Women with a pelvic mass: Indicators of malignancy

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Summary

Objective: To evaluate the efficacy of five methods: pelvic examination (PE), transvaginal ultrasonography (US), Doppler ultrasonography, serum CA125 assay and serum CA72-4 assay, alone or associated, to predict malignancy in patients presenting a pelvic mass originating in the ovary.

Methods: 92 patients underwent a standard protocol for physical examination, CA125, CA72-4, transvaginal ultrasonography and Doppler ultrasonography.

Results: Eighteen women were dropped from the study because they had clearly benign masses; two women were dropped from the study because they had clearly malignant lesions. Twenty-two malignant (30%) and 50 benign (70%) pelvic tumors were found. When one method was considered alone the best sensitivity (SENS) was found in physical examination (90%) and the best specificity (SPEC) was found in CA72-4: 88%. If all indicators were positive, the SPEC was 100% but the SENS was 40%. Logistic regression analysis prediction of the character of the pelvic masses was correct in 86%.

Conclusion: Some additional information to discriminate between malignant and benign pelvic masses can be obtained from the valuation of serum tumor markers, particularly CA72-4. Also Doppler ultrasonography appeared to be useful in the differential diagnosis of pelvic tumors. The prediction of the character of the pelvic masses calculated by a logistic model in which PE, US, CA 125, and CA72-4 are included is very good.

Key words: Pelvic mass; Pelvic examination; Ultrasonography; Doppler ultrasonography; CA125; CA72-4.

Introduction

This study evaluates the efficacy of pelvic examination (PE), transvaginal ultrasonography with selected use of Doppler ultrasonography, serum CA125 assay and serum CA72-4 assay to predict malignancy in patients presenting with a fixed pelvic mass. Serum CA125 is a known tumor marker used in the diagnosis and monitoring of epithelial ovarian carcinoma [1-4]. It was identified using a monoclonal antibody that was obtained by immunological contact with a cellular line of ovarian carcinoma by Bast and al. in 1981. Greater serologic levels are seen in 80-85% of women with ovarian epithelial carcinoma but not in the initial stage of ovarian malignancy nor in epithelial carcinoma; it results elevated in numerous clinical conditions like endometriosis and varied malignant symptomatic tumors. Generally a pathology that causes inflammation of the mesothelial membranes is associated with an increase of serum CA125 levels. This low specificity represents a potential problem because a possible false-positive could cause an unecessary surgical intervention to be performed. The serum CA72-4 test has an unclear role in the differential diagnosis of pelvic masses. It is an antigenic determinant on the mucin-like human tumor-associated glycoprotein. It was defined by the monoclonal antibody B 72-4 [5-7]. It is highly expressed in adenocarcinomas and is rarely expressed in benign lesions or normal adult tissues. Elevated levels of CA72-4 have been found in sera of patients with various forms of malignancy [8-10]. Ultrasonography (US) is the most commonly used imaging modality for evaluating a patient suspected of having pelvic malignancy [11, 12]. Transvaginal color Doppler imaging has facilitated the research in pelvic malignancy [13-15]. Previous studies suggested that the resistance index (RI) and pulsatility index (PI) of blood flow within the tumor could improve the predective value of pelvic ultrasonography. Particularly the low resistance index and low pulsatility index were frequently associated with malignancy [16, 17]. However low blood flow impedance can now be detected in a significant number of normal conditions and benign tumors [18]. If a statistical model that accurately predicts the probability of malignancy in patients with pelvic masses on the basis of clinical, serologic, and ultrasonographic variables were available, it would be important for patient counseling, selecting the optimal operative approach, incision type, and operative procedure.

Materials and Methods

In the Institute of Obstetrics and Gynaecology of the Second University of Naples in the period between January 1996 and March 2000, 92 women with a pelvic mass originating in the ovary were examined. The age of the patients ranged from 40 to 80 years. Each woman underwent a standard protocol for physical examination. The examination was considered to be abnormal when a palpable mass of any size was clinically distinguishable and separate from the gastrointestinal tract. The participating clinician was requested to define the mass as either benign or malignant. Blood samples were collected from all the patients. After clotting for 30 min at room temperature, serum was separated by centrifugation at 3000 rpm for 10 min, and stored at –20°C. Serum CA 125 and serum CA72-4 assay

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values were determined using CA125 IRMA assay, and CA72-4 IRMA. CA125 levels greater than 35 U/ml and CA72-4 levels greater than 3U/ml were considered abnormal.

