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What Do Contrast Media Add to Three-Dimensional Power Doppler Evaluation of Adnexal Masses?

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Aim. To investigate the potential usefulness of contrast-enhanced three-dimensional (3D) power Doppler sonography in the differentiation of benign and malignant adnexal lesions.

Methods. Thirty one patients with complex adnexal lesions of uncertain malignancy at transvaginal B-mode and/or color Doppler sonography were prospectively evaluated with three-dimensional power Doppler sonography before and after injection of a contrast agent. Presence of a penetrating pattern and a mixed penetrating and/or peripheral pattern suggested adnexal malignancy. The results were compared with histopathology.

Results. There were 10 cases of ovarian malignancy and 21 benign adnexal lesions. Of the 10 ovarian cancers, 6 showed vascular distribution suggestive of malignancy at nonenhanced 3D power Doppler sonography. After injection of a contrast agent, a penetrating vascular pattern and/or a mixed penetrating and peripheral pattern were detected in all cases of ovarian malignancy as well as in 2 benign lesions (fibroma and cystadenofibroma), which were misdiagnosed as malignant. The use of a contrast agent with three-dimensional power Doppler sonography showed diagnostic efficiency of 96.7%, superior to that of nonenhanced 3D power Doppler sonography (93.5%).

Conclusion. Contrast-enhanced 3D power Doppler sonography provides better visualization of tumor vascularity in complex adnexal masses. If used together with 3D morphological ultrasound assessment, enhanced 3D power Doppler imaging may precisely discriminate benign from malignant adnexal lesions.

Key words: *adnexa uteri; contrast media; Doppler ultrasonography, color; ovarian neoplasms; ultrasonography, Doppler, color; visual contrast sensitivity*

Since Folkman's first report in 1971, it has been well known that the development of new blood vessels is necessary to sustain the growth, invasion, and metastasis of tumors (1-3).

Tumor microvasculature differs from the vasculature of normal tissues. Tumor contains giant capillaries without media, many sinusoidal thin-walled spaces, and arteriovenous shunts without intervening capillaries. Newly formed vessels contain no smooth muscle cells in their walls, only endothelium with a small amount of fibrous connective tissue. This overgrowth of the newly formed tumor vessels produces a chaotic disorganized network of tortuous sinusoidal vessels traversing the tumor mass.

Introduction of transvaginal color Doppler brought a significant improvement in the study of tumor angiogenesis. Several studies showed that color and pulsed Doppler sonography can detect ovarian carcinoma at stage I (4-6). Although previous studies reported that both spectral Doppler and color Doppler ultrasound could provide clinically useful information related to adnexal tumor vascularity, these imaging modalities have inherent limitations, such as the lack of sensitivity to slow flow, angle dependency, and aliasing, which occurs when the Doppler shift frequency exceeds one half of the pulse repetition frequency (1).

The newly developed power or energy modes of color Doppler imaging, based on total integrated power of the Doppler spectrum, afford depiction of even smaller vessels. With the development of various sonographic contrast agents, the role of power Doppler sonography has increased (8-10).

The aim of our study was to evaluate the vascular pattern in questionable adnexal lesions by use of 3D power Doppler ultrasound with and without echo-enhancing contrast, to determine whether the imaging patterns of identified vessels could be correlated with histopathological results. We also evaluated whether information obtained with echo-enhanced 3D power Doppler ultrasound could improve the diagnostic accuracy in adnexal lesions compared with that of non-enhanced 3D power Doppler ultrasound. To the best of our knowledge, this is the first report in published work related to this topic.

Patients and Methods

Patients

The study population included a consecutive series of patients who had complex ovarian lesions of uncertain malignancy at transvaginal B-mode and/or color Doppler sonography during the period from February 1999 until February 2000. We tested whether penetrating or mixed penetrating and peripheral patterns of vessels were associated with malignancy. Exclusion criteria were typical benign cysts with absence of internal echoes, sharply defined and smooth vessel walls, no wall enhancement, and increased sonic-through transmission. A total of 31 patients with suspicious masses (21 benign adnexal lesions and 10 ovarian malignancies) were analyzed with 3D power Doppler sonography before and after injecting a sonographic contrast agent (Levovist, SHU 508A, Schering AG, Berlin, Germany). Eighteen of the studied women were premenopausal (mean age 34.0±9.3, range 19-49 years). Two women were perimenopausal (aged 47 and 54). The remaining 11 women were postmenopausal (mean age 62.0±5.8, range 51-77 years). Two postmenopausal patients had undergone hysterectomy, 12 and 7 years before entering the study.

