Evaluation of serum CA 125 level and its relation to surgical, histopathologic and ultrasonographic findings in patients with pelvic mass

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Summary

Objective: The aim of this study was to determine the relationship between the levels of tumour marker CA 125 antigen and pelvic tumour size, histopathological type, stage, bilateral status, ascites, type of surgery, and postoperative complications. *Materials and Methods:* A retrospective cross-sectional descriptive study was conducted on 203 patients with a pelvic mass who were visited in the Shahid Sadoughi hospital in Yazd, Iran from 2007 to 2010. Data were analyzed by software SPSS v.14. *Results:* Statistical analysis, based on Fisher's exact test, showed that patients with pelvic mass who presented with either of bilateral involvement/ ascites ($p = 0.000$), higher stage ($p = 0.001$), inability for complete resection ($p = 0.000$), or postoperative complications ($p = 0.001$) had significantly higher serum concentrations of CA 125 antigen. There was no relationship between serum level of CA 125 and such variables as tumor size ($p = 0.883$) and abdominal ultrasound findings ($p = 0.297$). *Conclusion:* Using CA 125 as a diagnostic and prognostic tool in patients with newly-discovered pelvic mass can be helpful in some aspects, but cannot estimate size of the tumor and its solid/cystic status. It also cannot predict post-surgical complications of malignant pelvic masses.

Key words: CA 125 antigen; Pelvic neoplasms; Tumour marker; Histopathology; Survival; Surgical complication.

Introduction

Pelvic masses are common clinical findings and are seen in women in all age groups [1]. Annually, 169,000 to 289,000 patients are hospitalized in the United States due to a pelvic mass or ovarian cyst [2]. In a study, about eight percent of asymptomatic women 20 to 40 years old who were randomly examined had pelvic cystic masses larger than 2.5 cm [3]. Unfortunately, most ovarian cancers are diagnosed in final stages while studies show that their survival rates are lower than 20% [4]. In the later stages of the disease, these patients usually present with metastatic lesion which is a worsening factor in their survival. One of the causes of progression of the disease to this stage is that there are no warning signs. Only 25% of ovarian tumours are diagnosed at Stage I [5].

The major anxiety and fear in dealing with patients with a pelvic mass stems from failure to diagnose a "probable malignancy". Limitations of physical examination, the patient's perception of the likelihood of malignancy, and invasive nature of examinations exacerbate anxiety. The effects of diagnostic and therapeutic methods on fertility of the patients before menopause will be more complicated in this group of patients [6]. In order to reduce late diagnosis of ovarian malignancy, combinations of different diagnostic methods are used.

Patients with pelvic mass are often asymptomatic and are discovered in routine examinations or during random radiological studies. Tumour markers are released from tumour tissue into circulation, and their presence in serum indicates existence of the tumour in the body [7]. No tumour marker with high accuracy has yet been introduced for screening of pelvic masses. Rather, tumour markers are used to confirm the presence of malignant tumour especially in postmenopausal women [6]. The panel of utilized tumour markers usually includes AFP, βHCG, CA 125, CA 19-9, CEA, and LDH serum levels [1]. Sensitivity and specificity of tumour markers vary in different studies, and some of them can be effective for early diagnosis. Also, they can be somewhat effective in estimating the relative size of the tumour, but most of the time, the results of clinical trials have been "has not been reproducible" [8]. Tumour markers are influenced by a variety of factors; for example, CA 125 antigen serum level varies according to race, age, and smoking [9-11]. Therefore, this study was designed to determine the relationship between the serum concentration of tumour marker CA 125 and tumour size, histopathological types, ultrasonographic findings, benign or malignant status stage. and postoperative compli-

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Table 1. — *Histopathologic types of tumours in patients (N = 203) and their serum concentration of CA 125 [number (percentage)].*

Serum CA 125 (Units/ml)	Invasive epithelial ovarian tumor	Borderline epithelial ovarian tumor	Sex cord stromal ovarian cancer	Benign uterine tumour	Malignant uterine tumour	Benign ovarian/ para-ovarian tumour	Metastatic to ovary	Mixed germ cell tumor	Total
<35	9 (23.7)	4 (44.4)	1 (100)	68 (95.8)	6 (85.7)	40 (56.3)	2 (40)	0 (0)	130 (64)
>35	29 (76.3)	5 (55.6)	0 (0)	3 (4.2)	1 (14.3)	31 (43.7)	3 (60)	1 (100)	73 (36)

Malignant tumours comprised 61 of these tumours, in whom 22 (36.1%) had CA 125 < 35 units/ml and the remaining 39 (63.9%) patients had CA 125 > 35 Units/ml. One hundred and twenty patients suffered from ovarian tumours, in whom 54 (45%) had CA 125 < 35 Units/ml (including 40 benign and 14 malignant tumours), and 66 (55%) had CA 125 > 35 Units/ml (including 31 benign and 35 malignant tumours). Fisher exact test showed that *p* value of differences between these two types of ovarian tumours regarding the serum level of CA 125 is 0.03 (valid).

