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The prognostic value of the post-treatment serum CA 125 level in patients with advanced endometrial cancer

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ABSTRACT

Objectives: The goal of this analysis was to assess the prognostic value of the post-treatment serum CA 125 level in each member of a group of advanced endometrial cancer (aEC) patients in comparison to other clinical and pathological parameters.

Material and methods: Records of 266 patients treated at the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch between the years 2006 and 2018 were included in the study. Follow-up ranged from 1 to 138 months. Progression free survival (PFS) and overall survival (OS) were set as the endpoints. The tests chi-squared, Fisher, log-rank, Mann-Whitney, Kruskal-Wallis and Cox proportional hazard ratio were used for statistical analyses.

Results: In the analysed group, there was a significant association between an elevated serum CA 125 level following adjuvant treatment and shorter PFS and OS. After setting a cut-off value for CA 125 there was a statistically significant correlation between the marker and PFS and OS. Multivariate analysis indicated that the post-treatment serum CA 125 level is an independent prognostic factor of the course of aEC.

Conclusions: The post-treatment serum CA 125 level correlates significantly with both PFS and OS in each patient with aEC. The marker is an independent prognostic factor in this group. A low post-treatment level of the marker is a strong indicator of good 5-year survival, with 82% of patients reaching 5-year OS.

Keywords: advanced endometrial cancer; CA 125; post-treatment; adjuvant treatment

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INTRODUCTION

Endometrial cancer (EC) accounted for 7% of all newly diagnosed malignancies in Poland in 2019 and is the most frequently diagnosed gynaecological cancer in developed countries. Though mostly diagnosed at an early stage, almost 20% of new reported cases were in advanced stages of the disease [International Federation of Gynecology and Obstetrics (FIGO) III and IV] [1–3]. Advanced endometrial cancer patients are a very heterogenous group, so individual approaches are required at each stage of the treatment.

CA 125 is a valid prognostic marker in the treatment of ovarian cancer, though its utility in EC patients has been studied mainly in pre-treatment settings. A high serum level of the protein prior to treatment corelates with a shorter overall survival (OS) rate, deeper myometrial invasion, lymphovascular space invasion, and nodal involvement.

Unfortunately, due to a high number of false negative results, it has not been useful in planning the extent of operative procedures. There are analyses focused on building a prognostic model based on CA 125 level combined with other factors [4–15].

In addition, there is paucity of data on the significance of the post-treatment serum CA 125 level in aEC patients. Given the assay is widely available and low-cost it has potential as a valuable addition in planning individual follow-up for aEC patients.

Objectives

The aim of this study was to assess the prognostic utility of obtaining a serum CA 125 level at the end of primary treatment and to compare the marker's value in relation to other clinical and pathological parameters.

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MATERIAL AND METHODS

This paper is a part of a larger retrospective analysis of medical data, where records of 266 patients treated at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch, between the years 2006 and 2018 were included in the analysis. The last patient included in the analysis finished treatment in 2013, resulting in the minimal possible follow-up of five years. We performed a detailed analysis of the known EC prognostic factors, comorbidity, biochemical test results, the type, duration, and extent of surgery, the hospital where surgery was performed, stage and grade of cancer, its histology and Bokhman type, the type of adjuvant treatment (AT), and the treatment outcomes expressed using the RECIST criteria.

The patient files contained data on the pretreatment level of CA 125 only in about 44% of cases, mostly lacking information about the type of assay used, because the majority of patients were initially treated outside our Cancer Centre. Over 70% of the medical data files included information about the CA 125 level after treatment, all assessed on site at our Cancer Center using the Abbott Alinity I CA 125 II Reagent Kit assay, which is a chemiluminescent microparticle immunoassay (CMIA). Samples were taken 2–6 weeks after adjuvant treatment completion.

Progression-free survival (PFS) and OS were set as the endpoints and were both assessed at 12, 36 and 60 months. Due to insufficient data, the study patients were not differentiated according to cause of death.

Qualitative data was analysed by counting the number and percentage of each value. Comparison of variables was made using the chi-squared test, or, in cases of groups with low expected quantity, the Fisher detailed test. Kaplan-Meier curves were used to demonstrate the results of the analyses of qualitative features, and their comparison was made using the log-rank test. Quantitative data were analysed by counting mean value, standard deviation, median, quartiles, minimal value, and maximal value. Comparison of those variables was made using the Mann-Whitney test. In cases of three or more groups, comparisons were made using the Kruskal-Wallis test. Features which showed statistically significant differences were analysed post-hoc with the Dunn test. The Cox proportional hazard ratio model was used to examine the influence of quantitative features on PFS and OS. Hazard ratios (HR) and 95% confidence interval (CI) values were used in reporting the results. The cut-off values for tests based on quantitative data were determined using receiver operating characteristic (ROC) curves. The utility of each quantitative variable as a predictor was assessed using the area under the ROC curve (AUC). The level of statistical significance was set at a value of $p < 0.05$. The analyses were made using R software.

