

# The role of CA125 and HE4 serum markers in predicting the locoregional stage of endometrial cancer

Ewa Iwanska<sup>1</sup>, Konrad Muzykiewicz<sup>1</sup>, Radosław Kosobucki<sup>1</sup>, Kazimierz Karolewski<sup>1</sup>, Maja Janeczek<sup>2</sup>, Paweł Blecharz<sup>3</sup>

<sup>1</sup> Department of Gynecologic Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland

<sup>2</sup> S. Zeromski's Hospital, Krakow, Poland

<sup>3</sup> St. John's Cancer Center in Lublin, Lublin, Poland

SUMMARY

**Aim:** The aim of this paper was to evaluate the usefulness of preoperative values of CA125 and HE4 serum markers in assessing the locoregional severity of endometrial cancer.

**Materials and methods:** We analyzed clinical material from patients with endometrial cancer who were initially treated surgically in the Center of Oncology (Krakow Branch) between 2012 and 2014. As part of preoperative preparation pelvic magnetic resonance imaging with an assessment of myometrial invasion was performed and CA125 and HE4 marker levels were determined. After this, patients were selected for surgery-hysterectomy with both salpingo-oophorectomy. Lymphadenectomy was performed on patients from high-risk group. We analyzed the relationship between the assessment of marker levels, on the one hand, and myometrial invasion, the presence of Lymphovascular Space Invasion (LVSI) and the severity and the risk of recurrence, on the other. The statistical evaluation of the results was based on the Mann-Whitney test and the Kruskal-Wallis test.

**Results:** We analyzed medical history of 128 patients with endometrial cancer. It was shown in the study group that CA125 levels were significantly higher in patients with affected lymph nodes as well as in patients with stages III and IV, the presence of LVSI and cervical infiltration, muscular infiltration exceeding 1/2 of the myometrial wall thickness, assessed preoperatively in both the MRI and clinical examination but this relationship was not observed in the final histopathological evaluation. Marker levels were also not affected by the histological type of the tumour. HE4 levels were significantly higher in patients with muscular infiltration exceeding 1/2 of the wall thickness assessed in MRI as well as in clinical and histopathological, in patients with stage III and IV, the presence of LVSI and cervical infiltration. There were no relationship between higher HE4 values and affected lymph nodes.

**Conclusion:** Our results confirm the utility of the CA125 and HE4 markers in EC. The sensitivity and specificity of each of them separately is not enough to make clinical decisions. However, when combined with other factors they can be an important criterion for determining the classification of patients who belong in the high-risk group.

**Key words:** serum markers, endometrial cancer, myometrial invasion, lymphovascular space invasion

## INTRODUCTION

Endometrial Cancer (EC) is the most common malignant neoplasm originating in the reproductive organ and the fourth most common malignant neoplastic disease in women [1, 2]. Diagnosis is most often made at an early stage, and the basic treatment is surgery. In 1988, the International Federation of Gynaecology and Obstetrics (FIGO) changed the classification method used to assess stages of endometrial cancer from clinical to surgical-pathological. This decision was motivated by the inaccuracy of clinical assessments in over 20% of cases, which could lead to an ineffective treatment approach [3].

According to some authors, one factor determining indications for systematic Lymphadenectomy (LND) is the local severity of early stage EC, assessed on the basis of Myometrial Infiltration thickness (MI) [4-6]. However, removal of pelvic and paraaortic lymph nodes extends the surgery time and increases both the risk of perioperative complications and perioperative mortality [7]. In addition, the MREC ASTEC study showed that lymphadenectomy in early EC had no effect on overall survival. Hence, systematic LND is not recommended for routine management in early stages of this disease [7, 8]. The optimal way to diagnose patients and to predict lymph node metastases has yet to be established. Analyses carried out in recent years have compared the usefulness of magnetic resonance imaging, transvaginal ultrasound, histological intraoperative examination and various serous tumour markers such as CA125, HE4, and CEA, whose effectiveness of MI assessment ranges between 70 and 95% [4-6, 9, 10].

