Comparison of Ultrasound and Tumor Marker CA125 in Diagnosis of Adnexal Mass Malignancies

Abstract

Background: CA125 is the most used tumor marker for ovarian cancer monitoring and diagnosis. This study aimed to evaluate the capacity to predict malignancy in women with adnexal tumors using CA125 measurement and ultrasound criteria before the pathological examination.

Materials and Methods: This observational diagnostic study was conducted on 300 patients with obvious diagnosis of adnexal mass consists of ovarian masses, fallopian tubes, and masses within the broad ligament referring to Alzahra and Beheshti Hospitals from 2018 to 2019. Ultrasound examinations were done before surgery and malignancy risk was investigated by the ADNEX criterion. Sensitivity, specificity, positive and negative likelihood ratio (likelihood ratio [LR]+ and LR−), and area under the curve (AUC) were calculated. Results: From 284 patients, 260 masses were categorized in benign, 18 were in borderline, and 18 masses were malignant. The mean age of patients with malignant tumors was significantly higher than the others (P = 0.01). Differences in the level of CA-125 were not statistically significant (P = 0.78). Furthermore, the proportion of ascites in the malignant group (16.3%) was significantly higher than the others (P = 0.003). The AUC in ADNEX model (cutoff ≥9%) for differentiation of benign and malignant tumors was 0.75 (95% confidence interval [CI]: 0.69–0.80) with a sensitivity of 0.63 (95% CI: 0.41–0.81) and a specificity of 0.80 (95% CI: 0.74–0.84). Receiver operating characteristic analysis for CA-125 revealed that this variable is not capable for discrimination between benign and malignant tumors as the AUCs of the aforementioned variable were 0.60, 0.60, and 0.52 for the whole patients, premenopause, and postmenopause categories. Conclusion: CA-125 marker, along with other ultrasound findings, can be more accurate in identifying the malignancy of the adnexa tumor.

Keywords: Ovarian Cancer, Malignancies, tumor marker CA125, ultrasound

Introduction

According to the current estimates, 1.4% of women born today, or 1 in 72 will be diagnosed with ovarian cancer at some point in their lifetime.[1] These cases arise from a much larger group of women presenting with adnexal abnormalities. The overall prevalence of adnexal abnormalities is estimated at 7%,[2,3] and it is expected that 5%–10% of American women will receive prophylactic surgery for suspected ovarian cancer at some point in their lives.[2] A pelvic examination is the primary clinical method by which adnexal masses are diagnosed, and it is estimated that for each case of ovarian cancer identified, 10,000 pelvic examinations will be performed.[3] A patient’s age and menopausal status are important factors to consider upon the identification of an adnexal abnormality because the associated risk of malignancy increases from 13% in premenopausal women to 45% in postmenopausal women.[4]

Although nearly all women diagnosed with ovarian carcinoma will initially present with an adnexal mass, only a small proportion of all masses detected will be malignant, and the expeditious triage of these patients is the most important component of their treatment regimen. Differentiation between benign tumors and malignant tumors is crucially important because it is helpful for the referral of patients and their treatment. Various studies have indicated that surgery of adnexal masses by gynecologists is effective in reducing complications of surgery and the need for re-operation and increasing duration of recurrence and survival period.[4] That is why the perfect staging and cytoreductive surgery are among the basic treatment principles in these patients. However, according to the figures reported in the USA, only half of adnexal masses are primarily...
under surgery by gynecologists.\textsuperscript{[5]} Thus, algorithms and triage protocols are needed for the assessment of adnexal masses. Although ovarian cancer is rare with a lifetime risk of 1.3% and an incidence of 6.6 per 100,000 women per year, it is the 7\textsuperscript{th} most common cancer and 6\textsuperscript{th} most common cause of cancer death for women globally. In Europe, there were 67,771 new cases of ovarian cancer and 44,576 deaths in women in the year 2018. The majority of cases are diagnosed at an advanced stage, after cancer has metastasized, leading to poor survival.\textsuperscript{[6]}

