

The role of transvaginal ultrasonography and serum CA 125 assay combined with age and hormonal state in the differential diagnosis of pelvic masses

A. Mancuso, A. De Vivo, O. Triolo, S. Irato

Department of Gynecological, Obstetrical Sciences and Reproductive Medicine. University of Messina, Messina (Italy)

Summary

Purpose of investigation: To evaluate the ability of CA 125 and echography, alone and in combination with clinical parameters (age over 50 years and post-menopausal state), in the diagnosis of a malignant pelvic mass.

Methods: 125 women were enrolled and underwent echography and CA 125 assay. For each methodology, positive and negative predictive value, sensitivity, specificity, diagnostic accuracy, pre- and post-test probability and likelihood ratios were calculated.

Results: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA) and positive likelihood ratio were identical for echography and CA 125 considered alone. Paired with the patient's age, the CA 125 assay showed better results than the associations echography-age (LR+ 26.9 vs 10.1) or CA 125-echography (LR+ 26.9 vs 17.8). Furthermore the combination of the postmenopausal state with CA 125 obtained the best result of a positive likelihood ratio (LR+ 29.7).

Conclusion: Our study pointed out that, in the prediction of a malignant adnexal mass, the best results were obtained from the association between CA 125 and menopause, probably because in this period there is a lower incidence of benign diseases related to this marker so that an increase of CA 125 level is more likely associated with a malignant mass.

Key words: CA 125; Echography; Ovarian cancer; Adnexal masses.

Introduction

Up until two decades ago the presence of a pelvic mass necessitated a laparotomy to exclude the presence of ovarian cancer. This need, caused by the lack of diagnostic instruments, led to numerous surgical procedures being performed on benign cysts with risk of iatrogenic damage. This situation has changed, firstly due to the introduction of ultrasounds and then with the discovery of tumor markers. Technological progress in recent years has led to an improvement of sonographic instruments so that it is now possible to visualize the pelvic organs clearly and consequently to differentiate normal images more easily from pathological ones. Transabdominal and especially transvaginal sonography is a reliable mean by which to define the structure of ovarian masses. Benign ovarian lesions are generally small in size (diameter < 10 cm), and are cystic in appearance, with a distinct border and no evidence of irregular solid parts or thick septa [1]. In contrast, abnormal structures have a complex or solid appearance, with evidence of excrescences, internal septa or papillae [2]. Tumor markers were successfully used in the 1980s, most of all to monitor the progression or regression of an ovarian cancer. The most extensively studied serum tumor marker is CA 125, which was first described by Bast in 1981. CA 125 is a cell membrane glycoprotein of approximately 2000 kDa. Its assay uses the monoclonal antibody OC 125 [3]. This glycoprotein is found in the blood of patients with various types of cancers and increased levels of it have also been associ-

ated with a variety of benign gynecological conditions [4]. The assay of CA125 in the preoperative assessment of an adnexal mass is now considered to be helpful in distinguishing benign from malignant ovarian lesions [5, 6].

The aim of our study was to evaluate the predictive ability of ultrasonography and biochemical markers in the study of malignant pelvic masses. In order to carry out this analysis we have not only applied the parameters of Bayes theorem (sensitivity, specificity and predictive value), but also used more recent parameters such as likelihood ratios, pre- and post-probability tests. Moreover, we have attempted to evaluate whether the joint use of ultrasonography and biochemical markers or one or the other of these techniques used in conjunction with clinical factors (age and hormonal state) leads to improvement in the ability to identify malignant pathologies in women with a pelvic mass.

Materials and Methods

The study was carried out on 125 women admitted to our Department because of an adnexal mass. Patients were aged between 18 and 82 years and averaged 42.2 years of age; in 82 cases they were under 50 (65.6%) therefore 43 were over this age (34.4%). Sixty-two patients were nulliparous (49.6%), whereas 63 were multiparous (50.4%), values from 2 to 8. As regards hormonal state, 76 women (60.8%) were fertile, whereas 49 (39.2%) were postmenopausal, with the postmenopausal period range between one and 30 years. As regards symptomatology, 68 patients reported pelvic pain varying in intensity and duration, in 22 cases (17.6%) menstrual disorder was the main symptom, five patients reported urinary or intestinal symptoms and 30 were asymptomatic (24%) (Table 1).

Revised manuscript accepted for publication September 30, 2003

Table 1. — Demographic characteristics.

Age < 50 years	82	65.6%
Age > 50 years	43	34.4%
Nulliparous	62	49.6%
Multiparous	63	50.4%
Fertile	76	60.8%
Menopausal	49	39.2%
Symptomatic	95	76%
Asymptomatic	30	24%

During their hospital stay each patient underwent standard preoperative assessment in addition to an ultrasound scan and a serum dosage of CA 125. The transvaginal echography, and in some cases also transabdominal, was performed using the instrument "Aloka SSD 550" equipped with a probe TV 3.75-7.5 Mhz and a probe TA convex 3.5-5 Mhz.

