complaint of a palpable mass in her right thigh for 2 years. (A) Grayscale ultrasonography shows an ovoid-shaped heterogeneous echoic nodule (dotted lines) over the right thigh. (B) 3D power Doppler ultrasonography shows only minimal vascularity within the tumor (VI, 0.5%; FI, 26.1; VFI, 0.14). (C) After contrast injection, 3D power Doppler ultrasonography shows marked hypervascularity (VI, 32.9%; FI, 32.6; VFI, 10.7). This tumor was a liposarcoma.

The standard deviation values for VI and VFI were very high compared with the mean values in benign and malignant tumors. One possibility for this finding could be that there was a very large variety in the range

Table 2. VI, FI and VFI in benign and malignant tumors after contrast medium injection*

	VI (%)	FI	VFI
Benign	20.85±22.45 (0.14–64.32)	37.33±5.32 (17.63–44.63)	8.52±10.06 (0.03–28.7)
Malignant	40.12±24.39 (3.04–95.64)	41.21±7.81 (32.64–48.59)	17.77±14.91 (1.19–40.71)
T	–1.889	–1.722	–1.834
p	NS	NS	NS

**Data presented as mean±standard deviation (range). VI=vascular index; FI=flow index; VFI=vascular-flow index; T=according to the results of a t test; NS=not significant.*

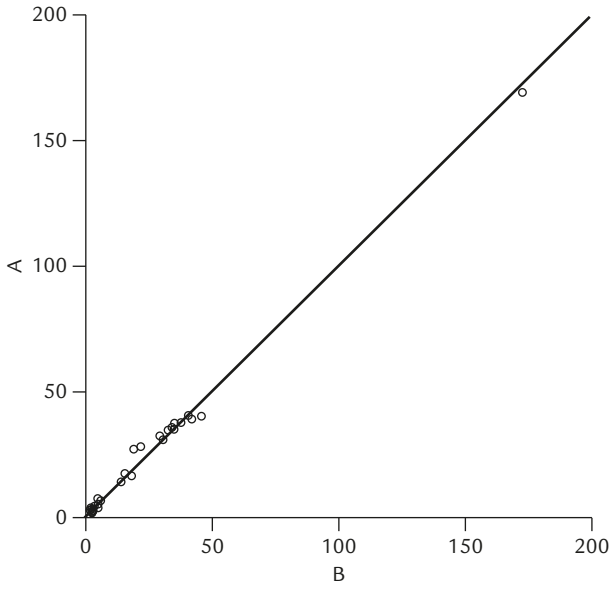


Figure 3. The correlation between the 2 sonographers' tracing of 18 soft-tissue tumors.

Table 3. Difference in VI, FI and VFI (after minus before contrast medium injection) in benign and malignant tumors*

	VI (%)	FI	VFI
Benign	17.63±20.98	5.07±4.58	7.45±9.58
Malignant	38.15±22.55	11.88±6.67	16.55±14.1
T	–2.167	–2.556	–2.167
p	0.03	0.01	0.03

**Data presented as mean±standard deviation. VI=vascular index; FI=flow index; VFI=vascular-flow index; T=according to the results of a t test.*

of VI and VFI in soft-tissue neoplasms. Therefore, there was no statistically significant difference between benign and malignant soft-tissue tumors as evaluated by 3D-PDUS, which is consistent with our previous study.[23]

There were no significant differences in volume, VI, FI, and VFI before contrast injection in this study between benign and malignant tumors, which is similar to the findings of our previous study.[22] In fact, this

phenomenon is similar to results obtained with 2D-CDUS, in which tumor vascularity grading could not be reduced to a single parameter to differentiate between benign and malignant tumors.[10,11] Some studies have also shown high vessel density in hemangioma.[25,26] Since volume data were acquired from the accumulation of 12 slices of CDUS images in this study, the information should be similar to isolated CDUS images.

CDUS application in soft-tissue tumors has been discussed in many reports that analyzed the sonomorphology of tumor vessels or the flow velocity and resistive index of tumor vessels, with variable results.[27,28] The presence of tumor vessels within the tumor does not provide sufficient information for a differential diagnosis of benign or malignant soft-tissue tumors; therefore, we added another parameter, echo-contrast enhancement grading. Grading (the difference between with and without contrast) of contrast enhancement was significantly different between benign and malignant tumors in this study. Malignant tumors showed more tumor vessels and a higher VI, FI and VFI after contrast medium injection compared with benign tumors.

We found that US with contrast images was markedly better than non-contrast images at detecting vessels in most tumors, although benign and malignant tumors showed no significant difference in VI, FI and VFI. Detailed data analysis showed a large-scale distribution of contrast enhancement in both benign and malignant tumors, which resulted in no statistical difference. Although malignant neoplasms need sufficient tumor vessels to supply nutrition, our study showed that vascularity was not higher in malignant soft-tissue tumors, which may be due to tumor necrosis resulting in tumor vessel destruction or reduced tumor size.[29] However, the number of tumors was limited in this study, and a larger study will be needed to draw firm conclusions.

In conclusion, 3D-PDUS is a valuable tool in the differential diagnosis of soft-tissue tumors, especially with injection of echo-contrast medium.

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