INTRODUCTION

Ovarian tumor is one of the reproductive system diseases with a high incidence in women, which can be divided into benign and malignant tumors. The incidence of malignant ovarian tumor ranks the second place among female reproductive system tumors, and its mortality rate ranks the first. The latest statistics show that the incidence of ovarian tumors is increasing in recent years, which seriously threatens the health and life safety of women.1-3 For early ovarian cancer, the curative effect of surgical radical and chemical treatment is good, but the 5-year survival rate of patients with ovarian cancer is still not significantly improved; the main reason is that more than 70% of ovarian cancer cases has been at the late stage at the time of diagnosis. For patients with advanced...
ovarian cancer or distant metastasis, the curative
effect of surgical radical and chemical treatment
is poor. Therefore, early diagnosis of ovarian
cancer is a key issue to improve survival rate.
The clinical symptoms of ovarian cancer patients
are not obvious in the early stage. Lumbar acid,
abdominal distension, abdominal pain, frequency
of urination, vaginal bleeding and abdominal mass
are the main clinical manifestations. The causes
of ovarian cancer are complex, so it is still difficult
to diagnose and differentiate early ovarian cancer
histologically. In the past, ovarian tumors were
found mainly by conventional gynecological
examination or general examination, with a high
rate of missed diagnosis. Many patients have had
distant metastasis when they visited the doctor,
missing the best treatment time. At present, many
researchers are devoted to exploring ovarian
tumor markers and imaging technologies with
high sensitivity and specificity and creating a
“golden standard” for early diagnosis, prognosis
analysis and monitoring of ovarian cancer
determine the best treatment method for
patients. In this study, 96 patients with ovarian
tumors who were admitted to our hospital were
selected as the research subject. The purpose of
this study was to compare the clinical value of
color Doppler ultrasound and ultrasound contrast
in the differential diagnosis of ovarian tumors.

METHODS

Ninety-six patients with ovarian tumors who
were treated in our hospital from May 2017 to July
2018 were selected as the study subjects. The age
of the patients ranged from 21 to 72 years, with
an average of (51.65±3.87) year. Among them,
22 cases were found to have ovarian tumors, 51
cases were found to have abdominal pain, 16 cases
were found to have irregular menstruation with
vaginal bleeding, and seven cases were found to
have changed defecation habits and unintentional
palpation of tumors. Inclusive criteria included 75
over years old, being diagnosed histopathologically
as primary benign or malignant ovarian tumors,
receiving no other treatment before this visit,
and having complete clinical, imaging and
laboratory data. Exclusion criteria were having
pelvic congenital malformation; having ovarian
metastatic tumors; having acute inflammation;
being in pregnancy and lactation period; having
liver and kidney insufficiency, heart failure and
hematological diseases; unable to cooperate with
researchers. This study was approved by the ethics
committee of the hospital, and all patients signed
informed consent.

Color Doppler ultrasound examination method:
The Logiq7 color Doppler ultrasound diagnostic
instrument (GE, USA) was used; a broadband linear
array probe was used, and the center frequency
was set as 7.5 MHz. The patients took a supine
position, and the ovarian parts of the patients were
scanned. The size, boundary, capsule and echo of
ovarian lesions were observed and recorded. The
distribution of blood vessels and blood flow in the
lesions were analyzed using Doppler flow imaging.
Sono Vue was used as contrast agent. The
prepared sulfur hexafluoride suspension was
intravenously injected into the patient from the
center of elbow, and then sodium chloride injection
was used for washing. The contrast lasted for 5
minutes, and the images were stored and analyzed
by TIC software. The enhancement and regression
of the contrast agent in tumors was observed using
ultrasound equipment, and the microcirculation
perfusion status and parameters of tumors were
observed.

