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Clinical value of human epididymis protein 4 and the Risk of Ovarian Malignancy Algorithm in differentiating borderline pelvic tumors from epithelial ovarian cancer in early stages

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ABSTRACT

Objective: The clinical value of human epididymis protein 4 (HE4) and the possibility of its use in the differential diagnosis in patients with benign, borderline and epithelial ovarian cancer in early International Federation of Gynaecology and Obstetrics (FIGO) stages.
Study design: The study group consisted of 205 women, including 60 with ovarian cancer, 18 with borderline tumors, 77 with benign lesions and 50 healthy subjects. In all the patients, before the treatment and in control groups, we determined CA 125 and HE4 in serum by electrochemiluminescence on the basis of the COBAS e601 system. For comparison of two independent groups, we used the *U* Mann–Whitney test. The analysis of the diagnostic power of the assessed parameters has been determined using the MedCalc statistical program. The probability of disease free survival (DFS) was evaluated using the log-rank test and Cox regression model.
Results: Concentrations of HE4, CA 125 and Risk of Ovarian Malignancy Algorithm (ROMA) value were significantly higher in early ovarian cancer than in patients with benign ($P < 0.0001$) and borderline tumors ($P < 0.002$), the receiver operating characteristics (ROC) curves, demonstrated the highest diagnostic sensitivity for the ROMA score, as well post (AUC = 0.817) as pre-menopausal (AUC = 0.806). HE4 concentrations ($P < 0.021$) and the value of the ROMA score ($P < 0.004$) were significantly higher in patients with relapse than in patients in remission. There was no connection between concentrations of the studied tumor markers and DFS.
Conclusions: Determination of HE4 serum concentrations has a significant clinical value, especially in patients with benign lesions and elevated CA 125 levels. The combined assessment of HE4, CA 125 and the ROMA algorithm is helpful in differentiating benign tumors and borderline pelvic tumors from epithelial ovarian cancer in early FIGO stages. Determination of HE4, CA 125 and ROMA algorithm is not helpful in differentiating patients with borderline from benign lesions.

Introduction

Ovarian cancer is one of the most difficult malignant tumors, both in terms of diagnostics and therapy, is the leading cause of death among patients with cancer of the reproductive organs. Despite the progress that has been made in many areas of medicine, treatment results are still unsatisfactory. Ovarian cancer affects primarily women in the peri- and postmenopausal age groups. The percentage of incidences increases with age. Poor prognosis of patients with ovarian cancer is associated primarily with an advanced clinical stage at the time of diagnosis. Because there are no specific clinical symptoms during the early stages of the disease and a lack of effective screening, the disease, in the majority of cases (over 70%) is recognized in the advanced stage.

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Poland is a country with an average incidence of cancer, epithelial ovarian cancer patients with advanced FIGO stages III–IV accounts for 75% of our population. Therefore, it is vital to search for sensitive and specific methods for the detection of the early stages of ovarian cancer.

The success of the treatment depends mostly on the proper classification of patients as well as determining the scope and method of surgery. Preoperative diagnosis of patients with ovarian tumors includes, in addition to the pelvic examination, imaging examinations and assessments of tumor markers [1].

Laparoscopy is a minimally invasive method that allows for the effective surgical treatment of benign ovarian tumors. However, in the case of malignant tumors the classic laparotomy is the standard due to the higher risk of rupturing of the tumor capsule and the potential spread during the laparoscopy [2]. Ovarian cancer is not a single disease entity but covers a whole spectrum of different forms of the disease. There is the number of other factors with proven prognostic value, as: age, degree of differentiation, histological type, the presence of a residual mass after surgery, as well as the serum level of tumor markers. The standard tumor marker CA 125, despite the relatively high sensitivity, as a single diagnostic test was found to be ineffective in the screening as well as in differentiating the nature of the tumor before treatment. CA 125 is a commonly used marker, which may be elevated in benign conditions such as inflammation of the pelvis and endometriosis, which significantly reduces its specificity in the diagnosis of ovarian cancer. In addition, the sensitivity of CA 125 in detecting early ovarian cancer is low, because it is elevated only in about 50% of patients [3]. In the literature of recent years, there have been reports on the clinical utility of human epididymis protein 4 (HE4). Its overexpression is observed in ovarian cancer, especially of the serum and endometrial histology. It seems that the determination of association of HE4 and CA 125 can increase the sensitivity and specificity of the test, alone, to allow more efficient detection of ovarian cancer in early clinical stages as well as in the selection of patients with benign changes. In addition, assessment of tumor markers can help determine which patients should be directed to cancer centers with the suspicion of ovarian cancer and which can be operated using a minimally invasive method, *e.g.* in cases of endometriosis [4–7].

