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# Contribution of Other Parameters to Malignancy Risk Index for Differentiation of Benign or Malignity in Adnexal Masses

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**Abstract:** Ovarian cancer is one of the most important causes of pelvic masses and is the fifth leading cause of cancer related mortality. As in all cancers, method of early diagnosis for ovarian cancer should be easily applicable, economically, has high safety and specificity. Our study included 155 cases that were operated due to adnexial masses at Obstetrics and Gynaecology Clinic of Trakya University. Inclusion criteria for the study were decision of surgery due to an adnexal mass and presence of preoperative evaluation for parameters examined in this study such as age, serum CA125 value, Ultrasound score, menopausal score and thrombocyte count. Risk of Malignancy Index was calculated. Localization and amount of vascular flows in adnexial masses were evaluated using Color Doppler USG. Ages of the cases ranged between 17-75 years. Histopathologically 122 benign, 6 borderline, 27 malignant masses were detected. As surgical approach to malignant tumours is similar to borderline tumours, they were assessed within malignant tumour group. Malignancy was suspected in 27 of 155 cases which were evaluated with RMI. Malignancy was suspected in 33 patients evaluated with CDUS and malignancy was suspected in 26 cases evaluated with thrombocyte count. Evaluation of RMI according to histopathological results revealed that there was no difference between the two assessment methods. Specificity of the RMI evaluation was 98.4% and its sensitivity was 75.8%. Thrombocyte count demonstrated malignancy in 16.8% of the cases. Evaluation of CDUS findings revealed that 122 cases diagnosed as malignant in pathology were also diagnosed as malignant in CDUS and the other cases were detected to be benign with Doppler. CA125 values were below 35 U/mL in 86.8% of the cases with benign adnexal masses and above 35 U/mL in 72.7% of the malignant cases. Better preoperative benign-malignant differentiation will enable performance of optimal surgery in experienced centres. RMI which can be used for early detection and differentiation of malignancy has opened the way for objective evaluation of adnexal masses.With use of parameters such as CDUS, thrombocyte count, and age together with RMI benign-malignant differentiation of adnexal masses can be made more effectively.

**Keywords:** Ovarian cancer, pelvic masses, adnexial masses.

## INTRODUCTION

Ovarian cancer which forms the most important part of adnexal masses is responsible from 4% of all malignancies in females and 20-25% of all gynaecologic malignancies. Every year, 204.000 females are diagnosed and 125.000 are dead in the World [1]. 1.4% of babies born each day will be diagnosed as ovarian cancer in later years of their lifetime [2]. Ovarian cancer is one of the most important causes of pelvic masses, it is the second most common gynaecologic malignancy, and is the fifth leading cause of cancer related mortality. It causes more mortality than other gynaecologic malignancies [3]. Early stage ovarian cancer is generally asymptomatic and treatment at a later stage is a cause of poor prognosis [4]. After diagnosis, less than 35% of ovarian cancers have a survival of more than 5 years. It is the 5th common cancer that affects women in the World [5]. Although it is the second common gynaecological malignancy, diagnosis is usually made late because it does not have early and specific warning signs. About 60-65% of the cases are diagnosed at an advanced stage and 5 years survival is 80% in the early phase and below 5% in the advanced phase. High

mortality rate is due to prolonged asymptomatic period and spread of disease to peritoneal surfaces and abdominal tissues when diagnosed [6,7]. If diagnosed at an early period survival of cases with malign masses may be prolonged, life quality may be increased, and treatment costs will be decreased [8]. Jacobs *et al*. [9] defined Risk of Malignancy Index to be used in malign-benign differentiation of adnexal masses which consists of CA125, menopausal status, and USG findings. Taking cut-off value as 200 for RMI, malign-benign differentiation can be made for adnexal masses with 85.4% sensitivity and 96.9% specificity. When malignant potential of adnexal masses is considered, directing the patient to experienced gynaecologic oncology centres is important to minimize residual tumour tissue and to perform complete staging surgery. Residual tumour tissue is one of the most important prognostic factors in survival and the most important target in treatment [10,11]. Because the cases are generally asymptomatic, more than 70% of the cases are diagnosed at an advanced stage. Only 25% of the cases are diagnosed at an early stage. Chance of 5 years survival is 90% at early stage and less than 30% at advanced stage. Therefore, early diagnosis has a great role to affect the outcomes. As in all cancers, method of early diagnosis and screening for ovarian cancer should be easily applicable, economically advantageous, safe, have high safety, reliability, specificity and acceptable positive and negative predictive values [12].

