GYNAECOLOGY

Doppler Indices for Prediction of Benign and Malignant Ovarian Tumor

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ABSTRACT

Objective   To determine the validity of pulsatility and resistance index of transabdominal Doppler ultrasound (e-flow) in distinguishing between benign and malignant adnexal masses

Study design   Cross-sectional descriptive study

Settings   Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University

Subjects   The patients scheduled for elective surgery due to adnexal masses at Maharaj Nakorn Chiang Mai Hospital between June, 2006 and July, 2007, were recruited into the study.

Methods   All patients were sonographically evaluated for pulsatility and resistance index aided with color e-flow within 24 hours of surgery. All examinations were performed by the same experienced sonographer, who had no any information of the patients, to differentiate between benign and malignant adnexal masses based on sonographic morphology. The final diagnoses, used as gold standard, were based on either pathological or operative findings.

Main outcome measure Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of pulsatility and resistance index, using the best cutoff points obtained from the receiver operating characteristic curve

Results   One hundred and seventy-nine patients were recruited and 15 were excluded since the masses were finally not proven to be adnexal masses. Of the remaining 164 cases available for analysis, 103 masses were benign and 61 were malignant. The sensitivity and specificity of pulsatility index were 95.1% and 88.3%, respectively and the sensitivity and specificity of resistance index were 95.1 % and 90.3%, respectively.

Conclusion   Pulsatility and resistance index of transabdominal Doppler ultrasound (e-flow) has high accuracy in differentiating between benign and malignant adnexal masses.

Keywords: Adnexal mass, Pulsatility index, Resistance index, Doppler ultrasound, Benign ovarian tumor, Malignant ovarian tumor

Introduction

The differentiation of benign from malignant adnexal masses is of great value, because therapeutic approach is markedly different between the two entities. Benign ovarian masses, functional change or neoplasm, need more conservative approach, either closed observation or laparoscopic surgery, whereas the malignant tumors require urgent laparotomy in most cases with planned systematic consultation of available oncologists.

Several attempts have been made to distinguish the both conditions, especially the use of pelvic ultrasound based on either morphological appearance[1-5] or Doppler waveforms.[6-9] With high-resolution ultrasound machine, color Doppler ultrasound has been proposed as a possible technique for differentiation of benign from malignant adnexal masses as well as for early diagnosis of ovarian carcinoma for several years.[6,7] Some reports showed the superiority of this technique in screening ovarian cancer,[8,9] other reported the ability in differentiating benign from malignant tumors preoperatively.[10-12] However, color Doppler application in such previous reports was often needed transvaginal ultrasound approach and this might be inconvenient to some patients. Currently, high-resolution color Doppler with extended flow (e-flow) has been developed, resulting in higher sensitivity in detection of blood flow in minute vessels even during transabdominal examination. Therefore, the purpose of the present study was to determine the sensitivity and specificity of pulsatility index (PI) and resistance index (RI), derived from transabdominal color Doppler e-flow, in differentiating benign from malignant ovarian tumor.

Materials and Methods

Between June 2006 and July 2007, 179 patients were admitted to Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University for elective surgery because of the detection of an adnexal mass either by pelvic examination or ultrasonography elsewhere or both.

Exclusion criteria consisted of known diagnoses of ovarian malignancy which was scheduled for second look operation, and patients undergoing operation beyond 24 hours after ultrasound examination. All of these women were counseled and invited to join the study with written informed consent.

All subjects underwent ultrasound examination within 24 hour of surgery by the same experienced examiner who had no any clinical information of the patients. The women were examined with real-time 3.5-5 MHz transabdominal curvilinear transducer connected to an Aloka model SSD alpha-10 (Tokyo, Japan). After thorough conventional examination, transabdominal color Doppler blood together with extended-flow (e-flow) examination was performed. On the color Doppler ultrasound examination, the sampling point on the line of the pulsed Doppler beam was positioned where the colored dots within the tumor revealed the presence of vessels and these positions were followed those proposed by Kurjak et al.[6] When no blood flow was detectable within the tumor, a signal was recorded by peripheral areas or the adnexal branch of the ovarian artery or uterine artery.

Both pulsatility index (PI) and resistance index (RI) were calculated. The value of each artery was calculated from a curve fitted to the average waveform over three cardiac cycles.

The formulas used for PI and RI were $PI = (S-D)/mean$ and $RI = (S-D)/S$ respectively, when S is the peak Doppler frequency shift and D is the minimum. Signals from various areas within the tumor were determined but the lowest PI and RI were considered for data analysis. Furthermore, the area distribution of visualized vessels in the adnexal masses was also categorized and recorded as center of the mass, in the septum, in the papillae, at tumor wall or peri-tumor areas.

