

# Predicting Malignancy in Entirely Solid-appearing Adnexal Masses on Gray-Scale Ultrasound Based on Additional Ultrasound Findings, Clinical Complaints and Biochemical Parameters: A Retrospective Study

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## ABSTRACT

**Purpose:** To determine which clinical, biochemical and other sonographic parameters could be useful to predict malignancy in sonographically solid adnexal masses.

**Materials and methods:** Clinical, biochemical and other sonographic features from 227 women diagnosed as having an entirely solid adnexal mass on B-mode gray-scale ultrasound were reviewed for this retrospective study. All patients had undergone surgery and mass removal. Definitive histologic diagnosis was available in all cases. All parameters were compared to final histological diagnosis (benign or malignant) in univariate statistical analysis. Then a stepwise forward logistic regression analysis was performed to identify those features that independently predict malignancy.

**Results:** A total of 227 masses were analyzed. Patients' mean age was 52.9 years (range: 15-84 years). A total of 150 masses were malignant and 77 were benign. In 52 cases carcinomatosis was observed on ultrasound scan and all these cases were malignant. In the remaining 175 cases, univariate analysis showed statistical differences between benign and malignant tumors all parameters except tumor's volume. After logistic regression analysis tumor contour, acoustic shadowing, amount of color and CA 125 were identified as independent predictors of malignancy. Using a logistic model 94.4% of malignant tumors and 85.7% of benign tumors would be correctly identified.

**Conclusion:** The presence of carcinomatosis is invariably associated to malignancy. In absence of carcinomatosis, irregular tumor contour, absence of acoustic shadowing, moderate or abundant blood flow and a high CA 125 are associated to malignancy.

**Keywords:** Solid adnexal mass, Malignancy, Ultrasound.

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## INTRODUCTION

Entirely solid adnexal masses constitute a diagnostic challenge for most sonologists and sonographers.<sup>1</sup> A significant number of these adnexal masses are malignant<sup>2,3</sup> but most of them are benign.<sup>4,5</sup> Therefore, accurate

differential diagnosis is essential for adequate referral and optimal management.<sup>6-8</sup>

Most studies involving the use of ultrasound for discriminating benign from malignant solid adnexal masses focus on ultrasound findings of the mass itself, whereas other factors such as clinical complaints, physical examination or other additional ultrasound findings have not been analyzed in detail.

Our hypothesis is that these factors may predict malignancy in entirely solid adnexal masses. Thus, in the present study we aimed to determine whether any clinical, biochemical or other sonographic parameter could be helpful for predicting malignancy in solid adnexal masses.

## MATERIALS AND METHODS

This is a retrospective study that comprises a consecutive series of women diagnosed as having an entirely solid adnexal mass on gray-scale ultrasound evaluated and treated at our institution between January 1995 and June 2011. IRB approval was obtained for this study. However, patients' informed consent was waived due to the retrospective design as well as for all tests performed was routine for diagnostic workup for adnexal masses.

Patients' records including clinical, biochemical and sonographic data were reviewed. For ultrasound data, ultrasound reports as well as digital stored images were reviewed.

In our institution diagnostic workup for all patients diagnosed as having an adnexal mass include complete medical history, pelvic examination, and serum CA 125 levels determination, except for simple cysts, as well as an ultrasound evaluation.

For this study, medical history focused on patient's complaints, age and menopausal status. Clinical data recorded were as follows:

1. *Patient's complaints:* Asymptomatic. Symptoms nonsuggestive of ovarian cancer such as pelvic pain—for example, suggestive of endometriosis or abnormal uterine bleeding. Symptoms suggestive of ovarian cancer, such as abdominal swelling, bloating and abdominal discomfort.

2. *Menopausal status*: Premenopausal or postmenopausal. Menopause was defined as 1 year of absence of menstruation in women older than 45 years. If hysterectomy had been performed, a woman was considered as postmenopausal if older than 50 years.