**Colour Doppler Ultrasound**

Evaluation of ovaries with colour Doppler ultrasound (CDUS) helps in early diagnosis of ovarian cancer. Ovarian malignancies are generally vascular. Neovascularization develops from present vessels. Neovascularization is required for malignant tumours. Newly formed vessels are at the centre of the mass and have abnormal features. There are diffuse arteriovenous shunts at the periphery. Neovascularization in malignant tumours is concentrated in solid component, papillary projection and septal structures. There is a muscular layer in normal arterioles but no tunica media is found in new arterioles formed due to tumour. Low vasomotor tonus due to lack of muscular layer and presence of arteriovenous anastomoses results in high end-diastolic values for blood flow and continuation of flow throughout diastole. The most important change detected by CDUS is the presence of low resistance flow towards the malignant tumour. Flow in the arterioles towards the tumour is high and there are regions of stenosis in defective neovascular structures in most of the malignancies. Systolic velocities are frequently high due to high pressures caused by the flow in the arterioles (> 20-25 cm/sec). In malignant ovarian masses pulsatility index (PI) and resistance index (RI) are low because end-systolic flow is low and end-diastolic flow is high in neovascular arterial structures [13]. Previous studies have shown that malignancy potential of the tumour was high if RI was below 0.4 and PI was below 1 [14]. Sensitivity of malignant-benign differentiation in ovarian tumours with CDUS was found to be 80-90% [15]. But neovascularization occurs in corpus luteum, acute inflammatory masses, uterine leiomyomas, and intestinal masses and low-resistance flow due to vasodilatation is observed in metabolically active tumours. There are studies which demonstrated utility of CDUS for benign-malignant differentiation of adnexal masses [16]. It gives an idea to differentiate adnexal masses by assessing blood flow and resistance parameters and when used in screening programs it is helpful to decrease false positivity and to proceed with surgery only in appropriate cases [13]. When blood flow is observed at multiple areas with a randomized vascular distribution mean flow should not be calculated and flow with the lowest resistance should be recorded. Because there is no abnormal vascular structure in benign adnexal tumours, medium-high resistance flow is detected.

**Risk of Malignancy Index**

Surgical staging and cytoreductive surgery are important in management of ovarian cancers. However, wide surgical staging methods should be performed in experienced gynaecological oncology centres. In cases with advanced stage the purpose is to reduce tumour load as much as possible. Residual tumour volume after surgery is an important prognostic factor for survival and quality of life. Using only morphological scoring systems is not adequate to differentiate between benign and malignant adnexal tumours when they have similar features [17,18]. In case the diagnosis could not be made precisely, explorative laparotomy and laparoscopy are tried for definite diagnosis. Advanced stage ovarian cancer patients are exposed to inadequate surgery due to the inability to perform complete staging surgery [19]. The evaluation should have objective criteria and should be feasible in clinical practice [10,11]. Because adnexal masses have a high prevalence in females it is not feasible to assess benign-malignant differentiation only in specialized gynaecological oncology centres. RMI was developed by Jacobs et al [9] to be used for malignant-benign differentiation of adnexal masses. For this evaluation menopausal status, USG score, and serum cancer antigen 125 (CA125) are used. When these parameters are evaluated independently, likelihood to differentiate benign-malignant is statistically significant. Similar significant relation could not be detected for age. When compared with each of these individual parameters RMI has higher sensitivity and specificity values [9]. CA 125, which is a high molecular weight, antigenic marker with a glycoprotein structure is elevated in ovarian malignancies but can't be used for the diagnosis of malignancy alone because it is also increased in 1% of ovarian malignancies. It may also increase in breast, intestinal, pulmonary, and pancreas cancers. Increased

levels may also be detected in endometrioma, myoma uteri, and pelvic inflammatory disease [20]. It is increased in 90% of cases with malign nonmucinous tumours. Rate of CA125 increase is 85% in serous ovarian malignancies and 70% in mucinous ovarian cancers [6]. It is found to be high in 50% of early stage serous ovarian cancers. Shalev *et al*. [22], preferred operative laparoscopy for 55 cases who had normal CA 125 values and did not have complex CA125 values and histopathology results for all of them were benign. At the same period, surgical preference for 75 cases that had complex cysts was laparotomy and malignancy was detected in 23 of them. In a postmenopausal case with adnexal mass if CA125 is higher than 35 U/mL it is 80% malignant and if CA 125 level is below 35 U/mL it is 85% benign. If evaluated together with USG, sensitivity and specificity of CA125 increases [23]. Jacobs et al recommended a cut-off point of 200 for RMI at which a benign-malignant differentiation can be made with 90% accuracy. With a 200 cut-off point preoperative benign-malignant differentiation could be made with 85.4% sensitivity and 96.9% specificity. The authors emphasized feasibility of RMI. They stated that performing optimal surgery in specialized oncology centres for cases referred due to predicted malignancy depending on objective criteria affects prognosis positively [9]. RMI was modified twice by Tingulstad *et al*. in 1996 [18], and in 1999. They tried to obtain better outcomes by scoring ultrasound findings as 0, 1, or 4 in 1996 and later as 1 and 3 instead of 0-1 in 1999 and scoring menopause as 1 and 4. A cut off point of 200 yielded 71% sensitivity and 92% specificity. Manjunath *et al.* [3], demonstrated that these changes did not yield statistically better outcomes than Jacobs et al study. RMI is recommended for preoperative evaluation especially at postmenopausal period. With RMI cases are classified into low, medium and high-risk groups which help to plan the most appropriate surgery for the cases or to refer cases with high malignancy to specialized centres [24].