Table 2. — *Frequencies of different variables in all patients (N = 203) and their serum concentration of CA 125 [number (percentage)].*

Serum CA 125 (Units/ml)	Ultrasound finding			Ultrasound evidence of bilateralism or ascites		Type of surgery				Postoperative complications	
	Cystic	Solid	Heterogenous	No	Yes	Optimal debulking	Suboptimal debulking	Preservation of uterus & contralateral ovary	Complete resection of tumour	No	Yes
< 35	43 (33.1)	8 (6.2)	79 (60.8)	129 (99.2)	1 (0.8)	67 (51.5)	0 (0)	32 (24.6)	31 (23.8)	122 (68.5)	8 (32)
> 35	21 (28.8)	9 (12.3)	43 (58.9)	61 (83.6)	12 (16.4)	39 (53.4)	8 (11)	25 (34.2)	1 (1.4)	56 (31.5)	17 (68)
p value (Fisher exact test)	0.297 (invalid)			0.000 (Valid)		0.000 (Valid)				0.001 (valid)	

cations to assist in deciding how to deal with patients with pelvic mass and optimum use of paraclinical studies, based on comprehensive review of the performance of these tests.

Materials and Methods

This study was a retrospective cross-sectional descriptive study. Information, using questionnaires, was collected from patients with a pelvic mass who were examined in Shahid Sadoughi Hospital in Yazd, Iran from 2007 to 2010.

Of 251 patients evaluated with respect to the inclusion criteria, 203 patients were finally included. An informed written consent form was signed by all patients before entering the study. In patients who were hospitalized due to a pelvic mass, blood sample was taken before surgery. All blood samples were sent to a single accredited laboratory for evaluation of tumour marker levels. The utilized method for measuring the CA 125 was electrochemiluminescence.

According to the manufacturer's kit, the normal level of CA 125 was less than 35 units/ml [12, 13]. The effect of smoking, because of its influence on some tumour markers [14], was studied and corrected according to self report by the patients. Based on patients' ultrasonographic reports, the size of their mass (less than seven cm or seven cm and more) [2, 10] and the abdominal ultrasound characteristics of tumour (cystic, solid or heterogenous) [15] were also recorded.

All these patients underwent comprehensive staging, hysterectomy, oophorectomy, omentectomy, para-aortic biopsy, and pelvic and peritoneal biopsies performed by a gynaecologist. During surgery, a sample of the mass was sent for pathologic assessment. All patients underwent supervision or secondary treatment according to their histopathology report. Results of serum CA 125 level and histopathologic types of tumour were assessed and analyzed. Surgical complications were defined as fever (measured orally) more than 39°C, lasting for more than three days, urethral, bowel, and/or bladder injuries.

To calculate the survival rate in patients with malignancy, the beginning time was considered from cancer diagnosis (according to the pathology report) until August 2010. Survival status of patients was monitored by following-up the patients (by phone) and was recorded per month and displayed by the Kaplan-Meier curves. All data was analyzed using the software SPSS v.14. For statistical analysis, Fisher's exact test was used. A *p* value less than 0.05 was considered significant difference.

Results

The youngest patient was two-years-old and the oldest was 80-years-old. Based on pathology reports, patients were classified into eight groups (Table 1). Benign uterine neoplasms and benign ovarian/para-ovarian masses were the most common tumours, each comprising 71 patients. In 49 patients there was a primary malignancy involving the ovary.

Frequencies of different variables in all patients (N=203) and their serum concentration of CA 125 are shown in Table 2. As is displayed, there was no significant relationship between CA-125 levels and the ultrasonographic characteristics of tumours ($p = 0.297$). However, the rate of postoperative complications was

Table 3. — *Frequencies of different variables in patients with malignancy (N = 61) and their serum concentration of CA 125 [number (percentage)].*

Serum CA 125 (Units/ml)	Ultrasound finding			Tumour size (cm)		Tumour stage				Postoperative complications	
	Cystic	Solid	Heterogenous	< 7	> 7	1	2	3	4	No	Yes
<35	1 (4.55)	4 (18.2)	17 (77.25)	8 (29.6)	14 (41.2)	12 (66.7)	3 (60)	5 (14.7)	2 (50)	17 (42.5)	5 (23.8)
>35	21 (28.8)	9 (12.3)	13 (58.9)	19 (70.4)	20 (58.8)	6 (33.5)	2 (40)	29 (85.3)	2 (50)	23 (57.5)	16 (76.2)
p value (Fisher exact test)	0.435 (invalid)			0.883 (valid)		0.001 (invalid)				0.173 (valid)	