Given the difference in survival in initial and advanced stages, screening programs or finding adnexal masses at initial stages are the other ways for increasing survival. Familial history, symptoms, physical examination, imaging, especially transvaginal sonography (TVS), and tumor markers are among the methods used for assessment of adnexal masses.\textsuperscript{[7,8]} CA125 is the most used tumor marker that was introduced since 1981, which is used for ovarian cancer monitoring and diagnosis. It is a glycoprotein, which is generated by mesothelial cells that cover the peritoneal, pleural, and pericardial cavity. Thus, its usage has limited value in premenopausal women because of its low specificity and due to raising in some benign conditions such as menstruation, endometriosis, follicular cysts, cystic adenoma, tuberculosis, and pregnancy.\textsuperscript{[9]}

The risk malignancy index (RMI) is the other method for the assessment of adnexal masses, which was originally introduced in 1990 by Jacob. Malignance condition is predicted by consideration of the premenopausal situation, ultrasound properties, and pelvic mass graphics and CA125 level.\textsuperscript{[10]} The sensitivity and specificity of RMI vary between 71\% and 88.5\% in different studies. Since ultrasound is a subjective method depending on individual skill and different interpretations are different from ovarian morphologic characteristics, it causes a discrepancy in RMI responses from a center to the other one. Thus, other methods for assessment of adnexal masses have also been considered.

The standard method for determining malignancy and benignancy status of tumors is pathologic investigation after removal of the mass. Surgery is costly for the patients and health organizations. It also would bring about risks for the patient. Various studies have been conducted for determining diagnostic ways of this mass. However, rare studies have been done for determining their malignancy and benignancy. Therefore, the current study was designed to help specifying the predictive role of ultrasound and CA125 tumor marker in malignancy and benignancy of adnexal masses before the pathological examination.

Materials and Methods
This observational diagnostic study was conducted on all cases with obvious diagnosis of adnexal mass referring to Alzahra and Beheshti Hospitals. The total of patients was counted as 300 during 2018–2019 and the convenience sampling method was used.

Patients diagnosed with adnexal mass consisted of ovarian masses, fallopian tubes, and masses within the broad ligament by a gynecologist who referred to Alzahra Hospital in 2018 were included in the study, and the probability of physiological cysts in patients was rejected with TVS. In the case of pregnancy, unwillingness to perform TVS, intervals of more than 180 days between ultrasound examination and mass removal, bilateral adnexectomy, and lack of access to pathologic outcomes, patients were excluded from the study.

Patients’ demographic information including age and menopause situation was taken from the patients’ files and was recorded in a preconstructed checklist.

The most common symptoms reported by women with ovarian mass included abdominal or pelvic pain, enlargement of the abdomen, bloating, urinary urgency, frequent urination or urinary incontinence, eating disorders, and weight loss. Most patients have these symptoms for several months. Transvaginal ultrasound is a standard assessment for adnexal masses and it was done by an experienced radiologist in all the patients. Findings suggesting malignancy in an adnexal mass include the presence of solid components, presence of thick walls (larger than 2–3 mm), bilateralism, and presence of Doppler flow to the solid part of the mass and associated with ascites. All pregnant women referring with the adnexal mass undergo a urine test. If this test is positive, quantitative measurement of human placental gonadotropin levels and ultrasound scanning of the vagina will be necessary. If the beta-human chorionic gonadotropin level is above 2000 mIU/mL and there is no vaginal pregnancy in vaginal ultrasound, it can be suspected of ectopic pregnancy.

Ultrasound examinations were done before surgery and radiologist reported the results regarding malignancy and benignancy, and these reports were not seen until pathologic tests. Malignancy risk was investigated by the ADNEX criterion. In addition, an estimated percentage was reported for the probability of malignancy. Sensitivity, specificity, positive and negative likelihood ratio (LR + and LR −), and area under the curve (AUC) were calculated.

This model consists of nine variables; age (years), serum CA-125 level (U/ml), type of center (oncology center/other hospitals), maximum diameter of the lesion (in mm), proportion of solid tissue (%), number of papillary projections (0/1/2/3/>3), more than 10 cyst locules (yes/no), acoustic shadow (yes/no), and ascites (yes/no). The formula for the risk calculation can be found in the original article.\textsuperscript{[7]} For use in clinical practice, an application is available at http://www.iotagroup.org/adnexmodel. The outcome of this model is an absolute risk estimate (expressed as a
Behnamfar, et al.: Ultrasound and tumor marker CA125 in diagnosis of adnexal mass malignancies

The adnexal mass of all patients was examined by the pathologist. Surgery and biopsy samples were collected from metastasis. A pathologist, who was unaware of the ultrasound results, classified tumors in terms of malignancy and benignancy based on the WHO criteria. In case of diagnosis of malignant tumor, its stage was specified based on the classification declared by the International Federation of Gynecology and Obstetrics (2012). Results related to pathology reports were recorded in the checklist.