**Thrombocytosis**

Thrombocyte count shows some characteristic features in cases with ovarian cancer because malignant ovarian cells produce cytokines which increase thrombocyte production. Thrombocytosis (thrombocyte count >400X$10^3$ u/L) is seen in 20-25% of the cases. But because it is also an acute phase reactant, increases may also be observed in situations such as trauma, vasculitis, infection, and surgical interventions [25]. Some studies have demonstrated that thrombocytosis may differentiate cases with malignant adnexal masses from benign ones and the results were detected to be significant. Levin et al [26] accepted thrombocytosis as >400.000u/L. They detected thrombocytosis in 28% of patients with malignant adnexal masses. Kerpsack and Finan [27] accepted cut-off values as >350.000u/L in their study which included 323 cases. Thrombocytosis was detected in 48.3% of the cases with a malignant mass and in 13.8% of the cases with a benign mass.

In our study RMI was evaluated prospectively in cases that were diagnosed with adnexal masses and operated. Contribution of CDUS, age, and thrombocyte parameters to RMI was evaluated for benign-malignant differentiation of adnexal masses taking post-operative histopathological findings into account. Role of CDUS, thrombocyte count, and age in addition to RMI for preoperative evaluation and management of adnexal masses were evaluated.

**METHODS**

Our study included 155 cases that were operated due to adnexal masses at Obstetrics and Gynaecology Clinic of Trakya University Medical School between 27-01-2012 and 27-02-2013. Ethics committee approval for this study was obtained from Trakya University scientific research ethics committee. Inclusion criteria for the study were decision of surgery due to an adnexal mass and presence of preoperative evaluation for parameters examined in this study such as age, serum CA125 value, USG findings, menopausal status, and thrombocyte count. All of the cases were evaluated with CDUS. Parameters that were preoperatively evaluated such as age, parity, history, pelvic and physical examination findings; family history, laboratory findings, thrombocyte count, menopausal status, USG findings, CDUS findings, and serum CA125 were recorded. Cut-off value for malignant-benign differentiation for CA-125 was determined to be 35 U/mL. For each patient correlation of these six parameters with histopathological results were evaluated. For ultrasonographic evaluation scoring system created by Jacobs et al was used: presence of multilocular cysts, bilaterality, solid areas in the cyst, presence of metastasis, and ascites in abdomen were evaluated and each was scored as 1 point. Ultasound score (U) was 0 if none of these findings were present; 1 if only one of them was present; and 3 if 2 or more of them were present (Table 1). Risk of Malignancy Index (RMI) was calculated using following formula RMI = (U) x (M) x (serum CA-125) [9]. To determine menopausal score (M), 1 point was given if the case was premenopausal and 3 points were given if the case was postmenopausal. At least 1 year of amenorrhea was the criterion for cases with natural menopause and being at or over 50 years of age was the criterion for pre-hysterectomized cases. CA125 was directly added to the formula.

Localization and amount of vascular flows in adnexal masses were evaluated using CDUS. Flow signals at the wall of the mass or at the periphery of the solid mass were classified as “peripheral” and flow signals at septum of the mass, papillary structure, solid parts, and centre of the solid mass were classified as “central”. When vascularity was detected with CDUS, pulse Doppler was used to obtain flow waveform.

When 3 or more consecutive similar velocity waveforms occurred resistance index (RI= systolic peak flow-end-diastolic flow/systolic peak flow) and pulsatility index (PI=systolic peak flow-end-diastolic flow/mean velocity) were calculated automatically by the USG device. When more than one vascular structures are observed PI and RI values were recorded. PI value <1 and RI value <0.4 were accepted as malignant and they were compared with histopathological results. Surgery findings of all cases and histopathological results were reviewed. Histopathological diagnosis was accepted as the golden standard for evaluation of the results. Adnexal masses were classified according to World Health Organization (WHO) criteria [28] and malignant tumours were staged according to International Federation of Gynaecology and Obstetrics (FIGO) descriptions [29]. For evaluation of thrombocyte count it had to be studied at least one and at most 30 days before the surgery and no findings of active infection such as leucocytosis and fever or stress factors such as trauma, or accidents be present. For evaluation of thrombocyte count >350.000u/L cut-off point was accepted as a malignancy criterion.

For statistical analysis Statistica 7.0 (License no: 31N6YUCV38) package program was used. To evaluate study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), qualitative findings belonging to the cases were compared. Student's t test was used for comparison of normally distributed data between groups and Mann-Whitney U test was used for comparison of non-normally distributed data between groups. McNemar chi-square test was used to compare qualitative data. For evaluation of results $P<0.05$ was accepted as significant. To differentiate between benign-malignant lesions RMI, thrombocyte count, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NGV) were calculated taking results of histopathological evaluation into account. To calculate sensitivity, percentage of cases with positive test results among malignant cases was determined; to calculate specificity, percentage of cases with negative test results among benign cases was determined; to calculate PPV, percentage of malignant cases that were detected to be malignant according to the test was determined; and to calculate NPV percentage of benign cases detected to be benign according to the test was determined. The results were evaluated with a 95% confidence interval and $p<0.05$ significance value.