The measurement of CA125 protein concentration in serum has been used to help diagnose gynaecological cancers for approximately 30 years. Although it is a useful marker for monitoring the treatment of advanced disease, it has limited application in its early stages [4, 10-12]. Despite the uncertain role played by CA125 and HE4 serous markers in the diagnosis of early forms of cancer, numerous studies are being conducted to assess their usefulness in predicting advanced stages of disease and the presence of lymph node metastases [10].

The aim of the study was to evaluate the usefulness of preoperative values of CA125 and HE4 serum markers in assessing the locoregional severity of endometrial cancer.

### Address for correspondence:

Ewa Iwanska, Department of Gynecologic Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Krakow Branch, Garncarska 11, 31-115, Kraków, Poland, Tel: +48 12 634 83 31, email: ewa.iwanska@onet.pl, dr.ewa.wojtas@gmail.com

**Word count:** 3048 **Tables:** 03 **Figures:** 02 **References:** 22

**Received:** - 16 April, 2020

**Accepted:** - 24 April, 2020

**Published:** - 08 May, 2020

## MATERIAL AND METHODS

The methodology applied in the study was based on a retrospective analysis of clinical material comprising women with endometrial cancer, who were initially treated surgically at the Center of Oncology, Cracow Branch in 2012-2014. During these years, 128 patients with EC were operated on at the Oncological Gynecology Clinic. As part of their preoperative preparation, patients underwent MRI of lower pelvis and CA125 and HE4 marker levels were determined with an Abbinity Alinity I analyser based on the chemiluminescence method. A concentration of up to 70 pM/ml was set as the laboratory norm for the He4 marker, and 35 U/ml for Ca125. After this, patients were selected for surgery, during which hysterectomy and bilateral salpingo-oophorectomy were performed. Lymphadenectomy was performed on patients who had in MRI or intraoperatively MI>1/2 thickness of myometrium, grade 3 histological differentiation (G3) or a non-endometrioid tumour type.

A retrospective analysis was performed to determine the relationship between the assessment of marker levels, on the one hand, and myometrial infiltration thickness, the presence of Lymph-Vascular Space Invasion (LVSI), and the severity and risk of recurrence, on the other. The optimal cut-off point was sought for these markers for MI>1/2 myometrial wall thickness, the presence of LVSI signs and of cancer outside the endometrium using the ROC (Receiver Operating Characteristic) curve (Table 1).

The statistical evaluation of the results was based on the Mann-Whitney test and the Kruskal-Wallis test.

To evaluate the effects of the treatment, the time until cancer recurrence was adopted as the benchmark, due to the good prognosis for this form of the disease and the short observation time.

Tab. 1. The clinical features of the analysed group	Characteristic feature	N	%
General health of patient according to the American Society of Anaesthesiologists (ASA)	ASA 1	16	12.50%
	ASA 2	51	39.84%
	ASA 3	51	39.84%
	No data	10	7.82%
Ca125	Normal	100	78.12%
	Above normal	22	17.19%
	No data	6	4.69%
HE4	Normal	44	34.38%
	Above normal	33	25.78%
MI in final histopathological examination	No data abnormal kidney parameters	51	39.84%
	<1/2 myometrial wall thickness	80	62.50%
	>1/2 myometrial wall thickness	46	35.94%
EC histological type	No data	2	1.56%
	Endometrial	111	86.72%
	Non-endometrial	17	13.28%
Peritoneal lavage cytology	Positive	6	4.69%
	Negative	107	83.59%
	No data	15	11.72%
EC severity (stage) according to FIGO	IA	66	51.57%
	IB	26	20.32%
	II	18	14.06%
	IIIA	1	0.78%
	IIIB	6	4.69%
	IIIC	3	2.34%
	IIIC1	2	1.56%
	IIIC2	1	0.78%
	IVA	3	2.34%
	IVB	2	1.56%
	EC histological differentiation	G1	55
G2		48	37.50%
G3		21	16.41%
No data		4	3.12%
Yes		14	10.94%
LVSI	No	112	87.50%
	No data	2	1.56%

## RESULTS

The mean age of patients was 64 years (30-85, median 65).

