Transvagınal Ultrasound And Computed Tomography Combıned Wıth Ca-125 Determınatıons In Preoperatıve Evaluatıon Of Ovarıan Masses In Premenopausal Women

Fatma Ferda VERİT, Mustafa PEHLİVAN
Department of Obstetrics and Gynaecology, Harran University Faculty of Medicine, Sanliurfa, Turkey.

Premenopozal Kadinlardaki Ovaryen Kitlelerin Preoperatif Tanisinda Transvaginal Ultrason Ve Komputerize Tomografinin Ca-125 İle Birlikte Değerlendirilmesi

Özet:
Amaç: Çalışmanın amaçları premenopozal kadınlardaki ovaryen kitlelerin preoperatif teşhisinde i) transvaginal ultrason (TVUS) ve kompüterize tomografi (CT) ve ii) bu görüntüleme yöntemleri ile kombine olarak CA-125 değerlerinin doğruluğunu karşılaştırmaktı.
Gereç-yöntem: Adneksiyal kitleden şüphe edilen 91 premenopozal kadın çalışma kapsamına alındı. Hastaların TVUS, CT ölçümleri ile CA-125 değerleri saptandı. Daha sonra değerler histopatolojik sonuçlarla kıyaslandı. Test sonuçlarındaki genel kanı ve kesin sonuçlar kappa istatistiği ile hesaplandı.
Bulgular: Histoloji sonuçlarına göre ovaryen tümorlerin 12si malign ve 79si benign idi. Aşağıdaki sonuçlar TVUS, CT ve TVUS ve CT nin CA-125 ile kombinasyonu olarak hesaplandı; sensitivite sırasıyla, 83%, 91%, 100%; spesifisite, 92%, 96%, 97% idi. Aynı zamanda, TVUS ve CT nin CA-125 ile kombinasyonu tek başına TVUS ve CT e göre daha yüksek doğruluk oranına sahipti (sırasıyla 0.90, 0.76 ve 0.89).
Sonuç: TVUS ovaryen lezyonların teşhisinde kost –effektif olmasına rağmen, sonografide kanser şüphelenilen vakalarda CT ve CA-125 ölçümleri yayılımı göstermede ve preoperatif evrelemede yararlıdır.

Summary
Background: The aims of the study were compare the accuracy of i)transvaginal ultrasound (TVUS) and computed tomography (CT) and ii)combined these imaging modalities together with CA-125 determinations in preoperative evaluation of ovarian masses in premenopausal women.
Methods: Included in this study were 91 premenopausal women with suspicious adnexal mass. Patients underwent TVUS, CT and CA-125 determinations. The findings were then compared with histopathological diagnosis. The overall agreement between the test results and the actual outcome was calculated by means of kappa statistic.
Results: Histology revealed 12 malignant and 79 benign ovarian tumors. The following data were calculated for TVUS, CT and TVUS and CT combined with CA-125 determinations, sensitivities, 83%, 91%, 100%; specificities, 92%, 96%, 97% respectively. TVUS and CT combined with CA-125 also had higher accuracy rate when compared with TVUS and CT alone (0.90, 0.76 and 0.89 respectively).
Conclusion: Although TVUS is a cost-effective method in the diagnosis of ovarian lesions, CT and CA-125 determinations should be useful when ovarian carcinoma is suspected on sonography, to investigate the extent of neoplastic disease and preoperative staging.

Key words: Transvaginal ultrasound, computed tomography, CA-125, ovarian masses, diagnosis

Introduction

Ovarian cancer has the highest mortality of all gynaecologic malignancies (1,2). The most prognostic factor in ovarian cancer is the stage of disease at the time of diagnosis (3). Clinical symptoms at early stages are rare, they may remain asymptomatic for extended periods, and diagnosis is often made at advanced tumor stages. This fact underscores the importance of early detection of these tumors and of the correct determination of epithelial ovarian tumors of low malignant potential (3, 4).
Diagnostic studies that allow accurate confirmation of benignity might reduce unnecessary surgery and accurate cancer staging should help determine surgical and chemotherapeutical planning. Some assays such as CA-125 tumor associated antigen, have been applied clinically as markers of disease status and may be helpful in the diagnosis of recurrent ovarian cancer
(5). However, as a screening tool its sensitivity and specificity is low (6, 7). CA-125 is elevated in less than half of the patients with early stage disease, while patients with benign adnexal masses such as endometriomas and inflammatory processes often show increased levels of CA-125 (8, 9).