## RESULTS

Ages of the cases ranged between 17-75 years and mean age was 46.94 ± 14.5 years. Histopathologically 122 (78.7%) benign, 6 (3.8%) borderline and 27 (17.4%) malignant masses were detected. As surgical approach to malignant tumours is similar to borderline tumours, they were assessed within malignant tumour group. Malignancy was suspected in 27 of 155 cases (17.4%) which were evaluated with RMI. Malignancy was suspected in 33 patients (21.3%) evaluated with CDUS and malignancy was suspected in 26 (16.8%) cases evaluated with thrombocyte count. Evaluation of menopausal status revealed that 92 (59.4%) cases were premenopausal and 63 (40.6%) were postmenopausal.

### Distribution of histopathological results

Evaluation of histopathological results in our study revealed that endometrioma (n=25) was the most common benign adnexal mass (43.8%) and the luteinized cyst (n=16) was the second most common (28.07%). Follicular cyst (n=7) (12.8%), haemorrhagic cyst (n=6) (10.52%), granulomatous oophoritis (n=2) (3.50%), and chronic salpengo-oophoritis (n=1) (1.75%) followed them. Mature cystic teratoma was found in 9 (5.8%) cases with neoplastic tumours.

Serous cystadenoma (n=20) was the most common among epithelial tumours (44.4%), serous adenofibroma-cystadenofibroma (n=15) was the second most common (33.3%), and mucinous cystadenoma (n=7) was the third (16.6%). Mucinous cystadenofibroma (n=2) (4.44%) and mixed type cystadenoma (n=1) (2.22%) followed them. Among sex cord stroma derived tumours that produce adnexal masses, a fibroma was seen in 7 (4.5%) cases, and a fibrotecoma was seen in 4 (2.5%) cases.

Borderline tumours form 18.1% of all malignant tumours. Among 6 borderline cases 3 (9.5%) had borderline mucinous tumours and 1 (3.01%) had borderline serous papillary tumour. Two cases (6.03%) had borderline serous fibroadenomas.

The most common group in malignant masses was malignant serous ovarian tumours. Serous carcinoma was the most common in 12 (36.3%) cases. Mucinous carcinoma was seen in 3 (9.09%) cases, endometrioid carcinoma was seen in 3 (9.09%) cases, mixed tumour was seen in 2 (6.06%) cases, clear cell carcinomas was seen in 1 (3.03%) case and squamous cell carcinoma was seen in 2 (6.06%) cases. Evaluation of the pathology results of cases with squamous cell carcinoma infiltration revealed that they were developed at immature cystic teratoma background. Malignant germ cell and sex cord stroma derived tumors were not detected at histopathological results of the cases.

Ninety-two (59.3%) cases were premenopausal and 63 (40.6%) cases were postmenopausal. Benign masses were detected in 80 (86.9%) and malignant masses were detected in 12 (13.04%) premenopausal cases. Rate of benign masses was higher in premenopausal cases ($p<0.05$) (Table 2). Among postmenopausal cases 42 (66.6%) were benign and 49 (33.3%) were malignant. Malignant mass

percentage was significantly higher in postmenopausal cases ($p<0.05$).

Evaluation of RMI according to histopathological results revealed that there was no difference between the two assessment methods (McNemar test, $p<0.05$). Kappa for concordance between the two methods was 79.4%. Specificity of the RMI evaluation was 98.4% and its sensitivity was 75.8%. PPV was found to be 92.6% and NPV was 93.8% (Table 3).

Evaluation of thrombocyte values according to histopathological results revealed no difference between the two assessment methods ($p<0,05$). Malignancy was seen in 21.3% in pathology and thrombocyte count demonstrated malignancy in 16.8% of the cases. Kappa concordance ratio between the two methods was 77%. Thrombocyte count suggested malignancy in 24 (15.5%) of 33 (21.3%) cases which were found to be malignant in pathology; other cases were found to be benign and so specificity of the test was 98.4% and sensitivity was 72.7%. PPV was found to be 92.26 % and NPV was 93.02% (Table 4).

Evaluation of CDUS according to pathology results showed no difference between the two evaluation methods ($p>0,05$). Pathology of the cases showed malignancy in 78.7% of the cases and CDUS showed malignancy in 78.7% of the cases. Kappa concordance rate between the two methods was 46.1%. Evaluation of CDUS findings revealed that 122 (78.7%) cases diagnosed as malignant in pathology were also diagnosed as malignant in CDUS and the other cases were detected to be benign with Doppler; so, sensitivity of the test was 100% and specificity was 100% (Table 5).

Evaluation of all cases demonstrated that CA125 value was at least 1.89 and at most 10.000. CA125 level was high in malignant cases. Mean value of CA 125 in malignant cases was 2764.15 and in benign cases were 169.2. CA125 serum values were below 35 U/mL in 86.8% of the cases with benign adnexal masses and above 35 U/mL in 72.7% of the malignant cases. Evaluation of thrombocyte counts in malignant and benign cases revealed that the mean value for malignant cases was 400.72 x $10^3$u/L and for benign cases was 258.6 x $10^3$u/L. Ultrasound scores (U) of the cases evaluated with USG were recorded. When rated with the ultrasound score (U) all adnexal masses suspected to be simple and benign (U=0) were benign pathologically (n=98). Number of masses that were evaluated to be semicomplex (U = 1) was 21 and results were benign in all of them. Among masses with malignant and complicated ultrasonographic findings (U=3) 27 were malignant and 6 were borderline.