The final diagnosis as gold standard was based on either pathological findings or intraoperative findings in case of no pathological specimen. The pathological diagnosis of borderline tumor was classified as malignancy. Therefore all of adnexal masses were divided into 2 groups as benign and malignant adnexal masses.

The sensitivity and specificity of various cut-off levels of PI and RI were calculated and the proper PI and RI for differentiating the tumors were determined by receiver operator characteristic curve (ROC curve). All data were analyzed by using SPSS software version 15.0 (Chicago, USA). The Student t-test was used to compare mean RI and PI between the benign and malignant group and a P value of < 0.05 was considered to be significant.

Results

Between June 2006 and July 2007, 179 patients initially diagnosed as ovarian tumors were recruited to undergo e-flow color Doppler ultrasound examinations. Fifteen patients were excluded because of pathological diagnoses of non-ovarian tumor including intramural myoma, hydrosalpinx, etc. The remaining 164 were analyzed. All were successfully performed via transabdominal ultrasound. The mean ($\pm$ SD) age of the patients was 44.7$\pm$12.9 years. Sixty-one (37.2%) were nulliparous. Most patients (115 women, 70.1%) were in reproductive age, 115 (28.7%) were menopausal and 2 of them were in pre-menarche period.

Histopathological examinations revealed 103 benign tumors, 7 low malignant potential tumors and 54 malignant tumors. Table 1 summarizes the type of ovarian tumors in this study.

Of 164 cases, the mean PI values of tumor arteries were 1.74 ($\pm$0.42), 0.99 ($\pm$0.34) and 0.89 ($\pm$0.37) for benign tumor, low malignant potential tumor and cancer, respectively. When cancer and low malignant potential tumors were considered together, their mean PI was 0.90 ($\pm$0.35). The mean PI in the benign and malignant group was significantly different ($p<0.001$). Based on receiver-operating characteristics (ROC) curve (Fig. 1) with area under curve of 0.952 (95% confidence interval; 0.921; 0.982), the best cut-off PI was 1.24, which gave sensitivity and specificity of 95.1% and 88.3%, respectively (Table 2).

The mean RI values were 0.81 ($\pm$0.21) , 0.50 ($\pm$0.14) and 0.44 ($\pm$0.13) for benign tumor, low malignant potential tumor and cancer, respectively. The mean RI was 0.45 ($\pm$0.13) if malignant and borderline tumors were considered together. The mean RI in the benign and malignant group was significantly different ($p<0.001$). Based on receiver-operating characteristics (ROC) curve (Fig. 2) with area under curve of 0.950 (95% confidence interval; 0.916; 0.985), the best cut-off RI was 0.64, which gave sensitivity and specificity of 95.1% and 90.3%, respectively (Table 3).

Blood flow velocity waveforms within the tumors were detected in all cases of the malignant group and in 57 of 103 cases of the benign one. In the remaining 46 patients, blood flow was detected only in either the ovarian artery or adnexal branch of the uterine artery. The sites of detected vessels are summarized in (Table 4).

Table 1. Distribution of the final pathological diagnoses of the adnexal masses

Tumor Categories	Final Diagnoses	Number	Percent
Benign tumors	Endometriotic cyst	39	23.8
	Mature teratoma (Dermoid cyst)	18	11.0
	Mucinous cystadenoma	9	5.5
	Serous cystadenoma	9	5.5
	Follicular cyst, Simple cyst	6	3.7
	Hemorrhagic cyst	4	2.4
	Subserous myoma	4	2.4
	Thecoma, Fibroma	4	2.4
	Hydrosalpinx , TOA	3	1.8
	Other Benign tumors	7	4.3
Low malignant potential tumor	LMP mucinous cystadenoma	7	4.3