RESULTS

As mentioned before, this is a part of a larger analysis based on a group of 266 advanced endometrial cancer patients. Table 1 contains detailed demographic and clinical characteristics of this group, while data on progression-free survival, overall survival, and follow up are shown in Table 2 [16].

There was paucity of data on the serum CA 125 level prior to treatment because the patients were treated in various hospitals, and it was not assessed in most treatment centers before surgery.

The post-treatment data was far more complete and of better quality since most of the results came from a single laboratory in COOK. The mean value was 139.33 U/mL,

Table 1. Demographic and clinical characteristic of the study group

Demographic and clinical characteristic of the study group			
Feature	**Mean (SD)**	**Median (quartile)**	
		n	**[%]**
Age [years]	65.47 (9.75)	66 (59–73)	
	22–44	5	1.9
	45–64	112	42.1
	65+	149	56
BMI	30.13 (5.93)	29.8 (25.98–33.85)	
	Underweight (< 18.5)	1	0.4
	Normal (18.5–25)	44	16.5
	Overweight (25–30)	72	27.1
	Obese (> 30)	113	42.5
	No data	36	13.5
Comorbidity	Total	192	72.18
	Hypertension	169	63.53
	Diabetes mellitus	58	21.8
Diabetic patients treated with metformin	Yes	33	56.90
	No	24	41.38
	No data	1	1.72
FIGO 2009 stage	IIIA	75	28.2
	IIIB	93	34.96
	IIIC	63	23.68
	IVA	5	1.88
	IVB	8	3.01
	No data	22	8.27
Bokhman type	Type I	182	68.42
	Type II	70	26.32
	No data	14	5.26
Histological Grade	G1	34	12.78
	G2	126	47.37
	G3	57	21.43
	No data	49	18.42

SD — standard deviation; BMI — body mass index; FIGO — International Federation of Gynecology and Obstetrics

Table 2. Overall survival and progression-free survival in the study group

Number of patients	Number of events	Overall survival			
		12 months	36 months	60 months	Median [months]
266	106	87.23%	59.54%	49.59%	60
Number of patients	Number of events	Progression-free survival			
		12 months	36 months	60 months	Median [months]
266	122	71.02%	53.14%	45.42%	50
Post-treatment follow-up [months]					
N	Mean	SD	Median	Min	Max	Q1	Q3
266	36.94	31.63	25	1	138	11	61

SD — standard deviation

Table 3. Results of the analysis of selected variables in relation to overall survival (OS)

Results of the analysis of selected variables in relation to OS

N	Variable	Unit	HR	95% CI		p value
1	Age at the moment of diagnosis	years	1.035	1.013	1.056	0.001
2	PLT before surgery	$10^3/\mu L$	1.003	1	1.005	0.02
3	LEU before AT	$10^3/\mu L$	1.073	1.046	1.101	< 0.001
4	PLT before AT	$10^3/\mu L$	1.005	1.003	1.006	< 0.001
5	NLR		1.06	1.034	1.086	< 0.001
6	PLR		1.001	1	1.002	0.011
7	Pre-treatment CA 125	U/mL	1	1	1.001	0.548
8	Post-treatment CA 125	U/mL	1.0003	1.0001	1.0005	0.001*
9	CA 125 pre-post treatment decline	U/mL	0.9998	0.9997	0.9999	0.029*

Variable	Number of patients	Number of deaths	Overall survival				p value
			12 months	36 months	60 months	Median [months]	
10. Histologic grade							
G1	34	8	93.21%	77.03%	64.19%	> max obs.	< 0.001
G2	127	40	92.22%	71.65%	63.24%	116	
G3	57	30	81.03%	37.82%	24.82%	25	
11. Bokhman type							
I	183	57	91.32%	69.08%	59.83%	116	< 0.001
II	71	42	75.24%	40.53%	28.43%	25	

HR — hazard ratio; CI — confidence interval

with the standard deviation at 786.84 U/mL, whereas the median was 16.5 U/mL, with the quartiles reaching 10.4––32.4 U/mL. We analyzed survival rates in the context of each patient's CA 125 level taken once after treatment, and in relation to many more variables. Results of the analysis for CA 125 and the variables which correlated significantly with PFS and/or OS are given in Tables 3 and 4.

Afterwards, the ROC curve was drawn for the post-treatment serum Ca125 level. The area under curve (AUC) value was 0.855 (Fig. 1). The optimal cut-off value for the examined parameter was assessed and identified as 21.38 U/mL with a sensitivity of 85.71% and specificity of 75.86%. This allowed

us to distinguish two groups of aEC patients. The low-level group, with CA 125 values below the newly established cut-off point, and the high-level group with values above this level.