**Table-1: Ultrasonographic findings that are used to calculate ultrasonography score (12)**

| Ultrasonography finding | Point |
|---|---|
| Presence of multilocular cysts | 1 |
| Presence of solid area in the cyst | 1 |
| Presence of metastasis | 1 |
| Presence of ascites in the abdomen | 1 |
| Presence of bilateral lesions | 1 |

**Table-2: Presence of menopausal status according to histopathology results**

| | | | | Menopause |
|---|---|---|---|---|
| | | Premenopausal | | Postmenopausal |
| Pathology | Benign | 80 | (% 86.9) | 42 (% 66.6) |
| | Malignant | 12 | (% 13.04) | 21 (% 33.3) |

**Table-3: Evaluation of risk of malignancy index results according to histopathology**

| | | | | Pathology | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Malignant | | Benign | | Total | | |
| | | n | % | N | % | n | % | p>0.05** |
| RMI | Malignant finding | 25 | 16.1 | 2 | 1.3 | 27 | 17.4 | |
| | Benign finding | 8 | 5,2 | 120 | 77.4 | 128 | 82.6 | |
| | Total | 33 | 21.3 | 122 | 78.7 | 155 | 100 | |

Mc Nemar test was used (Significance limit $p>0.05$).

**Table-4: Evaluation of thrombocyte count according to pathology results**

| | | | | Pathology | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Malignant | | Benign | | Total | | |
| | | N | % | N | % | n | % | |
| | | | | | | | | p>0.05** |
| Thrombocyte | Malignant finding | 24 | 15.5 | 2 | 1.3 | 26 | 16.8 | |
| | Benign finding | 9 | 5.8 | 120 | 77.4 | 129 | 83.2 | |
| | Total | 33 | 21.3 | 122 | 78.7 | 155 | 100 | |

** Mc Nemar test was used (Significance limit p>0,05)

**Table-5: Evaluation of Colour Doppler ultrasound according to pathology results**

| | | | | Pathology | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Malignant | | Benign | | Total | | |
| | | N | % | N | % | n | % | |
| | | | | | | | | p>0.05** |
| Doppler | Malignant finding | 122 | 78,7 | 0 | 0 | 122 | 78,7 | |
| | Benign finding | 0 | 0 | 33 | 21,3 | 33 | 21,3 | |
| | Total | 122 | 78,7 | 33 | 21,3 | 155 | 100 | |

Mc Nemar test was used (Significance limit p>0,05)

## DISCUSSION

Because ovarian masses are very common among adnexal masses and have malignancy risk differentiation between benign-malignant masses and better evaluation of cases for which surgery will be planned is very important. Ovarian masses are the most important causes of referrals to specialized gynaecology centres. The leading cause for referral is possibility of malignancy of the mass and need for an experienced oncologic surgery centre. 24% of premenopausal and 39-63% of postmenopausal ovarian masses are malignant. Ovarian cancer has the leading mortality rate among all gynaecologic cancers. Annual frequency of ovarian cancer increases with age. It is seen in 20 per 100.000 persons between 30-50 years of age and in 40 per 100.000 persons between 50-75 years of age [24]. Optimal and experienced surgery is important for survival and life quality and benign-malignant differentiation should be made before surgery. Epithelial ovarian cancer peaks at 60-70 years of age and is rare under 40 years of age [30]. USG evaluation of adnexal masses may determine characteristic features of the mass with a high probability (sensitivity 62-100%). However, specificity of USG varies between 73-95% and it does not suffice alone for benign-malignant differentiation [24]. Morphological scoring systems have been developed to increase diagnostic capacity of USG and to make benign-malignant differentiation with objective criteria. Although scoring systems have increased specificity of evaluation with USG they did not decrease false positivity [9]. Sassone *et al*. [31], created a scoring system that would help benign-malignant differentiation of adnexal masses with USG. Size of the mass, septum content, wall thickness, inner wall structures, ascites and presence of intraabdominal metastasis are evaluated with the scoring system. Its sensitivity was detected to be 100%, specificity was 83%, PPV was 37%, and NPV was 100%. With only morphological scoring systems differentiation between malignant and benign tumours is not always possible.

In our study pathology results for all of the adnexal masses thought to be benign with USG evaluation (U=0) were found to be benign (n=98). Number of semicomplex (U=1) masses was 21 and pathology results of all of them were benign. Among masses that have malignant or complicated findings (U=3) 27 were malignant and 6 were borderline.

Evaluation of menopausal status demonstrated that 92 (59.3%) cases were premenopausal and 63 (40.6%) were postmenopausal. Adnexal masses were benign in 80 (86.9%) cases and malignant in 12 (13.04%) cases. Percentage of benign masses was higher for premenopausal cases. Among postmenopausal cases 42 (66.6%) were benign and 49 (33.3%) were malignant. Percentage of malignant masses was higher for postmenopausal cases.