Pelvic exam was performed by staff specialists in Obstetrics and Gynecology. Findings were stated as follows:

1. 'Inconclusive', when no reliable information could be obtained.
2. 'Nonsuspicious', in the presence of a less than 8 cm maximum diameter adnexal mass, mobile at examination, of cystic or solid consistency but regular contours and no evidence of ascites.
3. 'Suspicious', in the presence of at least one of the following: Fixed and/or irregular adnexal mass regardless the size, evidence of ascites (fluid wave).

Transvaginal ultrasound evaluation was performed according to a predetermined protocol.<sup>9</sup> In cases of large tumors, presence of fluid in Douglas' pouch or suspicion of pelvic implants transabdominal ultrasound was also performed. Although IOTA consensus defined a solid tumor as a tumor being 80% or more solid,<sup>10</sup> in our study only tumors entirely solid (100% solid appearance) at B-mode examination (Fig. 1) were included in this study. Ultrasound parameters assessed were as follows:

1. Tumor volume was estimated according to the prolate ellipsoid formula ( $A \times B \times C \times 0.5233$ ) and expressed in ml.
2. Tumor contour, stated as 'regular' (Fig. 1) or 'irregular' (Fig. 2).
3. Acoustic shadowing; stated as 'absent' or 'present' (Fig. 3).
4. Bilaterality, stated as 'yes' or 'no'. In those women with bilateral masses we chose the largest one for statistical analysis.
5. The presence of ascites ('yes' or 'no'); defined subjectively by the examiner as the presence of fluid in pelvis surrounding the uterus and/or upper abdomen (Fig. 4).
6. The presence of tumoral implants—carcinomatosis—in pelvis or upper abdomen, stated as 'present' or 'absent' (Figs 5 and 6).
7. Subjective amount of flow within the mass based on color or power Doppler assessment; stated as 'absent', 'scanty' (Fig. 7), 'moderate' or 'abundant' (Fig. 8).

In all cases blood samples had been collected to measure CA 125 plasma concentration. CA 125 measurements were performed using an enzyme immunoassay with a monoclonal antibody (Cobas-Core CA 125 II, Laboratories Roche, Basel, Switzerland).



**Fig. 1:** Small solid adnexal mass with regular contour in a postmenopausal woman. Histopathology revealed an ovarian fibroma



**Fig. 2:** Large irregular solid mass in a postmenopausal woman. Ascites is also seen. Histology revealed a primary serous ovarian carcinoma



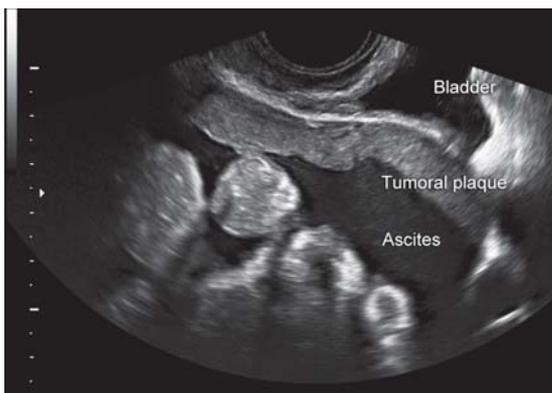
**Fig. 3:** Transvaginal ultrasound depicting a well-defined solid mass with acoustic shadowing. Histology revealed a benign ovarian Brenner tumor



**Fig. 4:** Transabdominal ultrasound depicting a significant amount of ascites within the abdomen and pelvis



**Fig. 5:** Transabdominal ultrasound depicting tumoral involvement of the greater omentum (omental cake)



**Fig. 6:** Transvaginal ultrasound that shows pelvic carcinomatosis, a tumoral plaque is seen involving the bladder peritoneum



**Fig. 7:** Transvaginal color Doppler ultrasound from a solid mass with scanty vascularization. Histology revealed a benign ovarian fibrothecoma



**Fig. 8:** Transvaginal power Doppler ultrasound from an ill-defined large solid pelvic mass with abundant vascularization. Histology revealed a malignant ovarian Sertoli-Leydig cell tumor

All tumors were surgically removed and definitive histological diagnosis obtained. Tumors were classified according to the World Health Organization.<sup>11</sup> Ovarian malignancies were staged according to the FIGO.<sup>12</sup> Low malignant potential tumors were considered as malignant.