Transvaginal ultrasound (TVUS) has been shown to be highly accurate in the detection of asymptomatic ovarian masses, however, is a clear differentiation among functional cysts, benign neoplasms, borderline malignancies, and malignant ovarian tumors is often not possible (10). Computed tomography (CT) is another imaging modality that can usually differentiate simple cysts from more complex lesions. Its use in assessing malignancy of adnexal masses is also limited because of its relatively poor soft tissue contrast (11).

To date, the method of choice for assessing the malignancy of asymptomatic is laparoscopy or laparatomy with histopathologic evaluation (12). The disadvantages of this procedure are that if the adnexal tumor is of only functional origin, surgery is unnecessary, but if the adnexal tumor is malignant and is resected with an ovary-conserving procedure, there is the risk of rupturing the tumor capsule and spreading tumor cells into the peritoneal cavity (3,11). Therefore, a noninvasive diagnostic procedure that helps to assess the malignancy of asymptomatic adnexal masses would be clinically useful in deciding the indication for laparoscopy.

The aims of the study were to investigate i)the accuracy of TVUS and CT and compared with histopathological diagnosis ii) the accuracy of these imaging modalities combined with CA-125 levels in preoperative evaluation of ovarian masses in women of reproductive age.

Materials and methods

The candidates were 91 premenopausal women with asymptomatic sonographically suspect adnexal mass aged between 18-55 years (mean age, 33.53 ± 10.93yr). Excluded from the study were those women in whom examinations unequivocally confirmed the malignant or benign nature of the process and those women in whom findings were bilateral. Also excluded were pregnant women, patients younger than 18 years and those who were previously treated with carcinoma.

TVUS Scanning

TVUS (Tosbee, Toshiba Inc., Tokyo, Japan) was performed by using 5.0 MHz vaginal transducer. The differentiation of benign from malignant masses was made according to the sonomorphologic index proposed by Sassone which included the evaluation of the inner wall structure, the wall thickness, the septa and the echogenicity and demonstrated a sensitivity of 100% and a specificity of 83% (13). Adnexal mass with a score of ≥9 was considered to be suspicious for malignancy (13).

CT Scanning

CT scans were performed with 10-mm coronal sections taken with a Toshiba X-Vision spiral CT device (Toshiba Inc., Tokyo, Japan).

Blood sample collection

Blood samples were collected at 9:00 and 11:00 a.m. after an overnight fast. The samples were centrifuged within 2 h after withdrawal.

Measurement of CA-125 levels

Analysis of CA-125 was performed with electrochemiluminescence immunoassay (ECLIA Elecsys 170, Roche, Germany).

At surgery, all ovaries were carefully observed and all ovarian masses were enucleated from the ovary or removed together with the ovary. The TVUS and CT images were then compared with the final histopathological diagnosis. Biochemial parameters such as CA-125 plasma levels were used to increase the accuracy of imaging techniques. A cut off level greater than or equal to 35 U/mL was used to discriminate malign from benign masses (14-16).

The sensitivity, specificity and positive and negative predictive values of CT, TVUS and all methods combined with CA-125 were calculated for ovarian carcinoma. To evaluate the overall agreement between a test result and actual outcome, the kappa index was calculated according to Fleiss (13).

Results

The average diameter of the study population was 7.43 ± 4.25cm ranged from 3cm to 30cm. The histopathologic analyses were summarized in Table 1. Of the 91 patients examined 79 patients (86.8%) had benign and 12 of them (13.2%) had malignant masses. In the malignancy group, 6 (50%) patients presented with serous cystadenocarcinomas, 3 (25%) mucinous cystadenocarcinomas, and with other malignancies (25%) (1 clear cell carcinoma, 1 sertoli leydig cell tumor, 1 granulosa cell tumor and 1 uterine sarcoma).

Table 1. Histopathologic diagnoses in 91 patients with suspected ovarian masses

Histopathologic diagnosis	n
Benign (n= 79)	
Serous cyst	19
Corpus luteum cyst	2
Dermoid cyst	13
Endometrioma	9
Paratubal cyst	3
Ovarian torsion	1
Ectopic pregnancy	3
Tuberculosis	2
Myoma uteri	8
Serous cystadenoma	14
Mucinous cystadenoma	4
Malignant (n= 12)	
Serous cystadenocarcinoma	6
Mucinous cystadenocarcinoma	3
Clear cell carcinoma	1
Sertoli Leydig cell tumor	1
Granulosa cell tumor	1
Uterine sarcoma	1

The sensitivity, specificity, positive and negative predictive values of TVUS, CT and combined with CA-125 were reported in Table 2. TVUS had a poorer sensitivity and specificity of 83% and 92% respectively, than CT (91% and 96%) (Table 2). The positive predictive value CT was 78% and negative predictive value 98% vs. 62% and 97% for TVUS. The kappa index of TVUS, CT and combined with CA-125 were also demonstrated in Table 2. The kappa value of TVUS, CT and CA-125>35U/mL was greater than kappa value of TVUS or CT alone (Table 2).