Each woman underwent a transvaginal ultrasound examination of the pelvis using an ESAOTE ANSALDO AU 5 HARMONIC ultrasound machine with a 6.5 MHz real-time sector electronic array endovaginal probe and a 5 MHz pulsed Doppler system equipped with a color velocity imaging system for color blood flow codification. Patients who had a large tumor underwent transabdominal scanning with a 3.5 MHz transducer (color imaging Doppler and pulsed Doppler frequencies were all 3.5 MHz). The ultrasonographic image of the tumor was classified based on the criteria reported by Valentin *et al.* (Table 1) [19]. All women underwent color Doppler ultrasonography. By the color Doppler technique the intratumoral resistance (RI = peak systolic velocity minus end diastolic velocity divided by peak systolic velocity) was evaluated [20]. RI < 0.4 was considered suspicious of malignancy. The Doppler examinations were conducted on days 5-7 during the menstrual cycle for premenopausal patients to avoid the effect of ovulation and the presence of the corpus luteum.

Statistical Analysis

The efficacy of pelvic examination, transvaginal ultrasonography, serum CA125 assay and serum 72-4 assay to discriminate benign from malignant pelvic masses is expressed as sensitivity (SENS) and specificity (SPEC). The gold standard is the histopathological diagnosis [21].

Multivariate logistic analysis was conducted and examined variables included pelvic examination, ultrasonography, resistance index of blood flow within the tumor, serum CA125 assay and serum 72-4 assay. Each variable was coded as non-suspicious [0] or suspicious [1]. A formula to predict malignancy was developed. The probability of having a malignant ovarian tumor was estimated according to the following equation: $p = 1/(1+e^{-z})$, where p is the probability of malignancy and z is the linear formula developed from the logistic regression analysis. Statistical analyses were performed using the program STATISTICA for Windows release 4.5.

Results

Eighteen women were dropped from the study because they had clearly benign masses and two women were dropped from the study because they had clearly malignant lesions; in fact they were distant metastases. Twenty-two malignant (30%) and 50 benign (70%) pelvic tumors were found. The main outcome of the calculations of SENS and specificity SPEC, with 95% CL are reported in Table 2. When one method was considered alone, the best SENS was found in PE: 90%; the best SPEC was found in CA72-4: 88%. However, it was paired to a SENS of only 59%. When all four diagnostic methods had a positive test result, the SPEC was 100% but the SENS only 40%.

Using the logistic regression analysis, the equation of the fitted model is:

$$Z = -5.39224 + 2.35132*US + 2.81806*PE + 1.58268*CA125 + 0.607183*CA72\text{-}4 - -1.11594*RI$$

the efficacy of pelvic examination appeared to be the most relevant followed by ultrasound, serum CA125, and serum CA72-4.

Figure 1 shows the frequency distribution of the estimated probability for malignancy calculated by the logistic regression analysis.

The prediction of the character of the pelvic masses was correct in 86% in this analysis (Table 3).

Discussion

The correct diagnosis of a patient presenting with a pelvic mass is extremely important for preoperative and intraoperative patient management. In fact, an accurate

Table 1. — *Criteria reported by Valentin et al. for classification of tumors at sonographic examination*

1) UNILOCULAR CYST (UC): a unilocular cyst without septa and without solid parts or papillary excrescences.
2) MULTILOCULAR CYST (MC): a cyst with at least one septum but no solid parts or papillary excrescences.
3) UNILOCULAR SOLID CYST (USC): a uniolocular cyst containing solid parts or papillary excrescences but no septa.
4) MULTILOCULAR SOLID CYST (MSC): a tumor with at least one septum and solid parts or papillary excrescences.
5) SOLID TUMOR (ST): a tumor with solid components in 80%° or more of the tumor.

Table 2. — *Calculations of sensitivity (SENS) and specificity (SPEC) of single parameters and combinations of PE, US, CA125, CA72-4 (PE+ = malignant clinical impression; US+ = multilocular solid tumor or solid tumor; CA125+ = >35 U/ml; NO = this method is not involved in this combination).*

PE	US	CA-125	CA72-4	SENS (%)	95% CL	SPEC (%)	95% CL
+	+	+	+	40	33-59	100	96-100
+	+	+	NO	54	44-70	100	87-98
+	+	NO	+	50	39-65	98	96-100
+	+	NO	NO	77	67-89	90	78-93
+	NO	+	+	45	36-62	100	96-100
+	NO	+	NO	63	51-76	94	86-97
+	NO	NO	+	50	43-69	98	96-100
+	**NO**	**NO**	**NO**	**90**	**81-97**	**74**	**64-82**
NO	+	+	+	45	35-61	100	93-100
NO	+	+	NO	54	47-73	94	83-96
NO	+	NO	+	54	43-69	88	55-75
NO	**+**	**NO**	**NO**	**86**	**75-94**	**72**	**59-78**
NO	NO	+	+	53	39-65	98	92-100
NO	**NO**	**+**	**NO**	**68**	**56-80**	**86**	**74-90**
NO	**NO**	**NO**	**+**	**59**	**47-73**	**88**	**86-97**