The patients were divided into two groups on the basis of the results from the echography. The first group (Group A) was made up of patients whose lesions had benign morphological characteristics, while the second (Group B) included patients with lesions suspected of being malignant (solid structure or cystic but complex, irregular walls, endocystic vegetations, thick septa), plus the cases in which the lesion was bilateral and also patients with ascites [2].

The CA 125 dosage was performed using a Cobas Core CA 125 II EIA (Roche) kit, which uses two specific monoclonal antibodies; 35 U/ml was selected as the cut-off and the patients were grouped according to whether their CA 125 levels were above or below this threshold. Having done this, the patients, by previous informed consent, underwent laparotomic or laparoscopic surgery. The type of surgery and technique, conservative or radical, was chosen after the patient had been thoroughly examined. The ultrasound data and the biochemical data were compared with the definitive histological examination carried out on surgical samples. The ability of the two methods, ultrasound scanning and CA 125 dosage, to detect a malignant pathology was assessed both individually and jointly. Where the methodologies were assessed independently of each other then the hormonal state and the age of patients (under/over the arbitrary limit set at 50 years) were also taken into consideration. We then calculated the sensitivity, specificity, and the positive (PPV) and negative predictive value (NPV) for each of these permutations. Our study was concluded by determining the diagnostic accuracy of each methodology and calculating positive (LR+) and negative (LR-) likelihood ratios. This parameter, in contrast with predictive value, has been found to be independent from the prevalence of a disease, thus it enables pre/post-probability tests to be calculated.

Results

The diameter of adnexal masses measured between 4 cm and 28 cm with a mean value of 7.9 cm. The lesion was bilateral in 13 cases (10.4%) and there was ascites in six cases (4.8%). The histological examination indicated 111 (88.8%) benign and 14 malignant lesions in all. The number of adnexal masses with benign sonographic patterns (Group A) was 88 (70.4%), whereas in 37 cases (29.6%) their appearance was suspicious (Group B). The histological results for the latter group indicated a malignancy in 14 cases (37.8%) (Table 2); while in the other 23 cases these results showed the lesions to be benign (62.2%). For the 88 patients whose pelvic masses pre-

Table 2. — Histological malignant lesions.

10 serous cystadenocarcinomas
1 lymphoma
1 granulosa cell tumor
1 endodermal sinus tumor
1 clear cell ovarian tumor

sented benign echographic patterns the histological examination revealed no cases of malignant lesions. As regards CA 125, the levels of this tumoral marker were found to be above the cut-off in 37 women (29.6%): 14 of these were cases where the lesion was malignant according to the histological results (37.8%), and 23 were patients where the histological examination indicated a benign condition (62.2%) (Table 3).

Table 3. — Cases with CA 125 levels > 35 U/ml.

14 malignant tumors
18 endometriomas
2 struma ovarii
1 simple ovarian cyst
1 ovarian fibroma
1 fibroadenoma

When the echographic results were analysed together with age and hormonal state, we found that 24 out of the 37 women with suspicious echography were over 50 years old and 26 were postmenopausal. The results obtained from combining personal data with CA 125 showed 17 patients to be over the age of 50 and that the same number were postmenopausal. All of the patients with positive histological test results for malignant pathology were postmenopausal and 13 were aged over 50. The results from echography in statistical terms showed that 14 of the cases indicating malignant neoplasia were confirmed by the histological test (true positive), while a suspicious echography was not confirmed by the histological test in the remaining 23 cases (false positive). The 88 women with benign echographic and histological test results were all true negative; no cases of false negative were recorded. The CA 125 dosage produced identical figures. In the identification of a malignant ovarian neoplasia, the echography and the CA 125 produced the same values for sensitivity (100%; 95% CL 100%-100%), specificity (78.6%; 95% CL 71%-86%), positive predictive value (37.8%; 95% CL 22%-53%) and negative predictive value (100%). The combined use of the two methodologies or when each method on its own was combined with parameters relating to age and menopause, showed a sensitivity range between 91% and 100% and a specificity between 91% and 96.6%. The highest PPV was obtained from CA 125 combined with menopause data (78.6%). The diagnostic accuracy of echographic investigation and CA 125, when considered individually, were similar (81%) but better results were achieved when the two methodologies were considered jointly (95%). The best result from the point of view of diagnostic accuracy was obtained by pairing CA 125 with menopause data (97%) (Table 4).

Table 4. — The predictive capacity of echography and CA 125 alone and in combination in the diagnosis of malignant masses.

Methodologies	Sensibility	Specificity	PPV	NPV	Diagnostic Accuracy
Echography	100%	78.6%	36.7%	100%	81%
CA 125	100%	78.6%	36.7%	100%	81%
Echography + Age	91%	91%	55.5%	98.8%	91%
CA125 + Age	91%	96.6%	76.9%	98.8%	96%
Echography + Menopause	100%	88.7%	52.4%	100%	90%
CA125 + Menopause	100%	96.6%	78.6%	100%	97%
CA125 + Echography	100%	94.4%	68.7%	100%	95%

PPV = positive predictive value; NPV = negative predictive value.