Finally, we used the RMI to differentiate the ovarian masses. This scoring system combines the ultrasound features of the mass (U), the menopausal status of the patient (M), and serum CA-125 (U/ml) into a risk score (U × M × serum CA-125). The ultrasound features are multilocularity, solid areas, bilaterality, ascites, and intra-abdominal metastases. Three principal variants of the RMI were applied that differ according to the points attributed to the different ultrasound variables and the menopausal status of the patient. A total score of ≥200 was used as a cutoff for malignancy.

Statistical methods

All the statistical analyses were performed in SPSS 18.0 (Chicago: SPSS Inc. IBM Corp.) and MedCalc 14.0 software (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). Descriptive statistics were reported as number (%) and mean ± standard deviation for qualitative and quantitative variables, respectively, and to compare groups, one-way analysis of variance or Fisher’s exact test and logistic regression model were used if appropriate. Moreover, to calculate sensitivity, specificity, positive predictive value and negative predictive value (NPV), and likelihood ratios (LRs + and LR−) for the optimum cutoff points of ≥9%, receiver operating characteristics curves (ROC curves) were performed, and AUC was estimated.

The outcome of this study was an absolute risk estimate (expressed as a percentage) for a tumor malignancy and a cutoff for the overall risk was considered to its prediction based on ROC analysis and P < 0.05 was considered as statistically significant.

Results

Out of 284 under study patients, 260 masses were categorized in benign, 18 were in borderline, and the other 18 masses were malignant. Our results showed that age was the only demographic variable that was significantly different among the three groups as the mean age of patients with malignant tumors was significantly higher than the others (P = 0.01). Moreover, assessing ultrasound features revealed that although the level of CA-125 among patients with malignant tumor was lower than the other patients, differences were not statistically significant [P = 0.78, Table 1]. Furthermore, the proportion of ascites in the malignant group (16.3%) was significantly higher than the others (P = 0.003).

The most common benign pathologies were functional cyst (38.5%) and endometriosis cyst (31.5%), followed by cystadenomas (20.8%), endometriomas, parasalpingeal (4.6), cystadenofibroma (3.1%), and fibroma (1.5%). On the other hand, the majority of malignancies consisted of epithelial ovarian carcinomas (45.8%) and a quarter of all malignant masses were borderline tumors. Furthermore, four patients were diagnosed with no epithelial, two with metastatic, and one with squamous cell carcinoma [Table 2].

The AUC in ADNEX model (cutoff ≥9%) for discrimination between benign and malignant tumors was 0.75 (95% confidence interval [CI]: 0.69–0.80) with a sensitivity of 0.63 (95% CI: 0.41–0.81) and a specificity of 0.80 (95% CI: 0.74–0.84) [Figure 1]. In addition, the AUCs of the ADNEX model for the premenopausal and postmenopausal subgroups were 0.77 and 0.61, respectively [Table 3].

The information of ROC analysis for RMI also is shown in Table 3. The AUC of RMI for the whole of the patients

![Figure 1: Area under the curve of four methods for the detection of malignant masses](image-url)
was 0.52 (95% CI: 0.46–0.58) with a sensitivity of 0.83 (95% CI: 0.63–0.95) and a specificity of 0.30 (95% CI: 0.24–0.36). Subgroup analysis showed that RMI for discriminating benign from malignant tumor has good sensitivity and poor specificity among premenopausal patients but poor sensitivity and good specificity among postmenopausal patients [Table 3].

ROC analysis for CA-125 revealed that this variable is not capable for discrimination between benign and malignant tumors as the AUCs of the aforementioned variable were 0.60, 0.60, and 0.52 for the whole patients, perimenopause, and postmenopause categories [Table 3].

Pairwise ROC curve comparisons in terms of AUC are shown in Table 4. Displayed results confirm that the proposed ADNEX model is the best among and it has higher accuracy compared to the maximal diameter of lesion, CA-125, and significantly higher accuracy than RMI \((P = 0.002)\). Furthermore, the AUC of CA-125 was significantly higher than RMI \([P = 0.005, \text{Table 4}]\).