CA125 is the best tumour marker which has shown clinical utility and benefit to evaluate cases with ovarian cancer and to follow-up response after treatments such as surgery and chemotherapy. Bast *et al.* [32] detected CA 125 in serum and demonstrated elevation (>35U/mL) of this tumour marker in 82% of the cases with epithelial ovarian cancer. Einhorn *et al*. [33], screened for CA 125 in 5550 women appearing healthy and detected specificity as 98.5% (>35 U/ml). But they couldn't demonstrate adequate sensitivity and specificity for CA 125 to be used as a screening method for the population. O"Connel *et al.* [34] took cut-off value for CA125 as 35 U/mL. To diagnose ovarian cancer its sensitivity was 100%, specificity was 43%, PPV was 60%, and NPV was 75%. A study by Milojkovic *et al*. [35] retrospectively evaluated serum CA 125 levels in cases that had 121 malignant and 91 benign adnexal masses. In this study when cut-

off value for CA 125 was taken as 35 U/mL for cases with malignant masses sensitivity was 80.2%, specificity was 76.1%, PPV was 81.5%, and NPV was 74.5%; when cut-off value was determined as 65 U/mL sensitivity was 72.7%, specificity was 90.2%, PPV was 90.7%, and NPV was 71.6%. The authors concluded that postoperative serum CA 125 measurement was helpful for benign-malignant differentiation of adnexal masses. In our study CA125 value was below 35U/mL in 16 (86.8%) cases with benign adnexal masses and above 35 U/mL in 24 (72.7%) of malignant cases.

We took cut-off value for RMI as 200 which have shown to be the best effectiveness in many studies. Andersen *et al.* [36] took RMI cut off value as 200 for 402 adnexal masses and found sensitivity as 70.6%, specificity as 89.3%, PPV as 66.1%, and NPV as 91.1%. Obeidat *et al*. [37] took RMI value as 200 in their study that investigated 100 adnexal masses. Sensitivity was detected to be 90%, specificity was 89%, PPD was 96%, and NPD was 78%. Tingulstad *et al*. [18] evaluated 365 cases and found sensitivity as 71% and specificity as 92%.

In our study malignancy was suspected in 27 of 155 cases (17.4%) evaluated with RMI. There is a statistically significant concordance between histopathology results and RMI results ($p>0.05$). Specificity of this evaluation was 98.4%, and sensitivity was 75.8%. PPV was 92.6%, and NPV was 93.8%. These results were consistent the other studies in the literature [18,36].

CDUS, which is noninvasive and detects angiogenesis and decreased vascular resistance in malignant tumours, has been used to evaluate adnexal masses. Evaluation of ovarian masses with CDUS gave important information about benign-malignant differentiation but its routine use in all centres was difficult [24]. Many authors suggested that CDUS may be used for differentiation of benign-malignant tumours [38,39]. Alcazar *et al*. [39] evaluated a total of 143 cases with primary ovarian cancer and metastatic ovarian cancer and found that blood flow to the mass was high and blood flow was especially to the centre of the mass. Kurjak *et al*. [40] evaluated 698 cases with adnexal masses 642 of which were benign and 56 were malignant according to CDUS. They determined in this study that 0.4 was an important cut-off value for RI in cases detected to have neovascularization and values below 0.4 were significant markers for malignancy. In this study sensitivity was 96.4%, specificity was 98.8%, PPV was 98.2%, and NPV was 99.7%. Thomas *et al.* [4] studied 1601 cases with adnexal masses and reported that PI<1 suggested malignancy. Weiner *et al.* [41], evaluated 53 cases with adnexal masses and found that 35 of 36 cases with a PI >1,0 was benign and 16 of 17 cases with a PI<1 was malignant. In this study sensitivity of PI to differentiate malignant ovarian tumours was 94% and specificity was 97%.

In our study PI value <1 and RI value <0.4 were accepted as malignancy criteria for adnexal masses. Evaluation of adnexal masses with CDUS suggested malignancy in 33 (21.3%) cases. Results of 6 masses suspected to be malignant came to be borderline. This demonstrated utility of evaluation with CDUS for benign-malignant differentiation [32].

Kerpsack and Finan [27], evaluated 323 cases and accepted cut-off value for thrombocyte count as 350.000. They found that thrombocyte count was above 350.000 in 42 of 87 (48.3%) cases reported to be malignant after histopathology results. Thrombocyte count was above 350.000 only in 31 of 225 (13.8%) benign masses. Thrombocytosis could not be detected in 11 borderline tumours. Levin and Conley [26], found thrombocytosis in 31 of 82 cases with malignant adnexal masses.

In our study increase in thrombocyte count suggested malignancy in 24 (15.5%) cases among 33 (21.3%) cases diagnosed as malignant; as other cases were evaluated to be benign, specificity of the test was 98.4%, and sensitivity was 72.7%. PPV was 92,26% and NPV was 93,02%. Pathology demonstrated malignancy in 21.3% of the cases although thrombocyte values suggested malignancy in 16.8% of these cases.

Better preoperative benign-malignant differentiation will enable performance of optimal surgery in experienced centres which is the most important prognostic factor for survival in ovarian cancer. Addition of age, thrombocyte count, and CDUS to RMI for adnexal masses makes differentiation of benign-malignant more effective. In malignant cases, it directs surgical approach and in benign cases it helps to avoid unnecessary surgical intervention.