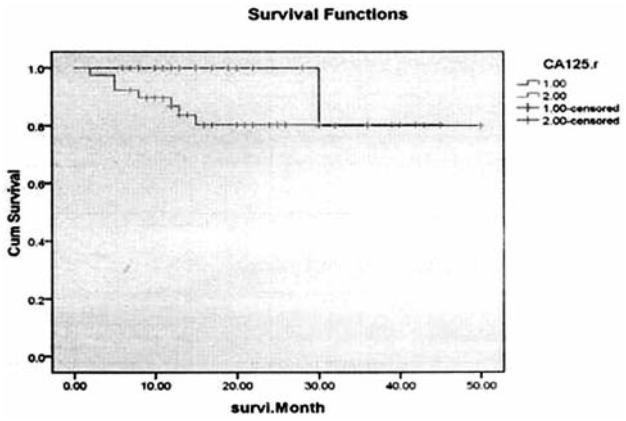

Figure 1. — The association of tumor markers (CA 125) and survival in patients with malignancy.

significantly more in patients with high serum CA 125 levels (p = 0.001). Bilateralism of tumour and ascites were also significantly more in those patients who had high serum CA 125 (p = 0.000). Inability to complete resection of tumour was also more likely when CA 125 was high (p = 0.000).

Table 3 shows frequencies of different variables in patients with malignancy (N = 61) and their serum concentration of CA 125.

Until the end of survival time, eight patients had died. No significant relationship was observed between the tumour marker level (CA 125) and the survival rate of patients (p = 0.18, Figure 1).

Discussion

In many cases referring to the Shahid Sadoughi hospital, as a referral center in the central and southern provinces of Iran, tumour markers had been found to be under-used. On the other hand, no obvious relationship was found between tumor markers and other clinical findings in patients with pelvic mass.

To assist in deciding how to deal with these patients, a comprehensive study examining the relationship between serum CA 125 and tumour size, histology, survival, complications, stage, and ultrasound features was designed on 203 patients with pelvic masses who were admitted to that center during four years.

Early diagnosis of cancer can increase survival chance of the patients. There are many tools to detect cases with pelvic masses, and the ovarian tumour marker CA 125 as a simple and non-invasive method, can help to improve treatment, early diagnosis, and follow up of these patients [10]. As high as 90% of these patients can be detected at an early stage by using this test [11]. While in the early stages most of the cases are asymptomatic, unfortunately they are usually discovered at higher stages in which they have only 20% chance of treatment and recovery.

Therefore, introducing an easy and accessible way that can quickly identify more of these patients and in a more economical way can certainly be useful. The relationship between tumour marker CA 125 levels and malignancy in this study was not statistically valid, due to the small number of samples that were divided into two groups, and therefore, the authors only relied on the description of these values. Based on abdominal ultrasound reports, masses were divided into cystic, solid or heterogeneous groups. About 31% of patients had cystic masses, 8.4% solid masses, and 60.1% had heterogeneous masses. This result is in accordance with the ultrasound data reported by McDonald *et al.* from Cancer Center in Kentucky Hospital, USA [13].

In this study, no significant relationship was observed between cystic, solid, or heterogeneous masses and tumour marker CA 125 levels. In reviewing the literature, no previous study that examined the level of tumour markers and ultrasound characteristics (cystic, solid or heterogeneous pelvic neoplasms) was found. There are only a few studies that have examined the relationship between cystic, solid, and heterogeneous masses [13, 14]. Therefore, further studies to investigate this relationship in more patients are recommended.

Postoperative complications were defined as injury to the urethra, bladder, intestines, and fever over 39°C for more

than three days. Given the low number of complications in patients and also simultaneous injury to multiple organs in some patients, we decided to divide the cases into two groups as complicated and uncomplicated groups. A significant association ($p = 0.001$) was found between the tumour marker CA 125 and complications after surgery. Only a few papers have addressed the levels of tumour markers, complications after surgery, and survival of patients with ovarian cancer, so more studies are needed in this area.

A study conducted by Gadducci *et al.* showed that a continuous increase in tumour marker CA 125 level in people with residual disease after initial treatment was present, especially in patients whose disease recurred within three to six months. They believe that CA 125 can be considered as a biomarker for patients' management instead of using it for early detection of pelvic masses. Nevertheless, in the present study, serum level of CA 125 was significantly related to the benign or malignant status and also to the stage of the disease [15, 16].