**Discussion**

With the exception of highly invasive procedures such as biopsy and surgery, the evaluation of circulating biomarkers offers the most definitive means of distinguishing benign from malignant pelvic masses. Several recent studies have evaluated various panels of circulating biomarkers in ovarian cancer patients and benign cases.\(^1\) As reported in the literature, serum CA 125 acted as a dominant method of detecting the risk

---

**Table 1: Descriptive statistics and ultrasound features for patients by tumor type \((n=284)\)**

| Variables                        | Benign \((n=260), \text{n} (\%)\) | Borderline \((n=6), \text{n} (\%)\) | Malignant \((n=18), \text{n} (\%)\) | \(P\) |
|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------|
| Age                              | 34.8±11.78                        | 34.17±6.80                       | 43.61±16.60                      | 0.01  |
| BMI                              | 28.1±4.00                         | 28.18±6.28                       | 28.51±2.47                       | 0.92  |
| Number of gravid                 | 2.01±2.29                         | 1.33±1.21                       | 2.89±2.89                       | 0.22  |
| Number of live children          | 1.55±1.86                         | 0.83±0.98                       | 2.28±2.02                       | 0.17  |
| Number of dead children          | 0.03±0.61                         | 0.00±0.00                       | 0.39±1.20                       | 0.23  |
| Number of abortion               | 0.28±0.64                         | 0.50±0.55                       | 0.22±0.55                       | 0.65  |
| CA-125 (U/ml)                    | 42.64±106.83                      | 38.42±55.78                     | 25.07±40.82                     | 0.78  |
| Maximal diameter of lesion in mm | 77.97±48.73                       | 126.33±57.46                    | 92.56±40.53                     | 0.03  |
| Menopausal state                 |                                   |                                   |                                  |       |
| Premenopausal                    | 238 (91.5)                        | 6 (100)                          | 16 (88.9)                       | 0.80  |
| Postmenopausal                   | 22 (8.5)                          | 0                                | 2 (11.1)                        |       |
| Virgin                           |                                   |                                   |                                  | 0.65  |
| No                               | 212 (81.5)                        | 6 (100)                          | 16 (88.9)                       |       |
| Yes                              | 48 (18.5)                         | 0                                | 2 (11.1)                        |       |
| Type of delivery                 |                                   |                                   |                                  | 0.71  |
| Nothing                          | 91 (35.0)                         | 2 (33.3)                         | 4 (22.2)                        |       |
| NVD                              | 77 (29.6)                         | 2 (33.3)                         | 5 (27.8)                        |       |
| C/S                              | 74 (28.5)                         | 2 (33.3)                         | 6 (33.3)                        |       |
| NVD and C/S                      | 18 (6.9)                          | 0                                | 3 (16.7)                        |       |
| Septa                            |                                   |                                   |                                  | 0.34  |
| No                               | 182 (70.0)                        | 6 (100)                          | 13 (72.2)                       |       |
| Yes                              | 78 (30.0)                         | 0                                | 5 (27.8)                        |       |
| Type of -                         |                                   |                                   |                                  | 0.006 |
| Solid                            | 25 (9.6)                          | 1 (16.7)                         | 4 (22.2)                        |       |
| Cystic                           | 206 (79.2)                        | 2 (33.3)                         | 10 (55.6)                       |       |
| Solid+cystic                     | 29 (11.2)                         | 3 (50.0)                         | 4 (22.2)                        |       |
| Irregular cyst wall              | 30 (11.5)                         | 1 (16.7)                         | 0 pre                           | 0.28  |
| Presence of blood flow in the papillary projections | 2 (0.8) | 0 | 1 (5.6) | 0.23 |
| Solid tissue                     |                                   |                                   |                                  | 0.06  |
| No                               | 253 (97.3)                        | 5 (83.3)                         | 17 (94.4)                       |       |
| Papillary                        | 6 (2.3)                           | 0                                | 1 (5.6)                         |       |
| Laterality                       | 1 (0.4)                           | 1 (16.7)                         | 0                               |       |
| Unilateral                       | 249 (95.8)                        | 6 (100)                          | 18 (100)                        | 0.99  |
| Bilateral                        | 11 (4.2)                          | 0                                | 0                               |       |
| Ascites                          | 2 (0.8)                           | 0                                | 3 (16.7)                        | 0.003 |

NVD: Normal vaginal delivery, C/S: Cesarean section
of malignancy in patients with pelvic masses.\[2\] Our study confirmed that the concentration of serum CA125 generally shows a higher level in ovarian cancer. However, only relying on the CA125 did not show a very accurate diagnosis and predictive value, so we combined a new diagnostic method with CA125.