## CONCLUSION

For adnexal masses evaluation only with USG may not be sufficient. RMI which can be used for early detection and differentiation of malignancy has opened the way for objective evaluation of adnexal masses. With use of parameters such as CDUS, thrombocyte count, and age together with RMI benign-malignant differentiation of adnexal masses can be made more effectively.

## REFERENCES

1. Aynacı, G. (2013). Adneksiyal kitlelerin benign malign ayrımında malignansi riski endeksine diğer parametrelerin katkısı.
2. Nolen, B., Velikokhatnaya, L., Marrangoni, A., De Geest, K., Lomakin, A., Bast, R. C., & Lokshin, A. (2010). Serum biomarker panels for the discrimination of benign from malignant cases in patients with an adnexal mass. *Gynecologic oncology*, *117*(3), 440-445.

3. Manjunath, A. P., Sujatha, K., & Vani, R. (2001). Comparison of three risk of malignancy indices in evaluation of pelvic masses. *Gynecologic oncology*, *81*(2), 225-229.
4. Bourne, T. H., Campbell, S., Reynolds, K. M., Whitehead, M. I., Hampson, J., Royston, P., ... & Collins, W. P. (1993). Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *Bmj*, *306*(6884), 1025-1029.
5. Anderson, J. R., & Genadry, R. (2008). Benign diseases of female reproductive tract. *Berek And Novak's Gynecology*, *14*, 100.
6. Boring, C. C., Squires, T. S., & Tong, T. (1991). Cancer statistics, 1991. *CA: A Cancer Journal for Clinicians*, *41*(1), 19-36.
7. Goldstein, S. R. (1996). Postmenopausal adnexal cysts: how clinical management has evolved. *American Journal of Obstetrics & Gynecology*, *175*(6), 1498-1501.
8. Westhoff, C., & Randall, M. C. (1991). Ovarian cancer screening: potential effect on mortality. *American journal of obstetrics and gynecology*, *165*(3), 502-505.
9. Jacobs, I., Oram, D., Fairbanks, J., Turner, J., Frost, C., & Grudzinskas, J. G. (1990). A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *BJOG: An International Journal of Obstetrics & Gynaecology*, *97*(10), 922-929.
10. Le, T., Krepart, G. V., Lotocki, R. J., & Heywood, M. S. (1997). Does debulking surgery improve survival in biologically aggressive ovarian carcinoma?. *Gynecologic oncology*, *67*(2), 208-214.
11. Van Der Burg, M. E., Van Lent, M., Buyse, M., Kobierska, A., Colombo, N., Favalli, G., ... & Pecorelli, S. (1995). The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *New England Journal of Medicine*, *332*(10), 629-634.
12. Dilks, P., Narayanan, P., Reznek, R., Sahdev, A., & Rockall, A. (2010). Can quantitative dynamic contrast-enhanced MRI independently characterize an ovarian mass?. *European radiology*, *20*(9), 2176-2183.
13. Fleischer, A. C., Romero, R., & Manning, F. A. (1991). *The Principles and practice of ultrasonography in obstetrics and gynecology*. Appleton & Lange.
14. Fleischer, A. C., Cullinan, J. A., & Keple, D. M. (1998). Color Doppler Sonography of Pelvic Masses In: Fleischer AC.
15. Mansour, G. M., El-Lamie, I. K., El-Sayed, H. M., Ibrahim, A. M., Laban, M., Abou-Louz, S. K., ... & Gad-allah, M. (2009). Adnexal mass vascularity assessed by 3-dimensional power Doppler: does it add to the risk of malignancy index in prediction of ovarian malignancy?: four hundred-case study. *International Journal of Gynecological Cancer*, *19*(5), 867-872.
16. Bourne, T., Campbell, S., Steer, C., Whitehead, M. I., & Collins, W. P. (1989). Transvaginal colour flow imaging: a possible new screening technique for ovarian cancer. *BMj*, *299*(6712), 1367-1370.
17. Yurkovetsky, Z., Skates, S., Lomakin, A., Nolen, B., Pulsipher, T., Modugno, F., ... & Menon, U. (2010). Development of a multimarker assay for early detection of ovarian cancer. *Journal of Clinical Oncology*, *28*(13), 2159.
18. Tingulstad, S., Hagen, B., Skjeldestad, F. E., Halvorsen, T., Nustad, K., & Onsrud, M. (1999). The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. *Obstetrics & Gynecology*, *93*(3), 448-452.
19. Van Gorp, T., Cadron, I., & Vergote, I. (2011). The utility of proteomics in gynecologic cancers. *Current Opinion in Obstetrics and Gynecology*, *23*(1), 3-7.
20. Baker, T. R., & Piver, M. S. (1994, July). Etiology, biology, and epidemiology of ovarian cancer. In *Seminars in surgical oncology* (Vol. 10, No. 4, pp. 242-248). John Wiley & Sons, Inc..
21. Einhorn, N., Bast, J. R., Knapp, R. C., Tjernberg, B., & Zurawski, J. V. (1986). Preoperative evaluation of serum CA 125 levels in patients with primary epithelial ovarian cancer. *Obstetrics and gynecology*, *67*(3), 414-416.
22. Shalev, E., Eliyahu, S., Peleg, D., & Tsabari, A. (1994). Laparoscopic management of adnexal cystic masses in postmenopausal women. *Obstetrics and gynecology*, *83*(4), 594-596.
23. Zurawski, V. R., Sjovall, K., Schoenfeld, D. A., Broderick, S. F., Hall, P., Bast, R. C., ... & Knapp, R. C. (1990). Prospective evaluation of serum CA 125 levels in a normal population, phase I: the specificities of single and serial determinations in testing for ovarian cancer. *Gynecologic oncology*, *36*(3), 299-305.
24. Morgante, G., Marca, A., Ditto, A., & Leo, V. (1999). Comparison of two malignancy risk indices based on serum CA125, ultrasound score and menopausal status in the diagnosis of ovarian masses. *BJOG: An International Journal of Obstetrics & Gynaecology*, *106*(6), 524-527.
25. Aynacı, G. (2013). Adneksiyal kitlelerin benign malign ayrımında malignansi riski endeksine diğer parametrelerin katkısı.
26. LEVIN, J., & CONLEY, C. L. (1964). Thrombocytosis associated with malignant disease. *Archives of internal medicine*, *114*(4), 497-500.
27. Kerpsack, J. T., & Finan, M. A. (2000). Thrombocytosis as a predictor of malignancy in women with a pelvic mass. *The Journal of reproductive medicine*, *45*(11), 929-932.