The only inclusion criterion was the diagnosis of an entirely solid mass. Exclusion criteria were as follows: No complete medical, laboratory or ultrasound records; surgery not performed in our institution.

## STATISTICAL ANALYSIS

We firstly performed univariate statistical analysis to find statistical differences in the parameters assessed between malignant and benign tumors. The Kolmogorov-Smirnov test was used to assess normal distribution of continuous data. Continuous data were compared using the one-way ANOVA or Mann-Whitney U test, according to their distribution. Categorical variables were compared using the Chi-square test for dichotomous variables and the Kendall's tau-b test for ordinal variables.

Once univariate analysis was done, we performed multivariate forward stepwise logistic regression analysis (MLR) including as independent variables only those variables found to be statistically different between malignant and benign tumors in the univariate analysis and as dependent variable the final diagnosis (malignant or benign). For MLR analysis dichotomous variables were stated as follows: Menopause (1 = yes, 0 = no), physical exam (1 = suspicious, 0 = nonsuspicious or inconclusive), symptoms (1 = suspicious, 0 = nonsuspicious), ascites (1 = yes, 0 = no), bilaterality (1 = yes, 0 = no), tumor contour (1 = irregular, 0 = regular), acoustic shadowing (1 = no, 0 = yes), amount of flow (1 = moderate/abundant, 0 = absent/scanty) and the CA 125 and tumor volume value were log transformed. The Hosmer-Lemeshow test was used to assess the goodness-to-fit of the model.<sup>13</sup>

A p value  $\leq 0.05$  was considered as statistically significant. All statistical analyses were performed using the SPSS 15.0 statistical package (SPSS Inc, Chicago, Il).

STROBE guidelines were used for reporting this study.<sup>14</sup>

## RESULTS

Three-hundred and twelve patients were eligible for this study. We excluded 85 women for the following reasons: 52 women underwent surgery out of our hospital and 33 women had incomplete records. Thus, 227 women were ultimately included in the study.

Patients' mean age was 52.9 years old (SD: 13.8), ranging from 15 to 84 years old.

Ninety-one (40%) women were premenopausal and 136 (60%) were postmenopausal.

One hundred and fifty (66%) tumors were proved to be malignant and 77 (34%) were benign (Table 1).

After univariate analysis all parameters were statistically different between benign and malignant lesions (Table 2).

We observed that in all 52 cases with evidence of carcinomatosis in ultrasound examination tumors were malignant and none were benign (100% specificity). So,

we decided to focus the analysis in those cases without sonographic evidence of carcinomatosis (n = 175).

Out of those 52 women with carcinomatosis, 44 (84%) had primary ovarian cancers (two stage II, 35 stage III and 7 stage IV) and eight (16%) had metastatic tumors to the ovary.

Univariate analysis in the remaining 175 cases showed statistical significant differences for all variables except for tumor volume (Table 3).

However, after MLR analysis only amount of blood flow, tumor contour, acoustic shadowing and log CA 125 were identified as independent predictors for malignancy (Table 4).

Using the model developed [ $Z = -6.236 + 27.334 \times (\text{amount of color}) + 6.006 \times (\text{acoustic shadowing}) + 3.193 \times (\text{tumor contour}) + 5.842 \times (\log \text{ CA } 125)$ ] 94.0% of malignant tumors and 85.7% of benign tumors were correctly identified (Table 5).