Diagnostic criteria for benign and malignant
tumors by color Doppler ultrasound were as
follows. Grading was mainly based on the
characteristics of blood flow morphology. A tumor
was evaluated as grade 0 if no blood flow signals
were found in the tumors, as Grade-I if there were
transient blood flow signals or occasional blood
vessels in the tumors, as Grade-II if there were
multiple blood flow signals in the tumors or clear
blood vessels passing through the lesions, and as
Grade-III if there were a large number of blood
flow signals in the tumors or clear
blood vessels passing through the lesions, and as
Grade-III if there were a large number of blood
flow signals in the tumors or clear blood vessels
passing through the lesions. Tumors with grade
0~I and regular blood vessels were evaluated as
benign tumors, and tumors with Grade-II~III and
complex and dilated blood vessels were evaluated
as malignant tumors.

Diagnostic criteria of ultrasound contrast for
benign and malignant tumors were as follows. According to the morphological characteristics
of blood flow, tumors could be divided into four
grades. A tumor was evaluated as grade 0 if there
was no enhancement inside the mass and there
was homogeneous enhancement outside the mass,
as Grade-I if the wall, segmental space and solid
area of the mass had enhancement, there was no
obvious curvature of the blood vessels, and the
density the enhancement area was even, as Grade-
II if the wall, segmental space and solid area of the
mass had enhancement, distorted vascular bundles appeared, and the density of the enhancement area was uneven, as Grade-III if there were a large number of disordered and distorted blood vessels in the solid area of the mass and the density of the enhancement area was extremely uneven. Tumors with grade 0 ~ I was evaluated as benign tumors, and tumors with Grade-II and III were evaluated as malignant tumors.

The diagnostic results of color Doppler ultrasound and ultrasound contrast were observed, and the sensitivity, specificity and accuracy were calculated: sensitivity=number of true positive cases/(number of true positive cases + number of false negative cases)×100%, specificity=number of true negative cases/(number of false positive cases+ number of true negative cases)×100% and accuracy=number of true positive cases +number of true negative cases/total number of cases×100%. The parameters of ultrasound contrast in diagnosing benign lesions and malignant lesions were compared, including time of initiation enhancement, time to peak and perfusion intensity.

Statistical analysis: SPSS 20.0 was used for data analysis. The measurement data were expressed by mean ± standard deviation and processed by t-test. The categorical data were processed by Chi-square test. The difference was thought as statistically significant if P<0.05.

RESULTS

Postoperative pathological diagnosis: Sixty-six cases of benign tumors were found after pathological diagnosis, including 10 cases of endometriotic cyst, 8 cases of mature teratoma, 10 cases of serous cystadenoma, 32 cases of simple cyst and 6 cases of salpingitis; 30 cases of malignant tumors were found by pathological diagnosis, including eight cases of granulosa cell tumors, 5 cases of metastatic tumor, seven cases of serous cystadenoma, seven cases of mucinous cystadenocarcinoma and 3 cases of theca cell tumors.

Comparison of diagnostic results between two methods: Color Doppler ultrasound confirmed 52 cases of benign tumors, and there were 12 cases of misdiagnosis and two cases of missed diagnosis; it confirmed 23 cases of malignant tumors, and there were six cases of misdiagnosis and one case of missed diagnosis. Ultrasound contrast confirmed 64 cases of benign tumors, and there were one case of misdiagnosis and one case of missed diagnosis; it confirmed 28 cases of malignant tumors, and there were one case of misdiagnosis and one case of missed diagnosis. The sensitivity, specificity and accuracy of ultrasound contrast were higher than those of color Doppler ultrasound, and the difference was statistically significant (P<0.05, Table-I).

The time of initial enhancement and time to peak of benign ovarian tumors were higher than those of malignant ones (P<0.05), and the perfusion intensity of benign lesions was lower than that of malignant ones (P<0.05, Table-II).

DISCUSSION

Early detection and correct benign and malignant determination of ovarian tumors have very important clinical significance. However, due to the complexity of ovarian histological types and the particularity of anatomical location, the early diagnosis and differential diagnosis of ovarian tumors are still insufficient and lack of mature early diagnosis methods, so it is still difficult to diagnose and differentiate early ovarian tumors histologically. At present, ultrasound has become a conventional way to detect ovarian tumors

Table-I: Diagnostic results between two methods [n (%)].

| Examination method       | Accuracy | Sensitivity | Specificity |
|--------------------------|----------|-------------|-------------|
| Ultrasound contrast      | 92(95.83)| 64(96.97)   | 28(93.33)   |
| Color Doppler ultrasound | 75(78.13)| 52(78.79)   | 23(76.67)   |
| X²                       | 12.183   | 9.154       | 8.657       |
| P                        | <0.05    | <0.05       | <0.05       |

Table-II: Ultrasound contrast parameters in diagnosing benign and malignant ovarian lesions.

| Examination method | Time of initial enhancement (s) | Time to peak | Perfusion intensity (dB) |
|--------------------|---------------------------------|--------------|--------------------------|
| Benign lesions (n=66) | 25.73±2.31                      | 27.93±5.17   | 6.06±3.28                |
| Malignant lesions (n=30) | 11.05±1.36                      | 18.16±4.26   | 18.83±2.34               |
| X²                 | 14.763                           | 7.539        | 11.728                   |
| P                  | <0.05                            | <0.05        | <0.05                    |
because of its convenience, non-invasive, intuitive and good repeatability. The commonly used new ultrasound technologies include Doppler ultrasound, three-dimensional ultrasound, and ultrasound contrast and so on.

The diagnosis of benign and malignant ovarian lesions is based on the theory that the formation of neovascularization is the premise and basis of tumorigenesis. Color Doppler ultrasound has high image resolution and wide scanning range, and its unique probe can improve the differential diagnosis rate of benign and malignant lesions in abdomen and superficial organs. The application of color Doppler ultrasound in the differential diagnosis of ovarian tumors can clearly show the pelvic organs and lesion sites to obtain good imaging of the hemodynamics and vascular distribution around the tumors. However, it has obvious limitations on the display of small blood vessels, low-velocity blood flow or blood flow in deep tumors.

Ultrasound contrast is based on the conventional color Doppler ultrasound, which has more advantages in revealing the blood perfusion information of tumors. It is different from color Doppler examination as it is not affected by breathing, movement and angle and can display small vessels with diameter less than 200 μm. Therefore, it can display the blood supply around and inside lesions, especially the small vessels with low velocity and also show the intensity of perfusion in different areas of the lesion and the sequence of perfusion and regression. Contrast agent can effectively enhance two-dimensional ultrasound image and Doppler flow signal through its strong scattering effect in blood flow to fully display the blood flow signal in lesions, including small blood vessels in tumors, low velocity blood flow or blood flow distribution in the deep part of the tumor and accurately evaluate the blood vessels in the tumor. It overcomes the influence of the size and depth of tumors on the blood flow display rate, achieves the purpose of differential diagnosis, and improves the accuracy of tumor diagnosis.

The parameters of ultrasound contrast are closely related to the blood perfusion of tumor tissues. The time of initial enhancement reflects the time when contrast agents appear in the tumor body. The peak intensity and time to peak reflect the maximum amount of contrast microbubbles in the vascular bed and the perfusion time needed to reach the maximum amount respectively. A previous study has shown that the ultrasound contrast of malignant tumors generally presents a pattern of fast forward and slow regression, while benign tumors mostly present a pattern of slow forward and slow regression. The results of this study showed that the time of initial enhancement, time to peak and perfusion intensity of malignant ovarian tumors were significantly larger than those of benign tumors. It was because the blood vessels of malignant ovarian tumors increased and distorted to form vascular loops or networks, and the microbubbles in the local blood vessels of the lesions accelerated after the injection of the contrast agent, resulting in fast penetration of the contrast agent and abrupt ascending branch.

Therefore, ultrasound contrast technology can effectively identify the benign and malignant nature of ovarian tumors, especially for those patients with new capillaries or slow blood flow in malignant tumors which cannot be detected by color Doppler. It can provide help for the early diagnosis of ovarian tumors and make up for the limitations of two-dimensional and color flow imaging in the detection of low-velocity blood flow and small blood vessels in ovarian tumors. The results of this study showed that ultrasound contrast was superior to color Doppler ultrasound in sensitivity, specificity and accuracy in the diagnosis of ovarian tumors, suggesting that ultrasound contrast was more effective than color Doppler ultrasound in the differential diagnosis of ovarian tumors, which is similar to the results of Kumazawa.

**CONCLUSION**

In conclusion, compared with color Doppler ultrasound, ultrasound contrast holds higher diagnostic accuracy in differential diagnosis and precise characterization of ovarian tumors. It can help diagnose early and facilitate in outlining the roadmap for treatment, therefore, increases the survival time of patients.

**Declaration of interest:** All authors declared there was no conflict interests involved.

**Grant Support & Financial Disclosures:** None.

**REFERENCES**

1. Matsuo K, Machida H, Takiuchi T, Grubbs BH, Roman LD, Sood AK, et al. Role of hysterectomy and lymphadenectomy in the management of early-stage borderline ovarian tumors. Gynecol Oncol. 2017;144(3):496-502. doi: 10.1016/j.ygyno.2017.01.019.

2. Li J, Condello S, Thomas-Pepin J, Ma X, Xia Y, Hurley TD, et al. Lipid desaturation is a metabolic marker and therapeutic target of ovarian cancer stem cells. Cell Stem Cell. 2017;20(3):303-314.e5. doi: 10.1016/j.stem.2016.11.004.
Differential diagnosis of ovarian tumor

3. Liu Y, Chen S, Zheng C, Ding M, Zhang L, Wang L, et al. The prognostic value of the preoperative C-reactive protein/albumin ratio in ovarian cancer. BMC Cancer. 2017;17(1):285. doi: 10.1186/s12885-017-3220-x.

4. Li HM, Qiang JW, Ma FH, Zhao SH. The value of dynamic contrast-enhanced MRI in characterizing complex ovarian tumors. J Ovarian Res. 2017;10(1):4. doi: 10.1186/s13048-017-0302-y.

5. Scaletta G, Plotti F, Luvero D, Capriglione S, Montera R, Miranda A, et al. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: a systematic review. Expert Rev Anticancer Ther. 2017;17(9):827-839. doi: 10.1080/14772560.2017.1360138.

6. Kurosaki A, Hasegawa K, Kato T, Abe K, Hanaoka T, Miyara A, et al. Serum folate receptor alpha as a biomarker for ovarian cancer: Implications for diagnosis, prognosis and predicting its local tumor expression. Int J Cancer. 2016;138(8):1994-2002. doi: 10.1002/ijc.29937.

7. Qiao JJ, Yu J, Yu Z, Li N, Song C, Li M. Contrast-enhanced ultrasound for the diagnosis and treatment of prostate cancer. Sensors. 2015;15(3):4947-4957. doi: 10.3969/j.issn.1674-6805.2013.28.043.

8. Li YT. Clinical value of dynamic contrast-enhanced MRI in characterizing complex ovarian tumors: comparison with Doppler ultrasound. J Med Ultras. 2013;40(1):81-84. doi: 10.1007/s10396-012-0380-9.

9. Strobel D, Krodle U, Martus P, Hahn EG, Becker D. Clinical evaluation of contrast-enhanced color Doppler sonography in the differential diagnosis of liver tumors. J Clin Ultrasound. 2015;28(1):9-15. doi: 10.1016/j.jus.2009.09.007.

10. Li QC. CT diagnosis and analysis of uterine myoma and ovarian tumor. Chin Foreign Med Res. 2013;28(11):62-63. doi: 10.3969/j.issn.1674-6805.2013.28.043.

11. Li X, Hu JL, Zhu LM, Sun XH, Sheng HQ, Zhai N, et al. The clinical value of dynamic contrast-enhanced MRI in differential diagnosis of malignant and benign ovarian lesions. Tumor Biol. 2015;36(7):5515-5522. doi: 10.1007/s13277-015-3219-3.

12. Buhling KJ, Lezon S, Eulenburg C, Schmalfeldt B. The role of transvaginal ultrasonography for detecting ovarian cancer in an asymptomatic screening population: A systematic review. Arch Gynecol Obstet. 2017;295(5):1259-1268. doi: 10.1007/s00404-017-4346-4.

13. Ma X, Zhao Y, Zhang B, Ling W, Zhuo H, Jia H, et al. Contrast-enhanced ultrasound for differential diagnosis of benign and malignant ovarian tumors: systematic review and meta-analysis. Ultras Obstetr Gynecol. 2015;46(3):277-283. doi: 10.1002/uog.14800.

14. Wang QM, Chen Y. Preliminary application of Trans-Channel contrast-enhanced ultrasound in differential diagnosis of ovarian tumors. J Front Med. 2014;18(21-23). doi: 10.3969/j.issn.2095-1752.2014.18.015.

15. Orden MR, Jurvelin JS, Kirkenin PP. Kinetics of a US contrast agent in benign and malignant adnexal tumors. Radiol. 2003;226(2):405-410. doi: 10.1148/radiol.2262011450.

16. Buhling KJ, Lezon S, Eulenburg C, Schmalfeldt B. The role of transvaginal ultrasonography in differential diagnosis of ovarian tumors with transvaginal color Doppler ultrasound. Acta Obstet Gyn Scan. 2011;75(4):316-329.

17. Sconfienza LM, Perrone N, Delnevo A, Lacelli F, Murolo C, Gandolfo N, et al. Diagnostic value of contrast-enhanced ultrasonography in the characterization of ovarian tumors. J Ultrasound. 2010;13(1):9-15. doi: 10.1016/j.jus.2009.09.007.

18. Hsieh CY, Wu CC, Chen TM, Chen CA, Chen CL, Wang JF, et al. Clinical significance of intratumoral blood flow in cervical cancer assessed by color Doppler ultrasound. Cancer. 2015;75(10):2518-2522.

19. Yasuhara K, Kimura K, Nakamura H, Uchibori T, Hirama M. New color Doppler technique for detecting turbulent tumor blood flow: a possible aid to hepatocellular carcinoma diagnosis. J Clin Ultrasound. 2015;25(4):183-188.

20. Chou CY, Chang CH, Yao BL, Kuo HC. Color Doppler ultrasonography and serum CA 125 in the differentiation of benign and malignant ovarian tumors. J Clin Ultrasound. 2010;22(8):491-496.

21. Tekay A, Joupilla P. Controversies in assessment of ovarian tumors with transvaginal colour Doppler ultrasound. Acta Obstet Gynecol Scand. 2011;75(5):316-329.

22. Yamamoto T, Kimura T, Yasuda T, Irie Y, Ishida H, et al. Diagnostic significance of intratumoral blood flow in cervical cancer assessed by color Doppler ultrasound. Cancer. 2015;75(10):2518-2522.

23. Hsieh CY, Wu CC, Chen TM, Chen CA, Chen CL, Wang JF, et al. Clinical significance of intratumoral blood flow in cervical cancer assessed by color Doppler ultrasound. Cancer. 2015;75(10):2518-2522.

24. Yasuhara K, Kimura K, Nakamura H, Uchibori T, Hirama M. New color Doppler technique for detecting turbulent tumor blood flow: a possible aid to hepatocellular carcinoma diagnosis. J Clin Ultrasound. 2015;25(4):183-188.