In our study the prevalence of ovarian neoplasia (pre-test probability) was 11% (14/125). The LR+ was low for both echographic and also biochemical methods when each was considered alone (4.82 and 4.68, respectively). When the results from these investigations were paired with data regarding age and hormonal state, the probability of diagnosing the disease increased substantially, except for the pair echography-menopause (LR+ 8.9). Post-test probability (36.7%) was low for the two methodologies when evaluated separately, as already emerged from the calculation of predictivity, while it was better (76.9% and 78.6%) for CA 125 examined in conjunction with age and menopause data, respectively (Table 5).

Table 5. — The predictive capacity of echography and CA 125 alone and in combination in the diagnosis of malignant masses.

Methodologies	Pre-test probability*	Likelihood ratio+*	Post-test probability*
Echography	11% (5.6%-16.7%)	4.7 (3.1-6.9)	36.7% (19.4%-53.9%)
CA 125	11% (5.6%-16.7%)	4.7 (3.1-6.9)	36.7% (19.4%-53.9%)
Echography + CA 125	11% (5.6%-16.7%)	17.8 (7.5-41.7)	68.7% (46%-91.4%)
Echography + Age	11% (5.6%-16.7%)	10.1 (5-20.1)	55.5% (32.6%-78.5%)
CA 125 + Age	11% (5.6%-16.7%)	26.9 (8.7-83.3)	76.9% (54%-99.8%)
Echography + Menopause	11% (5.6%-16.7%)	8.9 (4.9-15.9%)	52.4% (31%-73.7%)
CA 125 + Menopause	11% (5.6%-16.7%)	29.7 (9.7-90.2)	78.6% (57%-100%)

*in parenthesis 95% CL.

Discussion

In our study transvaginal echography and the CA 125 dosage produced analogous results in their ability to spot a malignant adnexal mass. The sensitivity and the specificity data for the sonographic investigation do not contradict those reported in the literature [7-10]. This also applies to CA 125 because series adopting the same cut-off (35U/ml) have reported similar results to our findings [12-15]. The diagnostic accuracy, meaning the number of

correctly diagnosed cases as a percentage of the total number of cases examined, of these two methodologies was just over 80%. Their PPV, the probability that a positive result is linked to the actual presence of a mass with malignant characteristics, was rather low (36.7%). The calculation of LR+ (4.8) also demonstrated that they were not useful in diagnosing a malignant tumor. The result for post-test probability (36.7%) confirmed our PPV findings: namely that a positive result from one of the two methodologies could only indicate about a third of pathological cases. The joint use of echography and CA 125 dosage led to increased specificity (94.4%) and diagnostic accuracy (95%). The increase in specificity demonstrates that it is unlikely that a malignancy is present if the two tests both give a negative result. Similarly, the LR+ (17.8) obtained from pairing echography with CA 125 demonstrated that when the results of both tests are positive then there is far more probability of the adnexal mass being malignant. Results for PPV and the post-probability test of the two methods combined were better than those found using a single methodology alone (68.7% vs 36.7%). There have been reports in the past of increased sensitivity and specificity of CA 125 when considered together with patient age [12]. Certainly, this clinical parameter must not be ignored for women in whom an adnexal mass has been discovered, because it is well-known that the incidence of malignant growth increases along with ageing [16].

In our study when each methodology was paired with an age over 50 years this produced a reduced sensitivity (91% vs 100%), but increased specificity, especially for the combination of tumoral marker plus age (96.6% vs 78.6%). The importance of personal data for the diagnosis of this type of pathology is also revealed by the increase of LR+, PPV and post-test probability. This demonstrates that assessing data from echography in conjunction with age is very reliable for the diagnosis of a malignant adnexal tumefaction and the CA 125 paired with age is more reliable still. Even better results were obtained for the combination CA 125 and hormonal state [17]. This pairing not only yielded the highest percentage values for sensitivity and specificity, but also, and most of all, for the positive predictive value and the post-test probability (78.6%).

A rational explanation for this finding may lie in the fact that the menopausal state determines a reduction in the incidence of gynecological diseases, such as endometriosis or uterine fibromatosis, that may caused heightened levels of CA 125. In conclusion, we can state that to obtain a precise evaluation of the nature of an adnexal neoforation, the two methods, echography and CA 125 dosage, must be used jointly or one or the other used alone but combined with other clinical data such as age or a woman's hormonal state. In this respect, the most positive results in our study were obtained by combining the marker data either with age or, best of all, with menopausal state.

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Address reprint requests to:
A. MANCUSO, M.D.
Via Duca degli Abruzzi is. 520/d
98121 Messina (Italy)