This study aimed to determine the role of ultrasound and CA125 tumor marker in malignancy and benignancy of adnexal masses before the pathological examination.

In the present study, 284 women with the mean age of 35.38 ± 12.89 were diagnosed with adnexal mass. In more than 50% of these patients, the body mass index was more than 25 kg/m\(^2\). There were 260 women in the premenopausal period and 24 of them in postmenopausal.

### Table 2: Pathology results of under study patients (\(n=284\))

| Result       | Pathology result | \(n\) (\%) |
|--------------|------------------|------------|
| Benign (\(n=260\)) |                  |            |
| Cystadenoma  | 54 (20.8)        |            |
| Endometriosis cyst | 82 (31.5)   |            |
| Functional cyst | 100 (38.5)  |            |
| Parasalpingeal cyst | 12 (4.6)  |            |
| Cystadenofibroma | 8 (3.1)    |            |
| Fibroma      | 4 (1.5)          |            |
| Endometriosis cyst | 82 (31.5)   |            |
| Functional cyst | 100 (38.5)  |            |
| Parasalpingeal cyst | 12 (4.6)  |            |
| Cystadenofibroma | 8 (3.1)    |            |
| Fibroma      | 4 (1.5)          |            |
| Malignant (\(n=24\)) |              |            |
| Borderline   | 6 (25.0)         |            |
| Epithelial   | 11 (45.8)        |            |
| No epithelial | 4 (16.7)    |            |
| Metastatic   | 2 (8.3)          |            |
| SCC          | 1 (4.2)          |            |

SCC: Squamous cell carcinoma

### Table 3: Diagnostic performance indices and 95% confidence intervals

| Variable       | All patients | Premenopausal | Postmenopausal |
|----------------|--------------|---------------|----------------|
| **ADNEX**      |              |               |                |
| Sensitivity    | 62.5 (40.6-81.2) | 59.1 (36.4-79.3) | 50.0 (1.3-98.7) |
| Specificity    | 79.6 (74.2-84.3) | 85.3 (80.1-89.5) | 100 (84.6-100) |
| PPV            | 22.0 (12.9-33.7) | 27.1 (15.3-41.9) | 100 (2.5-100)  |
| NPV            | 95.8 (92.2-98.1) | 95.8 (92.1-98.0) | 95.7 (78.1-99.9) |
| LR+            | 3.07          | 4.02          | NA             |
| LR–            | 0.47          | 0.48          | 0.50           |
| AUC            | 74.6 (69.1-79.6) | 76.6 (71.0-81.6) | 61.4 (39.5-80.3) |
| \(P\)          | <0.001        | <0.001        | 0.602          |
| **RMI**        |              |               |                |
| Sensitivity    | 83.3 (62.6-95.3) | 86.4 (65.1-97.1) | 50.0 (1.3-98.7) |
| Specificity    | 29.6 (24.1-35.6) | 27.3 (21.8-33.4) | 90.9 (70.8-98.9) |
| PPV            | 9.8 (6.1-14.8)  | 9.9 (6.1-15.0)  | 33.3 (14.0-90.5) |
| NPV            | 95.1 (87.8-98.6) | 95.6 (87.7-99.1) | 95.2 (76.2-99.9) |
| LR+            | 1.18          | 1.19          | 5.50           |
| LR–            | 0.56          | 0.50          | 0.55           |
| AUC            | 51.7 (45.7-57.6) | 51.4 (45.1-57.6) | 56.8 (35.2-76.7) |
| \(P\)          | 0.785         | 0.831         | 0.754          |
| **Maximal diameter of lesion** | | | |
| Sensitivity    | 66.7 (44.7-84.4) | 86.4 (65.1-97.1) | 100 (15.8-100) |
| Specificity    | 61.1 (54.9-67.1) | 45.0 (38.5-51.5) | 40.9 (20.7-63.6) |
| PPV            | 13.7 (8.0-21.2)  | 12.7 (7.8-19.1)  | 13.3 (1.7-40.4) |
| NPV            | 95.2 (90.8-97.9) | 97.3 (92.3-99.4) | 100 (66.4-100) |
| LR+            | 1.72          | 1.57          | 1.69           |
| LR–            | 0.55          | 0.30          | 0.00           |
| AUC            | 67.4 (61.7-72.9) | 69.5 (63.5-75.0) | 60.2 (38.4-79.4) |
| \(P\)          | 0.005         | 0.003         | 0.638          |