Table 2. Accuracy (% values in parentheses) of different techniques and methods in the differential diagnosis of malignant from benign ovarian tumors in premenopausal population

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Kappa value
TVUS	10/12 (83)	73/79 (92)	10/16 (62)	73/75(97)	0.76
CT	11/12 (91)	76/79 (96)	11/14 (78)	76/ 77(98)	0.89
TVUS, CT and CA-125>35U/mL	12/12(100)	77/79 (97)	12/14 (85)	77/77(100)	0.90

TVUS: Transvaginal ultrasound CT: Computed tomography

Discussion

Low survival rates in women with malignant processes of the ovary underscore the need for early detection and correct diagnosis of adnexal tumors. The objective of our study was the separate evaluation of imaging modalities and the potential for improved diagnostic accuracy in combination. Our patients, with 12 malignant and 79 benign tumors with various histologic diagnoses, should be considered representative of the group of women with suspicious, though usually clinically unremarkable, adnexal findings.

In patients with ovarian cancer the removal of the mass with radical margins at the time of the primary operation is critical for the

improvement of the patient survival. Patients with a residual tumor less than 2cm in diameter have a significantly better prognosis than those undergoing nonradical excision (17). Staging of ovarian cancer has also been an eminent challenge in cross-sectional imaging. The most frequent course of imaging investigation is initial diagnostic ultrasound followed by CT in complicated cases (17).

TVUS is a routinely performed modality that can usually differentiate between solid and cystic lesions. It is simple available and low cost technique. Its efficacy in revealing malignant versus benign ovarian processes, however, remains controversial, with sensitivities of 82–100% and specificities of 83–95% being reported in the literature (13, 18, 19). These figures correspond to the findings in our study which yielded a sensitivity of 83% and a specificity of 92%. Moreover, it has been known that ultrasonography is not able to identify abnormalities in the omentum, pelvic side walls, colon, paracolic gutters, iliac and paraaortic lymph nodes in cancer staging.

In order to improve the specificity of ultrasonography scoring systems were developed (13). By assigning numerical values to the presence of particular finding of high sensitivity only 83% accuracy was obtained and its sensitivity ranged from 56% to 95% (7, 13, 20-23). We used the Sassone's morphologic scoring system in the study.

For many years, CT has been widely used in the diagnosis of ovarian carcinoma (24). CT can also be used to investigate the presence of liver metastases, lymph node involvement, ascites and gross peritoneal spread with theoretical advantage in comparison with ultrasonography (17). Comparing CT and ultrasonography in the detection of ovarian malignancies in a patient population mix of pre and postmenopausal women it has been demonstrated that the sensitivity was significantly higher using CT (89% vs. 60%), whereas there was no difference in specificity (99% vs. 92%) (25). CT had a sensitivity of 91% and a specificity of 96% in detecting ovarian carcinoma our study. It was found to be slightly more sensitive in establishing the benign or malignant nature of a mass than TVUS. Our study also showed that CT possesses a high negative predictive value. Negative CT images, thus rule out carcinomas with a high level of certainty.

In addition, the present study also suggests that the combination of CA-125 levels, TVUS and CT had higher accuracy in differentiating malignant from benign ovarian masses than TVUS or CT alone with a sensitivity of 100% and a specificity of 97%. However, the studies about combination of these imaging modalities and CA-125 in the differential diagnosis of ovarian masses are limited. Guerriero et al. investigated that the combination of these assays had a closer accuracy and a higher kappa value in the diagnosis of ovarian malignancy that supported our study (25).

In conclusion, although TVUS remains a cost-effective method in the diagnosis of ovarian carcinoma in premenopausal women, CT and CA-125 determinations should be useful when ovarian carcinoma is suspected on sonography, to investigate the extent of neoplastic disease and preoperative staging.

References:

1. Hubner KF, McDonald TW, Niethammer JG, et al. Assessment of primary and metastatic ovarian cancer by positron emission tomography (PET) using 2-[18F]deoxyglucose (2-[18F]FDG). Gynecol Oncol, 1993; 51:197–204.

2. Maiman M. Laparoscopic removal of the adnexal mass: the case for caution. Clin Obstet Gynecol, 1995; 38:370–9.

3. Osmers R. Sonographic evaluation of ovarian masses and its therapeutical implications. Ultrasound Obstet Gynecol, 1996; 8:217–22.

4. Sengupta PS, Shanks JH, Buckley CH, et al. Requirement for expert histopathological assessment of ovarian cancer and borderline tumors. Br J Cancer, 2000;82:760–2.