In this study, survival rate of the patients was analyzed using the Log Rank, which showed no significant association with CA 125 levels. A study by Cooper *et al.* for assessment of the prognostic impact of CA 125 level on survival rate of patients with epithelial ovarian cancer, they found that the higher levels of this tumour marker are associated with decreased survival rate in these patients [17].

Durdević *et al.* also evaluated the role of CA 125 in survival rate of the patients with ovarian cancer, and showed that in cases where there is no residual tissue, levels of > 35 U/ml of this tumour marker, and in cases where there is residual tissue, levels of > 65 U/ml of this tumour marker are correlated with decreased survival rate of the patients [18]. The relationship between other tumour markers and patients' survival was not assessed. In the two aforementioned studies, the same authors checked the level of tumour marker in epithelial ovarian cancers. As it is difficult to compare the present study with theirs, further studies using greater numbers of patients are highly recommended.

Despite the advantages of CA 125, false-positive results in benign cases such as endometriosis and fibroids are still seen, and various studies have shown that CA 125 values are more reliable in post-menopausal women [19].

Oltmann *et al.* conducted a study on 424 cases in 2009, to risk classify malignant ovarian masses prior to surgery, and reported that the most common indicators of ovarian cancer before surgery were complaints of precocious puberty, ovarian tumours larger than seven cm or solid tumour in imaging reports. They believe that tumour markers (CEA, CA 125, βHCG, and AFP) - both positive and negative - might be useful just for follow-up [20].

Ayhan *et al*. in 2007 reviewed 60 cases with borderline ovarian tumours to determine the relationship between tumour marker panels (CA 125, CA 19-9, CEA, and CA 15-3) with tumour size and tumour histopathology. They concluded that high levels of tumour markers, especially CA 125 and CA 19-9 might be suggestive of larger size of tumour. They also suggested that increased CA 125 might indicate the likelihood of serous tumour while high levels of CA 19-9 and CEA implied a greater likelihood of borderline ovarian tumours [21].

To investigate the clinical value of tumour markers (CEA, CA 125), Jun-qing in 2007 studied 208 patients with pelvic pathology and found that increased CA 125, CA 19-9, and AFP are good markers in predicting the likelihood of malignancy of pelvic masses, while CEA is of limited clinical value [22].

Schutter *et al.* in 2002 reviewed 412 cases to assess the value of tumour markers (CA 125, CA 15-3, and CA 42-4) in differential diagnosis of the pelvic lesions, and concluded that simultaneous increase in all three tumour markers was seen in almost all cases of malignancy. It should be noted that increase in all of those three tumour markers was found in a small number of patients. It was also found that increased CA 15-3 was associated mostly with malignancy. The tumour markers' results were less accurate than ultrasound, physical examination, patients' age, and menopausal status [23].

In a large British study with a sample size of 200,000 postmenopausal women comparing the diagnostic sensitivity and specificity of CA-125 and transvaginal ultrasonography (TVUS), it was observed that sensitivity, specificity, and positive predictive value of CA 125 in all primary tumours of the ovary and fallopian tube cancers obtained were 89.4%, 99.8%, and 43.3%, respectively; while these values were 84.9%, 98.3%, and 2.8% for TVUS alone. However, from an economic point of view, there is no consensus in using a combination of these two methods in screening of ovarian tumours [24].

Milojkovic *et al.* in 2003 reviewed 212 patients to assess the value of CA 125 in differentiation of benign from malignant tumours before surgery, and concluded that measuring this tumour marker before surgery is an effective method in diagnosis of benign and malignant pelvic masses [25].

Behtash *at al.* studied 75 patients with adnexal masses using ultrasound and CT scan, and found that transabdominal ultrasound is a sensitive method for detection and staging of suspected ovarian tumours, but CT scans and tumour markers do not add further information about the nature of the masses [26]. Biomarkers, as screening tools, are usually most useful in people with high risk and family history of BRCA 1, BRCA2, and family history of colorectal cancer [8].

In an Iranian study performed by Yousefi *et al.* in 2007, it was observed that 42.1% of patients with ovarian tumours had high serum level of CA 125, while the level of CEA showed no increase in any of those patients [27].

Conclusion

Patients with pelvic mass who present with either of bilateral involvement, ascites, higher stage, inability for complete resection, or postoperative complications had significantly higher serum concentrations of CA 125. There was no relationship between serum level of CA 125 and such variables as tumor size and abdominal ultrasound findings. Using CA 125 as a diagnostic and prognostic tool in patients with newly-discovered pelvic mass can be helpful in some aspects, but cannot estimate size of the tumor and solid/cystic status of it. It also cannot predict post-surgical complications of malignant pelvic masses.

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