Table 3. — *Correct prediction of the character of pelvic masses calculated by the logistic model*

		Predicted		Total (n)	Correct
		Benign (n)	Malignant (n)		(%)
Observed	Benign (n)	45	5	50	90
	Malignant (n)	5	17	22	77
Total correct predicted		45	17	62/72	86

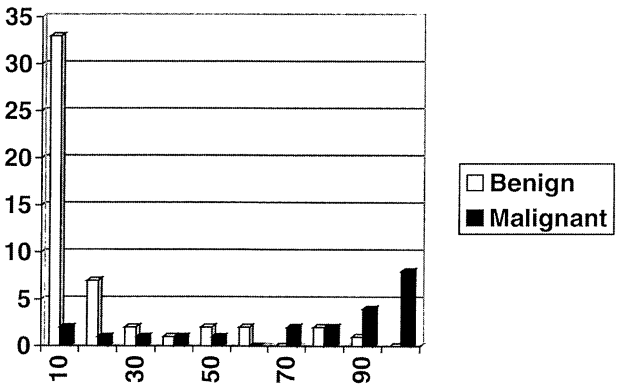

Figure 1. — Histogram of estimated probabilities of malignancy. The bars represent the number of actual cases of benign and malignant pelvic masses at each level of probability.

prediction of the type of pelvic tumor may provide, in cases of malignancy, the best chance for a long disease-free interval or cure. Pelvic examination, tumor markers, and sonography are the basic cornerstones to discriminate preoperatively benign from malignant pelvic masses in clinical practice [22, 23]. In screening programs, pelvic physical examination has generally been considered an unreliable predictive method. Although recent studies have highlighted its significance, with an accuracy of about 75% [24], its relevance seems to have been undervalued in clinically evident pelvic masses. Therefore it is possible that an overestimation of malignant pelvic masses might occur. The value of serum CA125 determinations in the discriminations of benign from malignant ovarian tumors is controversial. In premenopausal patients it has not been shown to be useful. In other studies, serum CA125 levels were elevated in only about half of the patients with early ovarian cancer [25, 26, 27]. This study shows that CA125 alone has a good SPEC (86%), and a sufficient SENS (68%). As a serum marker alone CA72-4 lacks sufficient SENS (59%). This is not surprising because this glycoprotein has been found in normal transitional colonic mucosa and normal secretory endometruim. However, the SPEC is remarkably good with 88%. Thus, this study shows that CA72-4 is useful as a malignant tumor marker. This result has also been found in other investigations [10].

Most studies have shown that some additional information can be obtained from a combination of serum tumor markers, but that other diagnostic modalities are needed for optimal and correct preoperative judgement of a pelvic mass. Also in this study the combination of CA125 and CA72-4 improves the SPEC to 98% and reduces SENS to 53%.

The literature has shown that ultrasound has been useful in the differential diagnosis of pelvic masses. Recently, the transvaginal ultrasound examination has given good results in comparison to the transabdominal approach [28]. Transvaginal color and pulsed ultrasonography was introduced in an attempt to improve the diagnostic accuracy of ultrasonography alone. Kurjac *et al.* performed transvaginal ultrasonography in 1,000 women, employing color Doppler in women who showed ecographic anomalies, and the sensibility was 96% with a specificity of 95%. This technique permits the appraisal of the blood vessels and the presence of abnormal proliferation [29, 30, 31]. In this study US alone had a good SENS (86.9%) although SPEC was found to be low (69%). The R.I. evaluated by the colour Doppler technique was a variable considered in the multivariate logistic analysis. The result of this valuation showed that this technique was useful in the differential diagnosis of pelvic tumors.

Thus, this study demonstrates that the use of combinations of more than one diagnostic method has opposite effects on the SENS and the SPEC. If all diagnostic tests are positive the SENS is low and the SPEC is high. If only one of the test results is elevated, SENS is high and SPEC becomes low, but this is not true when more serum tumor marker levels are evaluated.

A general conclusion is that some additional information to discriminate between malignant and benign pelvic masses can be obtained from the valuation of serum tumors markers, particularly from CA72-4. Also Doppler ultrsonography appeared to be useful in the differential diagnosis of pelvic tumors.

The purpose of this study was to individualise a model to predict malignancy in pelvic masses. The results are good because the prediction of the character of the pelvic masses calculated by the logistic model, in which PE, US, CA125, and CA72-4 were included, had a reliability of 86%.

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