### Relationship between CA125 concentration and microscopic features of cancer (infiltration thickness, presence of LVSI, cervical infiltration and lymph node metastases)

The mean preoperative CA125 level was 31.53 U/ml (median 16.39 U/ml, range 2.94-455.1 U/ml). It was shown in the study group that CA125 levels were significantly higher in patients with muscular infiltration exceeding 1/2 of the myometrial wall thickness, assessed preoperatively in both the MRI and clinical examination. On the other hand, this relationship was not observed in the final histopathological evaluation. Marker levels were also not affected by the histological type of the tumour. Higher CA125 values that were statistically significant were also observed in patients with affected lymph nodes as well as in patients with stages III and IV.

The presence of LVSI and cervical infiltration was also associated with higher marker values. The optimal cut-off point for CA125 at MI>1/2 was set at 21.97 U/ml, however, in the case of this value the sensitivity of the method was low. The cut-off values for the assessed clinical situations are presented in Table 2.

An analysis based on the Cox model showed that CA125 levels correlated with time until recurrence (p=0.034) and HR was 1.007. Figure 1 shows the Kaplan-Meier curve in patients with CA125 levels up to and above 16.39 U/ml.

### Relationship between HE4 concentration and microscopic features of cancer (infiltration thickness, presence of LVSI, cervical infiltration and lymph node metastases)

The mean HE4 level was 95.6 pmol/L (median 59.8 pmol/L, range 22.6 pmol/L-890.5 pmol/L). In the examined group, it was shown that HE4 levels were significantly higher in patients with muscular infiltration exceeding 1/2 of the wall thickness assessed in MRI as well as in clinical and histopathological examination with paraffin blocks, when compared with other patients. Significantly higher HE4 levels were also found in patients with stage III and IV cancer as well as in patients in whom postoperatively LVSI or cervical infiltration was found.

No significantly higher HE4 values were found in patients with affected lymph nodes. (Table 3).

An analysis based on the Cox model shows that HE4 correlated with time to recurrence (p=0.009), HR was 1.003. Figure 2 presents the Kaplan Meier curve for groups of patients with HE4 levels up to and above 59.8 pmol/L.

Clinical situations	Cut-off points for CA125 concentration	Sensitivity	Specificity
MI>1/2	21.97	48.89%	77.33%
LVSI	21.57	61.54%	71.03%
FIGO III/IV	30.34	52.94%	87.62%

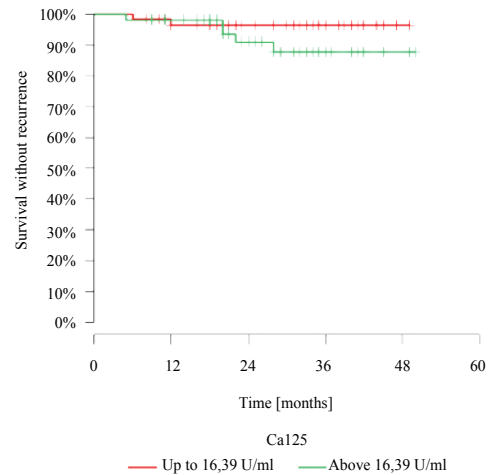


Fig. 1. Kaplan-Meier curve in patients with CA125 levels up to and above 16.39 U/ml

Clinical situation	Cut-off values for HE4 concentration	Sensitivity	Specificity
MI>1/2	72.6	63.33%	73.33%
LVSI	80.6	87.5%	69.12%
FIGO III/IV	117.3	61.54%	84.38%