Each patient filled out a questionnaire on parity, breast feeding, former or present use of oral contraceptives, ovulation drugs or hormonal replacement therapy, use of talc in feminine hygiene, smoking, diet, drinking habits, and family history of diseases. Two patients with ovarian carcinoma had one first-degree relative with such a cancer. Furthermore, ovarian malignancy was detected in a patient with a personal history of endometrial carcinoma and in a patient with breast cancer. Patients with benign adnexal lesions had no personal or family history of ovarian, endometrial, breast, or colorectal malignancy (Table 1).

All examinations in premenopausal patients were performed during the early proliferative phase of the menstrual cycle. Clinical information, family history, and data on CA 125 were not known to the sonographer. In all cases, the histopathological diagnosis was obtained after surgery, within one to two weeks after 3D power Doppler sonography. Histopathologist was unaware of the scan results.

Sonographic Contrast Agent

The sonographic contrast agent used in this study, Levovist, is a suspension of monosaccharide microparticles (galactose) in sterile water. A stabilized microbubble suspension of the agent was administrated intravenously at a concentration of 300 mg/mL. An 8.5 mL dose of contrast agent was injected slowly at a rate of 0.2 mL/s by hand to reduce artefacts and prolong the duration of enhancement. This was followed by an additional 10 mL of physiologic saline solution to flush the cannula, using the same injection rate.

Doppler Examination

Three-dimensional power Doppler measurements were performed with Voluson 530 D (Kretz Medison, Zipf, Austria). Volume data acquisition was performed using a 5-MHz transvaginal volume probe. The size of the volume influenced the duration of the scanning procedure (acquisition time approximately 30-60 seconds). Fixed preinstalled instrument settings for pulse repetition frequency (1.0), signal power (2.0), wall motion filter (61.0), persistence (rise 0.1, fall 0.3), center frequency (middle), grey/color balance (G>192),

Table 1. Demographic characteristics of 31 patients with complex adnexal lesions

Demographic characteristics	Number of adnexal lesions		
	benign (n=21)	malignant (n=10)	total (n=31)
Parity			
0	3	2	5
1	5	4	9
2	6	3	9
3	7	1	8
Breast feeding			
Yes	15	9	24
No	6	1	7
Oral contraceptives			
Never users	7	9	16
1 year	11	1	12
1-5 years	2	0	2
5-10 years	1	0	1
10 years	0	0	0
Ovulation induction			
Never users	19	9	28
Former users	1	1	2
Current users	1	0	1
Hormonal replacement therapy			
Never users	19	9	28
Former users	1	0	1
Current users	1	1	2
Talk use			
Never users	18	8	26
Former users	3	1	4
Current users	0	1	1
High fat diet			
Never users	10	7	17
Former users	9	2	11
Current users	2	1	3
Smoking			
Never users	8	5	13
Former users	6	3	9
Current users	7	2	9
Drinking			
Never users	11	3	14
Former users	7	5	12
Current users	3	2	5

quality (4.0), and density (8.0) of the volume scan were used throughout the examinations. Only power Doppler gain was adjusted to optimize signal quality. Volumetric data were stored on a hard disk to allow full evaluation without loss of information at a later point. During each examination, we defined a cube enclosing the vessels of the adnexal lesion, but excluded the iliac vessels or motion artefacts. Detection of the artefacts is very common due to the very sensitive power Doppler.

After performing an initial scan by 3D power Doppler, we injected the enhancing contrast agent. Thereafter, we had to reduce the power Doppler gain because the power Doppler noise, such as color blooming artefact, was produced by the effect of the contrast agent. We manipulated the power Doppler gain throughout the entire scanning at the highest possible level that did not produce considerable artefacts. The resultant power Doppler gains ranged from 70% to 85%. Volumetric data of the power Doppler images were stored on the hard disk at 60, 120, 180, 240, 300, 360, 420, and 480 seconds after the initiation of the contrast agent injection.

At 3D power Doppler ultrasound, the vascular distribution in adnexal lesions was classified as follows: pattern 0, no signal pattern (which indicated no detectable vessels); pattern 1, peripheral pattern, which indicated blood vessels that arose outside the lesion and surrounded the lesion; pattern 2, penetrating pattern, indicating that blood vessels arose outside the lesion and coursed towards the center; and pattern 3, mixed penetrating and peripheral pattern. Three-dimensional power Doppler findings after contrast injection were compared with those before the beginning of the procedure in terms of sensitivity, specificity, and positive and negative predictive values. Diagnostic efficiency was expressed as the sum of true positives and true negatives divided by the total number of patients. We tested whether penetrating or mixed penetrating and peripheral patterns of vessels were associated with adnexal malignancy.

Data Interpretation

Vascular features were separately analyzed for each time interval following the injection of the contrast medium, and the most representative 3D image of each patient was chosen for further interpretation.