A different group is tumors of borderline malignancy, whose biology in most cases resembles benign lesions, but in about 20% of cases they have a lesion beyond the ovaries. This lesion is usually in the form of peritoneal implants or lymph vascular space invasion (LVSI). Borderline tumors account for about 15–20% of all ovarian tumors and have been isolated in the WHO classification as a separate group of epithelial tumors in 1973. The main feature of borderline tumors is the lack of destructive stromal invasion, moderate atypia and mitotic activity, and excessive build-up of epithelial cells [8,9]. Due to the rarity of borderline tumors and their particularity, it may be interesting to study the usefulness of tumor markers in this group of patients as well.

The aim of the study was to evaluate the usefulness of HE4 in patients with ovarian cancer, the assessment of the relationship between its concentrations and its clinicopathological features, as well as the possibility to use the marker in the differential diagnosis of patients with benign and borderline tumors in the pelvic area. The aim was also to determine further if HE4 concentration has a possible prognostic value in disease-free survival (DFS) and overall survival (OS) assessment.

Materials and methods

The study involved all consecutive patients incoming for appointment to The Maria Sklodowska-Curie Memorial Cancer Center and Institute in Warsaw between 2009 and 2013 with pelvic tumor and elevated CA 125. In all patients, a pelvic tumor was confirmed by the transvaginal ultrasonography in a primary center or with indicated further assessment in the tertiary center. We recruited patients at the primary and tertiary center.

Assessment of the CA 125 and HE4 was performed in a total of 205 patients before beginning treatment. The group included 60 patients with histologically confirmed ovarian cancer (median age of 58.5), 18 patients with borderline malignancy tumors (median age 35), and 77 patients diagnosed with benign lesions (median age 40). The epithelial ovarian cancer (EOC) was further divided into subtypes: serous 31 (52%), mucinous 6 (10%), endometrial 12 (20%), clear cell 4 (7%), others (mixed non-differentiated) 6 (10%) and no data 1 (0.5%).

According to the FIGO classification, among this group of ovarian cancer patients: 15 were found to be in the early clinical stage (I + II) and 45 in the advanced stages (III + IV) (Table 1).

The control group consisted of 50 healthy women, with ages ranging from 26–58 (median age 53) Oncology Center workers.

The authors state that the ethics approval for this prospective study has been obtained (The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology Ethics Committee in Warsaw, the ID of the approvals: 27/2012).

Venous blood was taken from patients before treatment. To standardize clotting conditions, all sera were separated within 1 h

Table 1
Clinicopathological characteristics of study population.

	Benign tumors		Borderline tumors		Ovarian cancer patients		Patients in remission		Patients with progression	
	n = 77	%	*n* = 18	%	*n* = 60	%	*n* = 24	%	*n* = 28	%
Age (median, range)	40 (16–75)		35 (22–60)		58.5 (26–83)		54 (22–75)		64 (27–71)	
Menopausal status										
Premenopausal	59	77	14	78	15	25	9	38	2	7
Postmenopausal	18	23	4	22	45	75	15	62	26	93
FIGO stage										
I	x		11	61	8	13	6	25	1	4
II	x		2	11	7	12	3	13	2	7
III	x		x		37	62	14	58	20	71
IV	x		x		8	13	1	4	5	18
Histological grade (G)										
G1	x		x		5	8	4	17	0	0
G2	x		x		5	8	1	4	3	11
G3	x		x		30	50	13	54	17	61
Undefined	x		x		20	33	6	25	8	2

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics.