Color Doppler Ultrasonography and Serum CA 125 in the Differentiation of Benign and Malignant Ovarian Tumors

Cheng-Yang Chou, Chiung Hsin Chang, Bor-Lin Yao, and Hong-Chang Kuo

Abstract: Color Doppler ultrasonography and serum CA 125 were used to evaluate 114 adnexal tumors prior to surgery. Six patients were excluded from this study because of ovarian cancer, borderline ovarian malignancy, and tubal gestation. A total of 108 patients were eligible: 83 patients with benign and 25 patients with malignant ovarian tumors. Resistance index (RI) was used to determine the peripheral resistance of intratumoral vessels. The cutoff point for the RI was defined as 0.5. The blood flow was considered to be normal when the RI was greater than 0.5 and abnormal when it was less than 0.5. The blood flow was detected in 100% of malignant tumors and 59% of benign tumors. The initial cutoff value for CA 125 was 35 U/mL. Sensitivity, specificity, positive predictive value, and negative predictive value were compared in terms of RI, serum CA 125, and a combination of the two. Our conclusion is that the combination of RI and CA 125 gives a sensitivity of 100% and negative predictive value of 100%. If the cutoff point of CA 125 was raised from 35 to 65 U/mL, then a specificity of 100% and positive predictive value of 100% were also attained with the use of RI and CA 125 without changes in sensitivity or negative predictive value. We conclude that the combination of color Doppler ultrasonography and serum CA 125 is an effective method to differentiate benign from malignant ovarian tumors. © 1994 John Wiley & Sons, Inc.

Indexing Words: Color Doppler ultrasonography · Serum CA 125 · Ovarian tumors · Doppler ultrasonography

Ovarian cancer accounts for approximately 25% of all gynecologic malignancies. Because it is a silent disease, the overall 5-year survival rate remains low. Color Doppler ultrasonography has been widely used in the evaluation of uteroplacental flow in obstetrics during the past decade. It has also been used to detect abnormal intratumoral blood flow in many gynecologic tumors in recent years, especially in differentiating a benign ovarian tumor from ovarian cancer. Serum CA 125 is one of the most useful tumor markers in the evaluation and management of a patient with known or suspected ovarian cancer. However, currently available data suggest that the sensitivity of serum CA 125 for patients with cancer confirmed to the ovary is lower (50% or less) than that for the disease in more advanced stages (80% or more).

It has been speculated that the combined use of color Doppler ultrasonography and serum CA 125 might achieve better results in the early detection of ovarian cancer. We studied the results of combined use of color Doppler ultrasonography and serum CA 125 in the differential diagnosis of benign and malignant ovarian tumors. Evaluations were made in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

SUBJECTS AND METHODS
From January 1991 through February 1993, a total of 108 patients (114 minus 6) undergoing sur-
surgery at National Cheng Kung University Hospital for adnexal tumors were studied. In all of the patients, a previous sonographic examination or computed tomography or both had confirmed the presence of a pelvic mass, and all patients had already been scheduled for surgery independent of the findings of our examination. Six patients were ineligible and were excluded from this study because of ovarian carcinoma (3), borderline ovarian carcinoma (1), and chronic tubal pregnancy (2). The mean age of the 108 patients in this study was 38 years (range: 11 years to 85 years). Eighty-four patients were premenopausal, 19 patients were postmenopausal, and 5 patients were premenarchal. Before the surgery, a color Doppler ultrasound examination (ALOKA color Doppler SSD-680, Tokyo, Japan) was performed using a 3.5-MHz transvaginal transducer or a 5-MHz transabdominal probe or both.

A transabdominal approach alone was used to evaluate those patients who had had no sexual experience. Machine settings were adjusted for sample volume at 3 mm. A wall filter setting of 100 Hz was used to eliminate low-frequency signals, and intensities for color and pulsed Doppler modes were kept below 100 mW/cm² spatial peak temporal average.

Each examination initially included a morphologic study by ultrasonography, and the size of each tumor was determined by choosing the largest dimension measured from the tumor. A color Doppler scanning was performed subsequently with an attempt to visualize the intratumoral blood flow. A pulsed Doppler beam was focused on the intratumoral vessel and flow velocity waveforms were recorded. When internal vessels were absent, vessels in the wall of the tumor were analyzed. Impedance to flow was measured using the resistance index (RI) to determine the vascular resistance. At least three separate cardiac cycles were examined, and the lowest RI value was used for analysis. In accordance with the previous report of Kurjak et al, the cutoff point of RI was defined as 0.5. The RI of normal and abnormal blood flows could be readily detected by color Doppler ultrasonography in all malignant tumors (100%), but it was found in only 59% of the benign ovarian tumors. The mean RI for 49 benign lesions with detectable blood flow was 0.68 (range: 0.36 to 0.89) compared with a mean RI of 0.41 (range: 0.18 to 0.68) for the malignant lesions. The difference in RI for benign and malignant tumors was statistically significant (p < 0.0001). Vascular location also differed. In all of the malignant tumors, blood flow was detected within the mass, while only two of the benign tumors had intratumoral blood flow. The majority of benign ovarian tumor and ovarian cancer. In addition, the t-test was used to compare differences in various parameters between benign and malignant masses, and a difference was considered statistically significant when p < 0.05.

RESULTS

Of the 108 patients studied, 83 patients had benign ovarian tumors and 25 patients had ovarian cancers according to the histopathologic examination. The specific types and sizes of mass and the results of color Doppler ultrasound examinations are shown in Table 1. In the 84 premenopausal patients studied, 60 were examined in the proliferative phase of the menstrual cycle. Intratumoral blood flows could be readily detected by color Doppler ultrasonography in all malignant tumors (100%), but it was found in only 59% of the benign ovarian tumors. The mean RI for 49 benign lesions with detectable blood flow was 0.68 (range: 0.36 to 0.89) compared with a mean RI of 0.41 (range: 0.18 to 0.68) for the malignant lesions. The difference in RI for benign and malignant tumors was statistically significant (p < 0.0001). Vascular location also differed. In all of the malignant tumors, blood flow was detected within the mass, while only two of the benign tumors had intratumoral blood flow. The majority

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Numbera</th>
<th>Maximal Sizeb</th>
<th>RIc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (n = 83)</td>
<td></td>
<td>cm</td>
<td></td>
</tr>
<tr>
<td>Endometrioma</td>
<td>18/29</td>
<td>6.9 ± 2.0</td>
<td>0.66 ± 0.09</td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>6/11</td>
<td>18.3 ± 10.9</td>
<td>0.65 ± 0.19</td>
</tr>
<tr>
<td>Teratoma</td>
<td>8/16</td>
<td>9.7 ± 4.8</td>
<td>0.72 ± 0.13</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>6/13</td>
<td>6.4 ± 1.8</td>
<td>0.69 ± 0.10</td>
</tr>
<tr>
<td>Thecoma</td>
<td>3/3</td>
<td>14.0 ± 2.0</td>
<td>0.60 ± 0.23</td>
</tr>
<tr>
<td>Abscess</td>
<td>5/7</td>
<td>7.3 ± 2.2</td>
<td>0.70 ± 0.15</td>
</tr>
<tr>
<td>Corpus luteum hematoma</td>
<td>3/5</td>
<td>9.4 ± 5.4</td>
<td>0.63 ± 0.16</td>
</tr>
<tr>
<td>Malignant (n = 25)</td>
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<tr>
<td>Serous cystadenocarcinoma</td>
<td>10/10</td>
<td>93.0 ± 2.9</td>
<td>0.40 ± 0.12</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>3/3</td>
<td>11.0 ± 6.1</td>
<td>0.41 ± 0.07</td>
</tr>
<tr>
<td>Endometrioid carcinoma</td>
<td>2/2</td>
<td>12.5 ± 2.1</td>
<td>0.37 ± 0.03</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
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<td>7.0</td>
<td>0.42</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
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<td>18.6 ± 2.3</td>
<td>0.39 ± 0.16</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>1/1</td>
<td>20.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>5/5</td>
<td>8.8 ± 1.1</td>
<td>0.39 ± 0.04</td>
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</tbody>
</table>

RI: resistance index.
*aNumber of patients with detectable blood flow/total number of patients in each tumor type.
*bData given are mean ± standard deviation.
*cMean ± standard deviation of all patients with detectable blood flow in each tumor type.
*dStage I, 4; stage II, 1; stage III, 12; stage IV, 3.
of blood flow detected in benign lesions was at the periphery of the mass (Figure 1).

In four patients with benign ovarian tumors, abnormal flow (RI < 0.5) was detected. The histopathologic diagnoses were hemorrhagic corpus luteum cyst, thecoma, endometrioma, and cystadenoma, respectively, and the two patients with endometrioma and corpus luteum cyst were examined in the luteal phase. In 3 of the 25 patients with ovarian cancer, normal flows (RI > 0.5) were recognized. The histopathologic diagnoses were serous cystadenocarcinoma, endodermal sinus tumor, and immature teratoma, respectively. The mean value of serum CA 125 for benign lesions was 51.1 U/mL (range: 5 to 396 U/mL), whereas that for malignant lesions was 329.0 U/mL (range: 21 to 927 U/mL), a significant difference ($p < 0.0001$).

The comparison of the sensitivity, specificity, PPV, and NPV among RI, serum CA 125, and combined RI with CA 125 is shown in Table 2. A sensitivity of 100% and NPV of 100% for differ-

![FIGURE 1](image_url)
entiation of benign and malignant ovarian tumors was achieved by the combination of RI and CA 125 tests. If the cutoff point of serum CA 125 was changed from 35 to 65 U/mL in combination with RI, a specificity of 100% and PPV of 100% could be also achieved without a change in sensitivity or NPV (Table 2). Preoperative chemotherapies were given to two cases of known ovarian cancers. The mean RI shifted from 0.39 preoperatively to 0.54 postoperatively in one case of serous adenocarcinoma and from 0.41 to 0.73 in the case of stromal sarcoma. Although the total number of early-stage ovarian cancers was small, the RI seemed to show no significant difference between early (5 cases) and advanced (20 cases) ovarian cancers (0.40 ± 0.13 versus 0.41 ± 0.10).

DISCUSSION

Lack of a reliable diagnostic test at an early stage is a major obstacle for better treatment effect of ovarian cancer. An accurate preoperative diagnosis could engender better preoperative and intraoperative management, and the morbidity and even the mortality of these patients may be reduced. Ultrasonography, especially transvaginal sonography, is widely used to differentiate benign from malignant tumors by the morphological patterns of the tumors. However, the predictive value is not satisfactory. Color Doppler ultrasonography alone is not good enough, and further work is needed to determine which features, indexes, and cutoff values can be used to distinguish between benign and malignant lesions. Two reasons may account for the limited validity of color Doppler sonography: (1) the impedance to flow might be influenced by luteal hormones; (2) the location, maximum systolic velocity, and waveform shape of the specific vessel interrogated might influence the impedance to flow obtained.

To solve these arguments and to improve the validity of color Doppler study, Kurjak et al. and Timor-Tritsch et al. have presented a scoring system for the prediction of ovarian malignancies by combining some morphological and Doppler characters and have demonstrated very high sensitivity and specificity. However, Fleischer et al. argued that some benign tumors (such as endometrioma, tubo-ovarian abscess, and dermoid cyst) in premenopausal patients, especially when examined in the luteal phase of the menstrual cycle, may have low impedance waveforms and suspicious morphological findings.

Fleischer et al. have employed a multiparameter approach. They have shown that vessel location, flow impedance, and waveform shape were different between benign and malignant ovarian tumors and these parameters should be taken into consideration when color Doppler examination is applied. Their findings were partly confirmed by a recent report from Kurjak et al.

In this study, abnormal flow (RI < 0.5) was detected in 4 of the 83 benign tumors, which were hemorrhagic corpus luteum cyst, endometrioma, thecoma, and cystadenoma, respectively. The 2 patients with corpus luteum cyst and endometrioma were examined in the luteal phase of the menstrual cycle. The specificity for color Doppler sonography might be improved if we could examine these patients again in the early proliferative phase of the menstrual cycle. Among the malignant tumors, 3 of 25 showed normal flow pattern (RI > 0.5). Two of them had advanced epithelial ovarian carcinoma and the third had a stage I, well-differentiated immature teratoma.

In agreement with other authors, the blood flow detected was intratumoral in all of the malignant ovarian tumors reported here, whereas that for benign lesions was usually peripheral. The change of impedance to flow following chemotherapy merits attention although it was not the main subject of the present study. Intratumoral blood flow generally decreases after anticancer drugs (mean RI changed from 0.39 to 0.54 in one serous adenocarcinoma and from 0.41 to 0.73 in stromal sarcoma). Similar findings were originally reported by Hata et al. Color Doppler ultrasonography, therefore, can also be used to follow changes in tumor vascularity in malignant...
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gynecologic tumors before and after chemotherapy.

Due to either the low sensitivity (68%) or the low specificity (61%) of serum CA 125 for the detection of ovarian cancer previously reported,\textsuperscript{16,23} the combination of serum CA 125 determination and ultrasound examination is suggested as a more reliable screening method.\textsuperscript{25} A recent study from Schneider et al.\textsuperscript{26} showed that the combination of the RI with either the morphologic features detected with ultrasonography or CA 125 increased the sensitivity and NPV to 100%, with only a slight decrease in specificity and PPV. Our data partly confirmed the conclusion of Schneider et al. Moreover, in the present study using the combination of serum CA 125 and color Doppler ultrasound, the sensitivity and NPV reached 100%. When the cutoff point for CA 125 was increased to 65 U/mL, the best specificity (100%) and PPV (100%) were also reached. We recommend, therefore, that cases of ovarian tumors with serum CA 125 greater than 65 U/mL and color Doppler ultrasound findings indicating abnormal blood flow pattern (RI < 0.5) should be considered to be ovarian cancer until proven otherwise.

Color Doppler ultrasonography is a noninvasive method that can be performed easily without causing discomfort to patients. Serum CA 125 is considered one of the most useful tumor markers. The combination of these two, in our hands, has been a powerful tool for the differential diagnosis of benign and malignant ovarian tumors.

REFERENCES