| **CA-125** |              |               |                |
| Sensitivity | 41.7 (22.1-63.4) | 40.9 (20.7-63.6) | 50.0 (1.3-98.7) |
| Specificity | 80.8 (75.4-85.4) | 81.1 (75.5-85.9) | 95.5 (77.2-99.9) |
| PPV         | 16.7 (8.3-28.6)  | 16.7 (7.9-29.3)  | 50.3 (1.3-98.7) |
| NPV         | 93.8 (89.7-96.5) | 93.7 (89.4-96.6) | 95.4 (77.2-99.9) |
| LR+         | 2.17          | 16.7 (7.9-29.3)  | 11.00           |
| LR–         | 0.72          | 93.7 (89.4-96.6) | 0.52           |
| AUC         | 59.8 (53.9-65.6) | 60.4 (54.1-66.4) | 52.3 (31.1-72.8) |
| \(P\)      | 0.111         | 0.108         | 0.917          |

PPV: Positive predictive value, NPV: Negative predictive value, RMI: Risk of malignancy index, AUC: Area under the curve, LR+: Positive likelihood, LR–: Negative likelihood
According to pathologic findings, 260 women were diagnosed with benign tumors and 24 cases with malignant tumors. Based on ultrasonographic findings, the ADNEX model and maximal diameter of lesion had an acceptable diagnostic value compared to pathological results in identifying malignancy of the tumor (AUC > 65, P < 0.01) as the sensitivity and specificity of the ADNEX model were respectively 62.5% and 79.6% and it was 66.7% and 61.1% for maximal diameter of lesions. It should be noted that with the differentiation of women in the two categories of premenopausal and postmenopausal, these results remained valid in premenopausal women, but in postmenopausal women, these two criteria did not have acceptable diagnostic value; it can be due to have only 24 postmenopausal women in our study that this number was not statistically reliable for determining the diagnostic value of a reliable one. On the other hand, RMI and CA‑125 markers did not have a good diagnostic value in identifying malignant tumors of adnexa (P > 0.05). The RMI diagnostic criteria had a high sensitivity of 83.3% and a low specificity of 29.6%, whereas in the CA‑125 marker, it was found that the test had a very low sensitivity (41.7%) but had a high specificity (80.8%). In fact, it may be said that this marker, although high specificity, cannot be trusted due to its high NPV.

Few published studies have focused on CA‑125 serum levels in women with benign adnexal tumors. However, it has been reported that the level of serum CA‑125 is often elevated in women with endometriosis or endometriomas. For example, Jacobs and Menon found that CA‑125 serum levels exceeded 35 U/mL in approximately 10% of women with benign tumors and in a higher percentage of women with serous benign tumors than among those with cystic teratomas. Our results agree with those of others in that CA‑125 serum levels were elevated more often among premenopausal women with benign tumors than among postmenopausal women with benign tumors and thus were more useful in distinguishing between benign and malignant tumors in postmenopausal patients. These different results between pre- and postmenopausal patients could be explained by the different mixtures of tumor types in pre- and postmenopausal patients which are associated with increased levels of serum CA‑125 in the cases of endometriosis.

van Calster et al. in analysis of premenopausal patients found that CA‑125 alone provided the highest sensitivity and specificity, 70.7% and 87.5%, respectively, of any individual biomarker tested. This runs counter to most current notions concerning a lack of specificity for CA‑125 in premenopausal women. All of the women in this set were initially evaluated for an adnexal mass and CA‑125 results would be expected to receive priority consideration in patients in this age group, for which malignancy is more uncommon. In order to investigate the predictive role of ultrasound in malignancy of ovarian tumors, this study also indicated that the ADNEX model can be a good predictor between malignancy and benignancy of tumor, and further investigations are needed for examining other differences.