5. Rieber A, Nussle K, Stohr I, et al. Preoperative diagnosis of ovarian tumors with MR imaging: comparison with transvaginal sonography, positron emission tomography, and histologic findings. AJR Am J Roentgenol, 2001;177(1):123-9.

6. Alcazar JL, Errasti T, Zornoza A, Minguez JA, Galan MJ. Transvaginal color Doppler ultrasonography and CA-125 in suspicious adnexal masses. Int J Gynaecol Obstet, 1999; 66:255–61.

7. Franchi M, Beretta P, Ghezzi F, et al. Diagnosis of pelvic masses with transabdominal color Doppler, CA 125 and ultrasonography. Acta Obstet Gynecol Scand, 1995; 74:734– 9.

8. Komatsu T, Konishi I, Mandai M, et al. Adnexal masses: transvaginal US and gadolinium- enhanced MR imaging assessment of intratumoral structure. Radiology, 1996; 198:109–15.
9. Jacobs I, Bast R. The CA125 tumor associated antigen: a review of the literature. Hum Reprod, 1989; 4:1–12.
10. Van Vierzen PB, Massuger LF, Ruys SH, Barentsz JO. Borderline ovarian malignancy: ultrasound and fast dynamic MR findings. Eur J Radiol, 1998;28(2):136-42.
11. Fenchel S, Grab D, Nuessle K, et al. Asymptomatic adnexal masses: correlation of FDG PET and histopathologic findings. Radiology, 2002;223(3):780-8.
12. Minelli L. Ovarian cysts. Eur J Obstet Gynecol Reprod Biol, 1996; 65:81–9.
13. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. Obstet Gynecol, 1991;78(1):70-6.
14. Mogensen O. Prognostic value of CA 125 in advanced ovarian cancer. Gynecol Oncol, 1992; 44:207–12.
15. Makar AP, Kristensen GB, Bormer OP, Trope CG. CA 125 measured before second-look laparotomy is an independent prognostic factor for survival in patients with epithelial ovarian cancer. Gynecol Oncol, 1992; 45:323–8.
16. Niloff JM, Bast RC Jr, Schaetzl EM, Knapp RC. Predictive value of CA 125 antigen levels in second-look procedures for ovarian cancer. Am J Obstet Gynecol, 1985; 151: 981–6.
17. Huber S, Medl M, Baumann L, Czembirek H. Value of ultrasound and magnetic resonance imaging in the preoperative evaluation of suspected ovarian masses. Anticancer Res, 2002;22(4):2501-7.
18. Jain KA, Freidman D, Pettinger TW, et al. Adnexal masses: comparison of specificity of endovaginal US and pelvic MR imaging. Radiology, 1993 ;186:697–704
19. Yamashita Y, Torashima M, Hatanaka Y, et al. Adnexal masses: accuracy of characterization with transvaginal US and precontrast and postcontrast MR Imaging. Radiology, 1995 ;194:557–65.
20. Hata K, Hata T, Manabe A, Sugimura K, Kitao M. A critical evaluation of transvaginal Doppler studies, transvaginal sonography, magnetic resonance imaging, and CA 125 in detecting ovarian cancer. Obstet Gynecol, 1992; 80:922–6.
21. Reles A, Wein U, Lichtenegger W. Transvaginal color Doppler sonography and conventional sonography in the preoperative assessment of adnexal masses. J Clin Ultrasound, 1997; 25:217–25.
22. Ferrazzi E, Zanetta G, Dordoni D, et al. Transvaginal ultrasonographic characterization of ovarian masses: comparison of five scoring systems in a multicenter study. Ultrasound Obstet Gynecol, 1997;10(3):192-7.
23. Kurjak A, Predanic M. New scoring system for prediction of ovarian malignancy based on transvaginal color Doppler sonography. J Ultrasound Med, 1992; 11:631– 8.
24. Buist MR, Golding RP, Burger CW, et al. Comparative evaluation of diagnostic methods in ovarian carcinoma with emphasis on CT and MRI. Gynecol Oncol, 1994;52(2):191-8.
25. Guerriero S, Mallarini G, Ajossa S, et al. Transvaginal ultrasound and computed tomography combined with clinical parameters and CA-125 determinations in the differential diagnosis of persistent ovarian cysts in premenopausal women. Ultrasound Obstet Gynecol, 1997 ;9(5):339-43.

Corresponding address:
Dr. Fatma Ferda Verit
Department of Obstetrics and Gynaecology
Harran University, Faculty of Medicine
Arastirma ve Uygulama Hastanesi
Tr-63100 Sanliurfa, TURKEY
Tel: +90 414 316 8821
Fax: +90 414 315 1181
E-mail: fverit@harran.edu.tr