The same surgical team operated on all the cases and histopathological diagnosis was considered final. Malignant tumors were classified according to the International Federation of Gynecology and Obstetrics (FIGO) system (11). The study protocol was approved by the hospital's Ethical Committee and all the patients consented to participate in the study.

Results

From 31 patients referred for 3D power Doppler ultrasound due to indeterminate finding of the complex adnexal mass, 10 women were found to have ovarian cancer at laparotomy, whereas 21 had benign adnexal lesions. Histopathological examination of the ovarian malignancies revealed 6 cases of serous and 2 cases of mucinous cystadenocarcinoma, 1 endometrioid cystadenocarcinoma, and 1 clear cell carcinoma. According to FIGO guidelines, there were 5 stage I cases (three stage Ia, one stage Ib, and one stage Ic), 3 stage II cases, one stage III case, and one patient with stage IV ovarian carcinoma (11). Table 2 lists histopathological diagnosis of the adnexal lesions analyzed by enhanced and nonenhanced 3D power Doppler sonography.

In 25 patients, the best image quality was obtained 180 seconds after the initiation of the contrast injection, in 4 patients after 120 seconds, and in 2 patients after 240 seconds.

Using nonenhanced 3D power Doppler imaging of the 10 ovarian cancers, 4 showed penetrating vessels, 2 had mixed penetrating and peripheral pattern, 2 showed peripheral vessels, and in 2 cases no flow was detected. Malignant lesions in which penetrating vessels were found at 3D power Doppler ultrasound were 2.2-9.5 cm in diameter (mean 5.2 cm), lesions with mixed penetrating and peripheral pattern were 2.5-9.2 cm in diameter (mean 5.6 cm), lesions with peripheral vessels were 3-8 cm in diameter (mean 5.4 cm), and those with no detectable vessels were 9 and 12 cm in diameter. In the group of benign lesions, no detectable flow was found in 8 patients, peripheral vessels were seen in 12, and penetrating vessels were observed in 1 case. The benign lesion with penetrating vessels was subsequently found to be cystadenofibroma.

Table 2. Histopathological diagnosis of the adnexal lesions

Histopathology	No.
Cystadenoma	
serous	3
mucinous	2
Endometrioma	3
Ovarian dermoid	5
Chronic pelvic inflammatory disease	5
Hemorrhagic cyst	1
Cystadenofibroma	1
Fibroma	1
Ovarian carcinoma	10
Total	31

With the presence of centrally penetrating vessels as the diagnostic criterion for malignancy, 3D power Doppler ultrasound demonstrated a diagnostic sensitivity of 80% and specificity of 95.4%. The positive and negative predictive values were 80% and 91.3%, respectively (Table 3).

Contrast-enhanced 3D power Doppler sonography showed penetrating pattern in 8 (80%) and mixed penetrating and peripheral pattern in 2 (20%) patients with ovarian malignancy. Two malignant tumors with a lack of any signal on non-contrast 3D power Doppler sonography showed significantly increased power Doppler signals after the injection of a contrast agent. Peripheral and penetrating vessels with irregular course were clearly obtained in these patients. In the group of benign lesions, contrast-enhanced 3D power Doppler sonography demonstrated peripheral distribution of the vessels in 17 (80.9%) cases, whereas two (9.5%) lesions (ovarian dermoid and chronic pelvic inflammatory disease – PID) remained avascularized. In patients with fibroma and cystadenofibroma, contrast-enhanced 3D power Doppler sonography led to a misdiagnosis of malignant lesions due to the frank enhancement of the vessels of the solid components which were interpreted as penetrating vessels.

With regard to differential diagnosis between malignant and benign ovarian lesions, contrast-

Table 3. Sensitivity, specificity, positive and negative predictive values, and efficiency of enhanced and nonenhanced power Doppler sonography in detection of ovarian malignancy (values: mean ±95% confidence limits)[a]

Power Doppler	No. of detected tumors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Efficiency (%)
3D	8	80.0±16.9	95.4±5.9	80.0±19.9	91.3±11.0	93.5±9.9
Enhanced 3D	10	100.0	95.2±8.1	90.9±18.3	100.0	96.7±6.0

[a]Abbreviations: PPV – positive predictive value; NPV – negative predictive value; 3D – three-dimensional.

enhanced 3D power Doppler sonography reached diagnostic sensitivity and specificity of 100% and 95.2%, respectively. The positive and negative predictive values of this method were 90.9% and 100%, respectively. Therefore, the diagnostic efficiency ([true positive + true negative]/[true positive + true negative + false positive + false negative]) was improved by use of sonographic contrast agent from 93.5% to 96.7% (Table 3).