The study by Meys et al. (2016) was carried out for investigating the ultrasound role in predicting malignancy and benignity of adnexal masses. It lasted 4 years (2011–2015) and 326 women were examined and their tumor malignancy condition was investigated by a pathologist. Before surgery, malignancy of adnexal masses was predicted by the ADNEX model, simple ultrasound, logistic regression model 2 (LR2), and RMI. AUC in the ADNEX model was 0.93. AUC was 0.85 in other methods such as LR2, and it was 0.82 in RMI. The simple ultrasound method had the lowest sensitivity and specificity (0.89 and 0.9, respectively). Based on this study, the ADNEX model is the best predictor of malignancy and benignity of the adnexal mass.

In the study by Madadi Ghaan et al. entitled “compatibility of pathologic and ultrasound findings,” 100 patients with ovarian mass were studied in Oil Company Hospital. Findings were as follows: generally, the age range of patients was between 12 and 78 years. Ultrasound findings in benign tumors contained 80% benign and 14% malignant, 4% normal, and 2% suspected. As a result, the sensitivity of abdominal ultrasound in benign masses is 80%, its specificity is 92%, and its precision is 0.85. Ultrasound findings in malignant masses included 73% benign, 63.4% malignant, 2.4% normal, and 26.8% suspected. Therefore, abdominal ultrasound in malignant masses has a sensitivity of 63% and specificity of 80% with a precision of 0.7. As a result, abdominal ultrasound enjoys adequate specificity and sensitivity for the diagnosis of benign and malignant masses and can be used as the first diagnostic step, and even the only step. The age over 60 is a risk factor alone. If imaging results and CA125 levels are taken into account in examinations, the number of laparotomies can be reduced. Ultrasound alone can determine if more mass follow-up is required by magnetic resonance imaging or laparotomy. In addition, abdominal ultrasound has higher sensitivity, and if

| Variables                  | RMI          | Maximal diameter of lesion | CA‑125       |
|----------------------------|--------------|----------------------------|--------------|
| ADNEX                      | 22.9 (P=0.002) | 7.2 (P=0.37)              | 14.8 (P=0.06) |
| RMI                        | 15.8 (P=0.06) | 8.2 (P=0.005)             | 7.6 (P=0.41)  |
| Maximal diameter of lesion |              |                            |              |
| CA‑125                     |              |                            |              |

RMI: Risk of malignancy index
it is accompanied by computed tomography scan, vaginal ultrasound, and CA125 level measurement, its sensitivity and specificity are increased.\[14\]

In a cross-sectional descriptive study by Farzaneh et al. entitled “Malignance risk index in diagnosis before surgery of ovarian masses” in Taleghani Hospital, the following findings were obtained: in this study, 36 women were candidate for exploratory laparotomy; the average age of whom was 41. It was 38 years for women with benign mass and 46 years for women with malignant mass, and their difference did not show significance. According to histopathology results, 38.8% of patients had ovarian malignancy, and 61.2% had ovarian benignancy. Decreased appetite, weight loss, vomiting, and abdominal pain were significantly higher in women with ovarian cancer. The RMI above 95 had a sensitivity of 79% and specificity of 77%, which was the best result. When the US alone is used, it has a sensitivity of 64% and specificity of 77%. The ROC AUC for CA125 was also 0.73, which is below the ROC curve for the RMI, i.e. 0.78.\[15\] The standard method for the diagnosis of ovarian mass is exploratory laparotomy.\[16\] However, if malignant and benign ovarian masses can be somehow diagnosed before surgery, the best treatment can be considered for the patient. The most common method is using a mathematical formula, in which three factors of menopausal status, CA125 serum level, and ultrasound findings are used. According to the studies, CA125 is closely related to the type and stage of tumor. In addition, findings such as shape and size of tumor, simplicity or complexity, segmental involvement, ecchymosis, presence of papillary parts, multiple loci, and cyst wall structure in imaging are also helpful in malignancy diagnosis.\[17\][18\]

In this study, the CA125 cutoff was lowered because of the small sample size. Considering the age difference in the prevalence of ovarian mass in Iranian women, the difference in etiology, RMI, and CA125 factors can be found about them.

Finally, comparing the diagnostic value of the studied criteria showed that the ADNEX model had a better diagnostic value compared to the RMI (\(P < 0.05\)), and there was no significant difference between the two models of maximal diameter of lesion and CA-125 marker (\(P > 0.05\)). In addition, the RMI had a lower diagnostic power compared with the CA-125 marker (\(P < 0.05\)).