28. Serov, S. F., Scully, R. E., & Sobin, L. H. (1973). International histological classification of tumors. No. 9. *Histological typing of ovarian tumours. WHO, Geneva*, 1-56.
29. Norris, H. J., & Jensen, R. D. (1972). Relative frequency of ovarian neoplasms in children and adolescents. *Cancer*, *30*(3), 713-719.
30. Piver, M. S., Baker, T. R., Piedmonte, M., & Sandecki, A. M. (1991, June). Epidemiology and etiology of ovarian cancer. In *Seminars in oncology* (Vol. 18, No. 3, pp. 177-185).
31. Sassone, A. M., Timor-Tritsch, I. E., Artner, A., Westhoff, C., & Warren, W. B. (1991). Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstetrics and gynecology*, *78*(1), 70-76.
32. Bast Jr, R. C., Klug, T. L., John, E. S., Jenison, E., Niloff, J. M., Lazarus, H., ... & Zurawski Jr, V. R. (1983). A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *New England journal of medicine*, *309*(15), 883-887.
33. Einhorn, N., SjÖvall, K., Knapp, R. C., Hall, P., Scully, R. E., Bast, J. R., & Zurawski, J. V. (1992). Prospective evaluation of serum CA 125 levels for early detection of ovarian cancer. *Obstetrics and gynecology*, *80*(1), 14-18.
34. O'connell, G. J., Ryan, E., Murphy, K. J., & Prefontaine, M. (1987). Predictive value of CA 125 for ovarian carcinoma in patients presenting with pelvic masses. *Obstetrics and gynecology*, *70*(6), 930-932.
35. Milojkovic, M., Hrgovic, Z., Hrgovic, I., Jonat, W., Maass, N., & Buković, D. (2004). Significance of CA 125 serum level in discrimination between benign and malignant masses in the pelvis. *Archives of gynecology and obstetrics*, *269*(3), 176-180.
36. Obeidat, B. R., Amarin, Z. O., Latimer, J. A., & Crawford, R. A. (2004). Risk of malignancy index in the preoperative evaluation of pelvic masses. *International Journal of Gynecology & Obstetrics*, *85*(3), 255-258.
37. Obeidat, B. R., Amarin, Z. O., Latimer, J. A., & Crawford, R. A. (2004). Risk of malignancy index in the preoperative evaluation of pelvic masses. *International Journal of Gynecology & Obstetrics*, *85*(3), 255-258.
38. Fleischer, A. C., Rogers, W. H., Rao, B. K., Kepple, D. M., & Jones, H. W. (1991). Transvaginal color Doppler sonography of ovarian masses with pathological correlation. *Ultrasound in Obstetrics & Gynecology*, *1*(4), 275-278.
39. Alcázar, J. L., Galán, M. J., Ceamanos, C., & García-Manero, M. (2003). Transvaginal gray scale and color Doppler sonography in primary ovarian cancer and metastatic tumors to the ovary. *Journal of ultrasound in medicine*, *22*(3), 243-247.
40. Kurjak, A., Zalud, I., & Alfirevic, Z. (1991). Evaluation of adnexal masses with transvaginal color ultrasound. *Journal of ultrasound in medicine*, *10*(6), 295-297.
41. Weiner, Z., Thaler, I., Beck, D., Rottem, S. H. R. A. G. A., Deutsch, M. I. C. H. A. E. L., & Brandes, J. M. (1992). Differentiating malignant from benign ovarian tumors with transvaginal color flow imaging. *Obstetrics and gynecology*, *79*(2), 159-162.