**Table 1:** Histologic diagnoses of those masses included

	N	%
Endometrioma	2	0.9
Teratoma	24	10.5
Cystadenofibroma	2	0.9
Tubo-ovarian abscess	2	1.3
Fibroma/fibrothecoma	24	10.5
Uterine leiomyoma	14	6.2
Brenner tumor	6	2.6
LMP carcinoma	2	0.9
Ovarian cancer*	104	46.3
Metastatic cancer**	47	20.7
Total	227	100.0

\*Epithelial ovarian cancer—94; Sex-cord stromal tumors—2; Germ cell tumor—4; Primary lymphoma—2; Sarcoma—2; \*\*Breast—11; Colon sigmoid—11; Stomach—10; Lung—2; Uterine leiomyosarcoma—2; Endometrium—1; Liver—1; Appendix—1; Biliary tract—1; Ureter—1

## DISCUSSION

In this study, we aimed to assess whether any clinical, biochemical or other ultrasound parameters could be helpful for predicting malignancy in solid-appearing adnexal masses on gray-scale ultrasound. We found that carcinomatosis is

**Table 2:** Univariate statistical analysis for all 227 masses

Parameter	Benign (n = 77)	Malignant (n = 150)	p-value
Patient's age (years)*	48.6 (14.4)	55.1 (13.0)	<0.001
Symptoms of OC	9/77 (11.7%)	68/150 (45.3%)	<0.001
Postmenopausal status	36/77 (46.8%)	100/150 (66.7%)	0.003
Suspicious physical examination	16/77 (20.8%)	101/150 (67.3%)	<0.001
Median CA 125 (IU/ml)**	18.3 (5.0-1760.0)	231.7(5.6-31494.0)	0.005
Median tumor volume (ml)**	54.0 (1.8-3453.8)	75.6 (1.5-1776.0)	0.118
Ascites	9/77 (11.7%)	93/150 (62.0%)	<0.001
Bilaterality	5/77 (6.5%)	43/150 (28.7%)	<0.001
Acoustic shadowing	35/77 (45.5%)	10/150 (6.7%)	0.001
Irregular contour	16/77 (20.8%)	107/150 (71.3%)	<0.001
Moderate or abundant flow	12/77 (15.6%)	126/159 (84.0%)	<0.001
Signs of carcinomatosis	0/77 (0%)	52/150 (34.7%)	<0.001

OC: Ovarian cancer; \*Expressed as mean, standard deviation (SD) in parentheses; \*\*Expressed as median, range in parentheses

**Table 3:** Univariate statistical analysis for 175 masses without carcinomatosis

Parameter	Benign (n = 77)	Malignant (n = 98)	p-value
Patient's age (years)*	48.6 (14.4)	53.8 (13.4)	0.014
Symptoms OC	9/77 (11.7%)	41/98 (41.8%)	0.001
Postmenopausal status	36/77 (46.8%)	60/98 (61.2%)	0.039
Suspicious physical examination	16/77 (20.8%)	59/98 (60.2%)	0.001
Median CA 125 (IU/ml)**	15.4 (5.0-1760.0)	128.0 (5.6-1,4247.0)	0.001
Median tumor volume (ml)**	54.0 (1.8-3453.8)	75.3 (1.5-1,776.0)	0.095
Ascites	9/77 (11.7%)	47/98 (48.0%)	0.001
Bilaterality	5/77 (6.5%)	20/98 (20.4%)	0.007
Irregular contour	16/77 (20.8%)	62/98 (63.3%)	0.001
Moderate or abundant flow	12/77 (15.6%)	82/98 (83.7%)	0.001
Acoustic shadowing	35/77 (45.5%)	6/98 (6.1%)	0.001

OC: Ovarian cancer; \*Expressed as mean, standard deviation (SD) in parentheses; \*\*Expressed as median, range in parentheses