**Conclusion**

Therefore, it can be said that although the CA-125 marker cannot be used as an acceptable criterion for detecting malignancy in the adnexal tumor, it is not significantly different from the overall ADNEX model, and other diagnostic criteria have a more under curve area than the others, so, it can still emphasize that the use of the CA-125 marker, along with other ultrasound findings, can be more accurate in identifying the malignancy of the adnexa tumor.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Sagi-Dain L, Lavie O, Auslander R, Sagi S. CEA in evaluation of adnexal mass: Retrospective cohort analysis and review of the literature. Int J Biol Markers 2015;30:e394-400.
2. Ries LA, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al. SEER cancer statistics review, 1975–2005. Bethesda, MD: National Cancer Institute; 2008. p. 2999.
3. Bozkurt M, Yumru AE, Aral I. Evaluation of the importance of the serum levels of CA-125, CA15-3, CA-19-9, carcinoembryonic antigen and alpha fetoprotein for distinguishing benign and malignant adnexal masses and contribution of different test combinations to diagnostic accuracy. Eur J Gynaecol Oncol 2013;34:540-4.
4. Zheng H, Tie Y, Wang X, Yang Y, Wei X, Zhao X. Assessment of the diagnostic value of using serum CA125 and GI-RADS system in the evaluation of adnexal masses. Medicine (Baltimore) 2019;98:e14577.
5. Sagi-Dain L, Lavie O, Auslander R, Sagi S. Clinical Use and Optimal Cutoff Value of Ca15-3 in Evaluation of Adnexal Mass: Retrospective Cohort Study and Review of the Literature. Am J Clin Oncol 2018;41:838-44.
6. Aust S, Seebacher-Shariat V. Screening for ovarian cancer: Is there still hope?. Memo Mag Eur Med Oncol 2020;13:189-92.
7. Meys EM, Kajser J, Kruitwagen RF, Slagen BF, van Calster B, Aertgeerts B, et al. Subjective assessment versus ultrasound models to diagnose ovarian cancer: A systematic review and meta-analysis. Eur J Cancer 2016;58:17-29.
8. Dong X, Men X, Zhang W, Lei P. Advances in tumor markers of ovarian cancer for early diagnosis. Indian J Cancer 2014;51 Suppl 3:e72-6.
9. Nossov V, Amneus M, Su F, Lang J, Janco JM, Reddy ST, et al. The early detection of ovarian cancer: From traditional methods to proteomics. Can we really do better than serum CA-125? Am J Obstet Gynecol 2008;199:215-23.
10. Yoshida A, Derchain SF, Pitta DR, Crozatti N, Andrade LA, da Silva RF, et al. Preoperative measurement of serum C-reactive protein: Is it useful in the differential diagnosis of adnexal masses? Int J Biol Markers 2017;32:e83-9.
11. Jacobs IJ, Menon U. Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics 2004;3:355-66.
12. van Calster B, van Hoore K, Valentin L, Testa AC, Fischerova D, van Holsbeke C, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: Prospective multicentre diagnostic study. BJM 2014;349:g5920.
13. Meys EM, Jeehoff LS, Achten NM, Slangen BF, Lambrechts S, Kruitwagen RF, et al. Estimating risk of malignancy in adnexal masses: External validation of the ADNEX model and comparison with other frequently used ultrasound methods. Ultrasound Obstet Gynecol 2017;49:784-92.
14. Madadi Ghahan R, Agharafajollahi S, Zareyi S. Refractory evaluation of sonografic and pathologic findings in 100 patients with ovarian mass in Naft hospital. EBNESINA 2007;10:16-20.
15. Farzaneh F, Saburi M, Rahimi F. Risk of malignancy index
in preoperative diagnosis of ovarian tumors in Iranian women referred to Taleghani Hospital. Iran J Gynecol Obstet 2010;5:50-5.
16. Varras M. Benefits and limitations of ultrasonographic evaluation of uterine adnexal lesions in early detection of ovarian cancer. Clin Exp Obstet Gynecol 2004;31:85-98.
17. Rauh-Hain JA, Krivak TC, Del Carmen MG, Olawaiye AB. Ovarian cancer screening and early detection in the general population. Rev Obstet Gynecol 2011;4:15-21.
18. Timmerman D, van Calster B, Testa A, Savelli L, Fischerova D, Froymen W, et al. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. Am J Obstet Gynecol 2016;214:424-37.