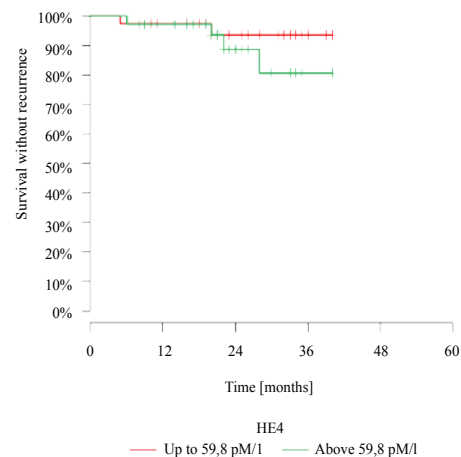


Fig. 2. Kaplan Meier curve for groups of patients with HE4 levels up to and above 59.8 pmol/L

## DISCUSSION

EC is the most common malignant gynaecological cancer, which is usually detected at an early stage. Pre-operative identification of patients with a low risk of metastases makes it possible to select the optimal scope of surgical treatment and minimize the risk of perioperative complications.

Determining CA125 and HE4 markers in serum is not a recommended test for screening gynaecological cancers, but it is accepted as part of the preoperative assessment of disease severity and also as a parameter for assessing the response to treatment in ovarian cancer [13-15]. In the last few years there have been many studies evaluating their utility in preoperative assessments of patients with EC. Nilof et al. were the first researchers to use CA125 measurements in patients with endometrial cancer. They showed in this way that elevated marker levels could be observed in 78% of patients with advanced EC (FIGO IV) and in relapse patients [11]. In response to this publication,

many authors have demonstrated a relationship between elevated CA125 values and a higher degree of EC [4, 10-12, 16-18]. Sood et al. showed a relationship between an increase in a marker and the presence of cancer outside the uterus. In cases involving positive peritoneal lavage cytology, MI>1/2, the presence of metastases in lymph nodes and higher stage FIGO, the marker was significantly higher. Multifactorial analysis showed that CA125 is the most important predictor of worse survival. A preoperative level>65 U/ml increased 6.5x the risk of neoplastic foci outside the uterus and the test sensitivity was 62% (with 91% specificity) [16].

Hsieh et al. studied the usefulness of CA125 as a factor determining eligibility for lymphadenectomy in EC. They also showed a significant relationship between the stage of the disease, tumour size, MI>1/2, cervical infiltration, and LN metastases. The cut-off point when predicting the presence of metastases in LN was 40 U/ml [17].

Zhou X. et al. compared several variables, including WBC, Ca19-9, CA125, CEA and tumour histological features and evaluated their usefulness in predicting LVSI. They showed a relationship between CA 125>21.2 U/ml and the presence of cancer cells in LVSI. His search result for the cut-off point is comparable to ours [18].

In 2010-2012 Angioli et al. conducted a study assessing the relationship between levels of CA125 and HE4 and prognostic factors such as FIGO grade, MI, cervical infiltration and the histological type of the cancer. It showed a significantly lower

level of HE4 in IA and IB (median 63.4 pmol/L vs. 108.7 pmol/L) and considerable differences in the level of this marker for each of the more advanced stages of the disease [19].

In another work evaluating the role of HE4 in predicting the FIGO grade, Capriglione presented the results of his search for the cut-off points for different stages of the disease. Using ROC, they determined the following points 61.3 pmol/L for FIGO IA, 89.2 pmol/L for IB, 104.3 pmol/L for II, 152.6 pmol/L for III and 203.8 pmol/L for IV. Their published results were much higher than those presented in our study [20].

As in our work, Moore et al. showed no correlation between the level of HE4 and the presence or absence of metastases in lymph nodes [21].

Due to the higher sensitivity of HE 4 in stage I of the diseases compared to Ca125 it also has potentially higher predictive value in the diagnosis of early recurrence [22].

## CONCLUSION

To sum up, our results confirm the utility of the CA125 and HE 4 markers in EC. The sensitivity and specificity of each of them separately is not enough to make clinical decisions. However, when combined with other factors they can be an important criterion for determining the classification of patients who belong in the high-risk group. Further large prospective studies are required to confirm their usefulness.

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