**Table 4:** Multivariate logistic regression analysis

Variable	Coefficient	Odds ratio	95% CI	p-value
Moderate/abundant flow	3.308	27.334	8.429-88.646	0.001
Absence acoustic shadow	1.793	6.006	1.389-25.808	0.016
Log CA 125	1.765	5.842	2.312-14.765	0.001
Irregular tumor contour	1.161	3.193	1.002-10.381	0.049

**Table 5:** Agreement between histology and predictive model in solid adnexal masses without ultrasound signs of carcinomatosis

		Histology	
		Benign	Malignant
Predictive model	Benign	66	6
	Malignant	11	92

best predictor for malignancy. In cases with no carcinomatosis detected on ultrasound, irregular tumor contour, absence of acoustic shadowing and elevated CA 125 are predictor of malignancy.

Our study has some limitations. First, when facing with a solid adnexal mass the differential diagnosis should be established between those lesions from ovarian origin, benign or malignant, and other lesions from extraovarian origin, such as benign uterine leiomyoma or cancers from other origin.<sup>15</sup> In our study, according to ultrasound reports and stored digital images all tumors were considered to be as adnexal origin. However, we had 14 cases of pedunculated uterine myomas.

Pedunculated uterine leiomyomas can be easily recognized when both ovaries are identified independently from the tumor and the tumor is seen arising from the uterine wall.<sup>16,17</sup> This may be considered as a limitation in our study since many asymptomatic pedunculated leiomyomas seen in our institution during study period did not undergo surgery, thus our results may overestimate malignancy rate of entirely solid pelvic masses.

Another limitation of our study is that we did not assess interobserver agreement for some subjective ultrasound features such as tumor contour or the assessment of amount of blood flow.

Finally, we included cases of truly cystic lesions (endometriomas, teratomas, tubo-ovarian abscess). Certainly, these masses may exhibit ‘solid’ appearance but indeed they are not solid. We recognize that including these cases could bias our results.

Studies focusing on solid adnexal or pelvic masses are scanty. Some authors have reported that clinical assessment may be useful for the differential diagnosis.<sup>15</sup> However, many women present asymptomatic and the tumors are accidentally found out during routine examination. As a matter of fact, in our study patients’ complaints and pelvic exam findings were not independent predictors for malignancy.

Regarding the clinical implications of our findings we found that the presence of carcinomatosis on B-mode ultrasound was invariably associated with malignancy and no single benign tumor had this finding. This finding could be expected but our study confirms that in presence of carcinomatosis other features of the tumor are less relevant and the patient should be referred to a gynecologic oncologist. Furthermore, this finding should prompt a thorough transabdominal ultrasound in the presence of a solid tumor in transvaginal ultrasound. Some studies have shown that carcinomatosis can be assessed by ultrasound.<sup>18,19</sup>

In cases with no evidence of carcinomatosis, some sonographic tumor features are helpful to discriminate benign from malignant solid adnexal tumors. The presence of moderate or abundant blood flow within the tumor and/or irregular tumor contour as well as the absence of acoustic shadows are predictive for malignancy. As a matter of fact, acoustic shadowing has been reported as a common finding in some types of benign solid ovarian tumors.<sup>20,21</sup> Whereas irregular solid tumor has been associated to malignancy.<sup>22</sup>

Another interesting issue is the use of CA 125. Recent studies have shown that CA 125 does not add relevant information to ultrasound for discriminating between benign and malignant adnexal masses.<sup>23,24</sup> However, according to our data CA 125 could be helpful if a solid mass with no evidence of ascites or carcinomatosis is found out at ultrasound examination.

Regarding the generalizability of our findings, it is difficult to determine since this is a retrospective study and our data need to be confirmed in prospective studies.

## CONCLUSION

We have shown that malignancy can be predicted in entirely solid adnexal tumors analyzing other ultrasound features such as the presence of carcinomatosis, tumor contour, acoustic shadowing and amount of flow.

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