Cancer	Serous cystadenocarcinoma	18	11.0
	Endometrioid carcinoma	10	6.1
	Metastatic adenocarcinoma	7	4.3
	Mucinous cystadenocarcinoma	5	3.0
	Clear cell carcinoma	3	1.8
	Sex cord stromal tumor	2	1.2
	Endodermal sinus tumor	1	0.6
	Immature teratoma	1	0.6
	Dermoid with squamous cell carcinoma	1	0.6
	Dysgerminoma		
	Other malignant tumors	1	0.6
		5	3.0
Total		**164**	**100.0**
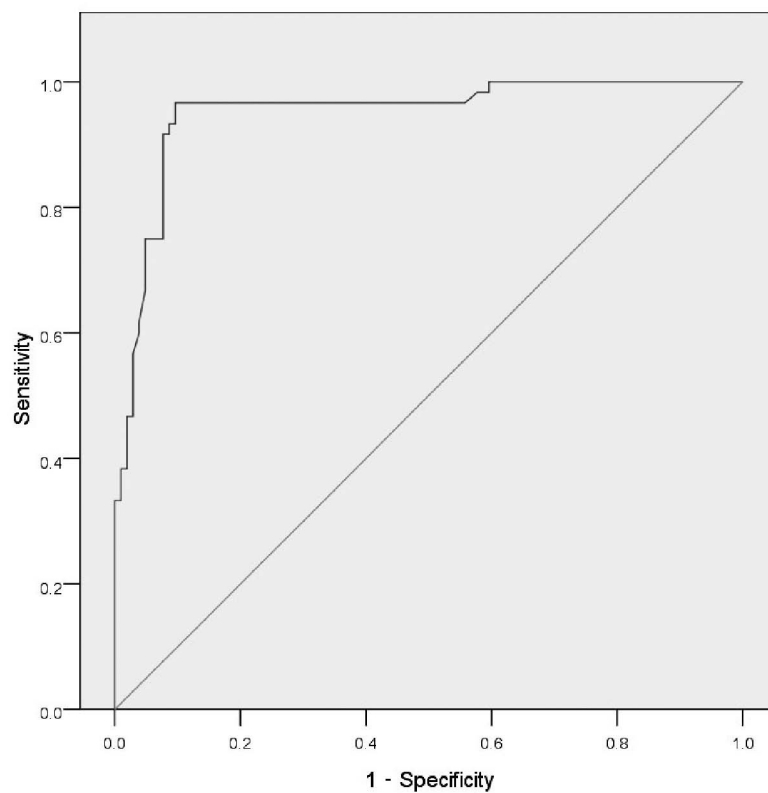
Fig. 1. Receiver operating characteristic (ROC) curve of PI in differentiating benign from malignant adnexal masses

Table 2. Diagnostic indices of pulsatility index (PI) of color e-flow Dopper in differentiating benign from malignant adnexal masses, using cut-off value at 1.24

Pulsatility Index (PI)	Benign Masses (Number)	Malignant Masses (Number)	Total
PI < 1.24	58	12	70
PI ≥ 1.24	3	91	94
Total	**61**	**103**	**164**

Sensitivity	= 95.08% (58/61)	95% CI: 0.854; 0.987
Specificity	= 88.35% (91/103)	95% CI: 0.802; 0.936
Positive predictive value	= 82.90% (58/70)	95% CI: 0.716; 0.905
Negative predictive value	= 96.80% (91/94)	95% CI: 0.887; 0.994
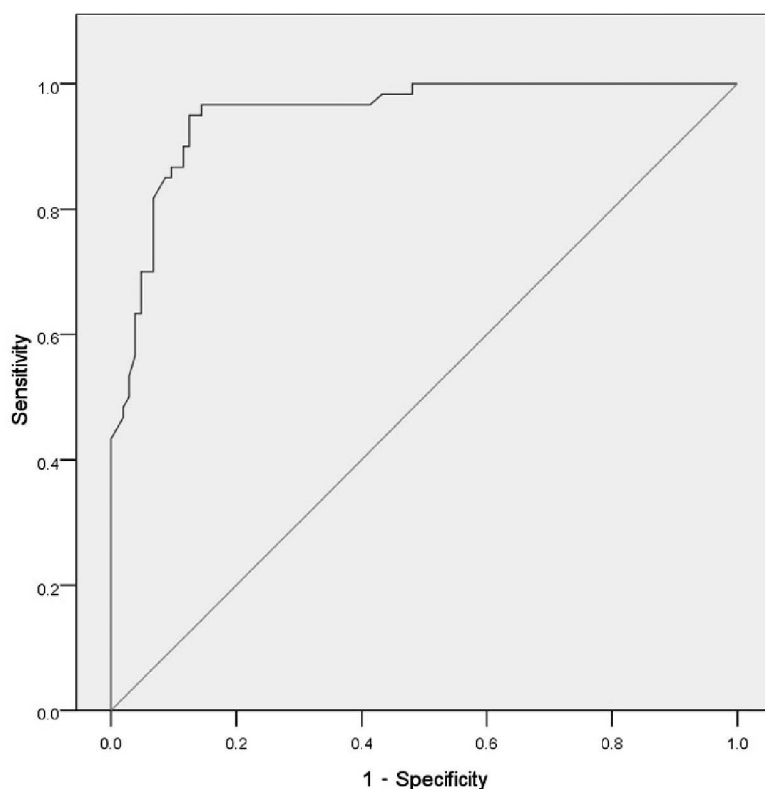
Fig. 2. Receiver operating characteristic (ROC) curve of RI in differentiating benign from malignant adnexal masses

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Table 3. Diagnostic indices of resistance index (RI) of color e-flow Dopper in differentiating benign from malignant adnexal masses, using cut-off value at 0.64

Resistance Index (RI)	Benign Masses (Number)	Malignant Masses (Number)	Total
RI < 0.64	58	10	68
RI ≥ 0.64	3	93	96
Total	**61**	**103**	**164**

Sensitivity	= 95.08% (58/61)	95% CI: 0.854; 0.987
Specificity	= 90.29% (93/103)	95% CI: 0.825; 0.950
Positive predictive value	= 85.30% (58/68)	95% CI: 0.742; 0.923
Negative predictive value	= 96.90 (93/96)	95% CI: 0.886; 0.994

Table 4. The location of vessel distribution in the adnexal masses

Location	Number	Benign (%)	Low malignant potential (%)	Cancer (%)
Central areas	29	9 (31.0)	2 (6.90)	18 (62.1)
Peripheral areas	14	8 (57.1)	1 (7.1)	5(35.8)
In the septae	30	16 (53.3)	2 (6.7)	12 (40.0)
In the papillae	36	19 (52.8)	1 (2.8)	16 (44.4)
At the tumor wall	9	5 (55.6)	1 (11.1)	3 (33.3)
Peri-tumor areas (No vessels in tumor)	46	46 (100)	-	-
Total	**164**	**103 (62.8)**	**7 (4.3)**	**54 (32.9)**

Discussion

Differentiation of benign from malignant tumors might be achieved by several methods such as clinical signs and symptoms, serum CA 125,[13-15] and ultrasound.[1,16] Conventional ultrasound parameters for the differentiation of malignant from benign tumors are based merely on morphological features. The introduction of color Doppler ultrasound, especially high-resolution color e-flow Doppler with higher sensitivity in detection of blood flow in minute vessels, might allow a step forward from morphological to functional evaluation of the masses. The theoretical background comes from the observation that the new tumor vessels that grew as a result of angiogenesis differ from the normal vessels with respect to cellular composition,

basement membrane structure and permeability. As a result, the hemodynamics of these vessels are changed.[6]

Considering angiogenesis as a neoplastic marker for malignancy, color Doppler ultrasound allowing a better insight in the biological behavior of the tumor, the early diagnosis of cancer could become possible by detecting neovascularization in the tumor.[6,9,12,17]

In previous studies, some authors suggested the existence of clear cut-off points of PI and RI of benign and malignant tumors; Kurjak et al[8] reported only one false positive and two false negative results in a screening program involving 624 benign ovarian tumors and 56 malignant tumors by using a cut-off value of RI 0.4. Sengoku et al[18] reported sensitivity

and specificity of 81.3% and 91.7% respectively when the cut-off value of PI 1.5 were used. Timor-Tritsch et al[19] reported the RI value of 0.4 had sensitivity 93.8% and specificity of 98.7% which was different from the study of Zanetta et al (RI 0.56)[20].

In this study 54% of benign and 100% of malignant including borderline tumors had detectable arterial blood flow in the tumors using a color Doppler unit. This information may enable us to conclude that tumor without detectable blood flow is very unlikely to be malignant. Our cut-off PI value of 1.24, giving the sensitivity and specificity of 95.1% and 88.3%, respectively, was different from the study of Sengoku et al[18] but was consistent with the data reported by Weiner et al.[10] Considering RI value of 0.64 as the cut-off point, the sensitivity and specificity were 95.1% and 90.3% respectively, slightly different from the studies of Timor-Tritsch et al[19] and Zanetta et al[20] in which RI value were 0.4 and 0.56 respectively.

The scanning approach (transvaginal or transabdominal) and frequency of the probes might partially explain inconsistent results reported previously by different authors.[20] Unlike previous reports in which they firstly used transabdominal probe and then transvaginal probe is performed if transabdominal examination was unable to visualize, our study with e-flow color Doppler we could identify the tumor in all cases. This may be the advantage of new high-resolution ultrasound technology permitting us avoiding the inconvenience of transvaginal approach.

Although there are different opinions about cutoff values, all authors agree that recognition of angiogenesis as a reference point for malignant changes within the ovary has proved to be a highly sensitive parameter. Given that neovascularization is an obligate event in malignant change, this recognition may enable us to observe the earliest stages in ovarian oncogenesis.

The bias in this study might have existed. This was due to the fact that Doppler evaluation of the tumor was not a blind method as the examiner had known the morphology of the tumor from conventional sonographic images. Therefore, the nature of the mass could have been anticipated. Consequently, the signs of neovascularization in tumors considered benign by conventional ultrasound might be missed by insufficient evaluation of the vascularity, whereas the tumors with suspicious of malignancy would be examined more thoroughly until the expected lowest PI and RI were found. However, we tried to examine all arterial signals to find out the lowest ones in each case to reduce the bias described.

In the future, research should be directed to compare the new color e-flow Doppler ultrasound with other modalities other than conventional ultrasound, especially three-dimensional color Doppler for detecting ovarian malignancy. Because of low incidence of ovarian cancer, one can initiate this ovarian malignancy screening program in high-risk population so that the efficacy of this method can be evaluated.

In conclusion, pulsatility and resistance index of transabdominal Doppler ultrasound (e-flow) has high accuracy in differentiating between benign and malignant adnexal masses.

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การใช้คลื่นเสียงดอพเลอร์ในการแยกเนื้องอกรังไข่ชนิดธรรมดากับชนิดร้ายแรง

วิธิดา นียลาวีระ

วัตถุประสงค์ : เพื่อประเมินความถูกต้องในการทำนายแยกก้อนในอุ้งเชิงกรานชนิดร้ายแรงและชนิดธรรมดาโดยด้วยค่า pulsatility index และ resistance index ของคลื่นเสียงดอพเลอร์ (ชนิดe-flow)

รูปแบบการศึกษา : การศึกษาแบบตัดขวาง เชิงพรรณนา

สถานที่ทำการศึกษา : ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

ตัวอย่างการศึกษา : ผู้ป่วยที่ได้นัดมาผ่าตัดเนื่องจากมีก้อนที่ปีกมดลูก ที่โรงพยาบาลมหาราชนครเชียงใหม่ ในช่วงระหว่างเดือนมิถุนายน 2549 ถึง กรกฎาคม 2550

วิธีการศึกษา : ผู้ป่วยที่ถูกคัดเลือกเข้าสู่การศึกษาจะได้รับการตรวจก้อนที่ปีกมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้องภายใน 24 ชั่วโมงก่อนการผ่าตัด ซึ่งได้รับการตรวจโดยผู้มีประสบการณ์สูงด้านอัลตราซาวน์ ซึ่งไม่ทราบข้อมูลใดๆ และทำนายก้อนปีกมดลูกว่าเป็นชนิดร้ายแรงหรือชนิดธรรมดา โดยประเมินจากค่า pulsatility index และ resistance index ของคลื่นเสียงดอพเลอร์ การวินิจฉัยขั้นสุดท้ายถือตามผลตรวจทางพยาธิวิทยาหลังการผ่าตัด

ผลที่ต้องการวัด : ความถูกต้อง ความไว ความจำเพาะ ค่าทำนายผลบวก และค่าทำนายผลลบของการประเมินโดย pulsatility index และ resistance index ของคลื่นเสียงดอพเลอร์ ซึ่งใช้จุดตัด (cut-off) ที่เหมาะสมที่สุดจาก receiver operating characteristic curve

ผลการศึกษา : ผู้ป่วยที่เข้าร่วมในการศึกษาทั้งหมด 179 ราย ถูกตัดออกจากการวิจัย 15 รายเนื่องจากผลการผ่าตัดไม่ใช่ก้อนที่ปีกมดลูก มีก้อนที่ปีกมดลูก 164 ราย ซึ่งเป็นชนิดธรรมดา103 ก้อน และชนิดร้ายแรง 61 ราย ค่าpulsatility indexมีความไว และความจำเพาะเป็นร้อยละ95.1 และ 88.3 ตามลำดับ และค่า resistance index มีความไว และความจำเพาะเป็นร้อยละ 95.1 และ 90.3 ตามลำดับ

สรุป : ค่า pulsatility index และ resistance index ของคลื่นเสียงดอพเลอร์ (ชนิดe-flow) มีความถูกต้องสูงในการแยกก้อนที่ปีกมดลูกว่าเป็นชนิดร้ายแรงหรือชนิดธรรมดา

คำสำคัญ : ก้อนที่ปีกมดลูก, คลื่นเสียงดอพเลอร์, ก้อนเนื้องอกรังไข่ชนิดธรรมดา, ก้อนเนื้องอกรังไข่ชนิดร้ายแรง