Discussion

Although our study population included only 31 patients, the use of a contrast agent in 3D power Doppler ultrasound seems to improve the sensitivity for differentiating benign from malignant adnexal lesions because, in comparison with imaging without contrast, it allows better detection of malignant tumor perfusion. In the present study, contrast-enhanced 3D power Doppler ultrasound showed 100% negative predictive value for malignant ovarian lesions and 90.9% positive predictive value, and the latter was similar to value of non-contrast-enhanced power Doppler ultrasound. Furthermore, our results show that the pattern of irregularly branched penetrating vessels in suspicious adnexal lesions demonstrated at 3D power Doppler ultrasound with or without contrast enhancement is an important feature that should be considered with other sonographic criteria to predict the likelihood of malignancy. The obvious limitation of this study is relatively small number of patients, but these preliminary results already show the usefulness of this technique.

Vessels can be detected in benign lesions very often, but their architectural structure and morphology are usually distinguishable from those in malignant tumors. We observed neovascularization in a number of malignant neoplasm cases, where the tumor vessels were usually randomly dispersed within the stroma and periphery, and some of them formed several tangles or coils around the surface. The course of the main tumor vessel was usually irregular with more complicated branching. The diameter of these vessels was "uneven" and "thornlike". These findings can be compared with previous studies with conventional color Doppler ultrasound (5,12). However, the appeal of a 3D display is that it is more comprehensive and allows physicians to interactively understand the 3D architecture of the microcirculation. In addition, the resolution of current power Doppler is sufficient to detect vessels of around 1 mm in diameter (13). In the deep lying and necrotic adnexal lesions, confirmed by histopathology, nonenhanced 3D power Doppler sonography did not demonstrate intratumoral vessels due to low velocity flow. In two cases of ovarian malignancy measuring 9 and 12 cm, the initial scan by 3D power Doppler did not reveal intratumoral vascularity. Contrast-enhanced 3D power Doppler imaging was used for evaluation of adnexal tumor vascularity without considering morphological findings which would suggest malignancy. Administration of the contrast medium increased the strength of returning signal, generating a clear image of central stellate feeding vessels, on the basis of which a diagnosis could be made. Therefore, we believe that contrast-enhanced 3D power Doppler is a promising tool in the evaluation of angiogenesis of pelvic tumors, especially when a malignant neoplasm is suspected. This technique brings us a step closer to angiographic images.

Contrast-enhanced 3D power Doppler ultrasound was especially useful in patients with ovarian dermoids (n=5), chronic pelvic inflammatory disease (n=5), and organizing hematoma in a patient with a hemorrhagic cyst. In these cases, contrast-enhanced 3D power Doppler ultrasound examination did not reveal signs of vascularity, or detected only discrete peripheral vascularization within the solid parts, which was mandatory to avoid false positive results for malignancy. However, in 2 patients with benign lesions (one fibroma and one cystadenofibroma), contrast-enhanced 3D power Doppler sonography demonstrated the penetrating vessels within the solid component, which led to the misdiagnosis of ovarian malignancy. Because the treatment of benign lesions with suspicious morphology consists of surgical resection, these false positive results did not affect the patients' management protocols.

The accuracy of contrast-enhanced 3D power Doppler findings for the differentiation of adnexal tumors may be increased if analyzed together with morphological parameters obtained by 3D ultrasound. Power Doppler imaging can accurately detect characteristic structural abnormalities of the malignant tumor vessels, such as microaneurysms, arteriovenous shunts, tumoral lakes, disproportional calibration, elongation, coiling, and dichotomous branching. Arteriovenous shunts, which are pathognomonic for ovarian malignancy, can be initially diagnosed by pulsed Doppler analysis by visualization of both arterial and venous blood flow patterns. Three-dimensional power Doppler ultrasound can prove this finding as communications between two vessels within the adnexal tumor.

Three-dimensional power Doppler display allows the physician to visualize many overlapping vessels easily and quickly, as well as to assess their relationship to other vessels or other surrounding tissues. It permits an ultrasonographer to view the structures in three dimensions interactively, rather than to assemble the sectional images in his/her mind. Interactive rotation of power Doppler rendered images provides improved visualization of the tumor vasculature. Usually, tumor vessels are randomly dispersed within the stroma and periphery, sometimes forming several tangles or coils around the surface. Furthermore, sonographic findings suggesting malignancy, such as irregular and thick cystic walls, solid component, papillary protrusions, thick septa, and non-homogeneous echogenicity can be precisely analyzed with 3D ultrasound (14). Therefore, we expect the combined use of 3D ultrasound and enhanced 3D power Doppler modality to be very useful in making differential diagnosis of questionable adnexal masses and particularly in discriminating malignant from benign lesions.

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