The results of the univariate analysis of the relation between dichotomized post-treatment CA 125 values (high — above cut-off, low — below cut-off) and OS and PFS are given in Table 5, and on Figure 2.

A multivariate analysis of the prognostic value of the post-treatment serum CA 125 level was then conducted with inclusion of known significant prognostic factors such as age, histological grade, Bokhman type. The results showed

Table 4. Results of the analysis of selected variables in relation to progression free survival (PFS)

Results of the analysis of selected variables in relation to PFS

N	Variable	Unit	HR	95% CI		p value
1	Age at the moment of diagnosis	years	1.026	1.006	1.046	0.009
2	PLT before surgery	$10^3/\mu L$	1.003	1	1.005	0.027
3	LEU before AT	$10^3/\mu L$	1.064	1.043	1.085	< 0.001
4	PLT before AT	$10^3/\mu L$	1.004	1.003	1.005	< 0.001
5	NLR		1.054	1.03	1.078	< 0.001
6	PLR		1.001	1	1.002	0.036
7	Pre-treatment CA 125	U/mL	1	1	1.001	0.548
8	Post-treatment CA 125	U/mL	1.0003	1.0001	1.001	< 0.001*
9	CA 125 pre-post treatment decline	U/mL	0.9997	0.9995	0.9999	0.017*

Variable	Number of patients	Number of events	Overall survival				p value
			12 months	36 months	60 months	Median [months]	
10. Histologic grade							
G1	34	10	80.40%	73.09%	63.34%	> max obs.	
G2	127	47	82.92%	65.18%	57.61%	93	< 0.001
G3I	57	34	52.86%	27.11%	23.24%	15	
11. Bokhman type							
I	183	68	80.24%	62.69%	55.13%	93	< 0.001
II	71	46	48.74%	32.63%	24.16%	12	
11. Depth of myometrial invasion							
< 1/2	39	10	88.89%	75.00%	71.43%	> max obs.	0.018
> 1/2	163	69	80.54%	58.59%	47.84%	58	

HR — hazard ratio; CI — confidence interval

that the post-treatment serum CA 125 level was the only independent prognostic factors for both 5-year OS and PFS in the study group. Hazard ratios of a high post-treatment serum CA 125 level were 9.9 for death and 4.8 for progression. Detailed results of this analysis are presented in Table 6.

DISCUSSION

Most studies on the relevance of the serum CA 125 level in endometrial cancer patients relate to their values before treatment. Currently the ESMO-ESTRO-ESGO consensus does not recommend the routine use of this parameter during treatment and follow-up of patients with EC [17]. The largest metanalysis by Patsner and Won Yim comprises only 25 papers published internationally between 1984 and 2012, and they all deal with the significance of the preoperative serum CA 125 level. Their data indicate that 15–25% of patients whose disease was preoperatively qualified as confined to the uterus had an elevated serum CA 125 level prior to treatment, and in 75% of those cases there was nodal involvement or metastatic disease in the final pathologic report. There is a correlation between a high serum CA 125 level and shorter OS and PFS. Most of the papers in that
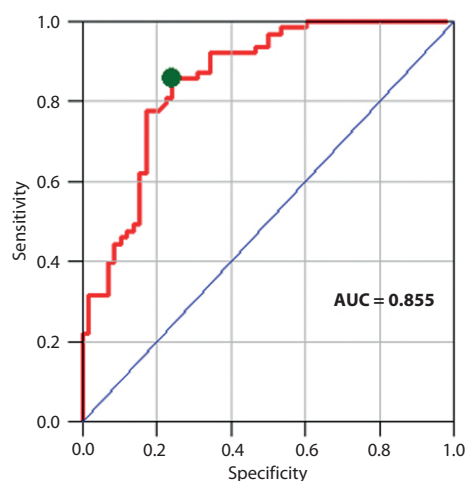

Figure 1. Receiver operating characteristic curve for the post-treatment serum CA 125 level; AUC — area under curve

metanalysis focused on the utility of CA 125 as a marker of nodal, peritoneal, or adnexal involvement. It seems to be a fairly good tool in this setting, indicating the necessity for a more radical surgical approach, with cut-off values ranging from 20 to 210 U/mL, and in most cases a range of

Table 5. Prognostic value analysis of the post-treatment serum CA 125 level as qualitative variable in relation to overall survival (OS) and progression free survival (PFS)

Prognostic value analysis of the post-treatment serum Ca125 level as qualitative variables in relation to OS and PFS

Variable	Number of patients	Number of deaths or events	Overall survival				p value
			12 months	36 months	60 months	Median [months]	
1. OS							
CA 125 low-level	102	17	98.99%	89.92%	81.68%	> max obs.	0.001
CA 125 high-level	68	45	80.04%	36.44%	24.18%	26	
2. PFS							
CA 125 low-level	102	26	95.03%	84.07%	70.85%	> max obs.	0.001
CA 125 high-level	68	48	52.71%	26.50%	23.85%	15	
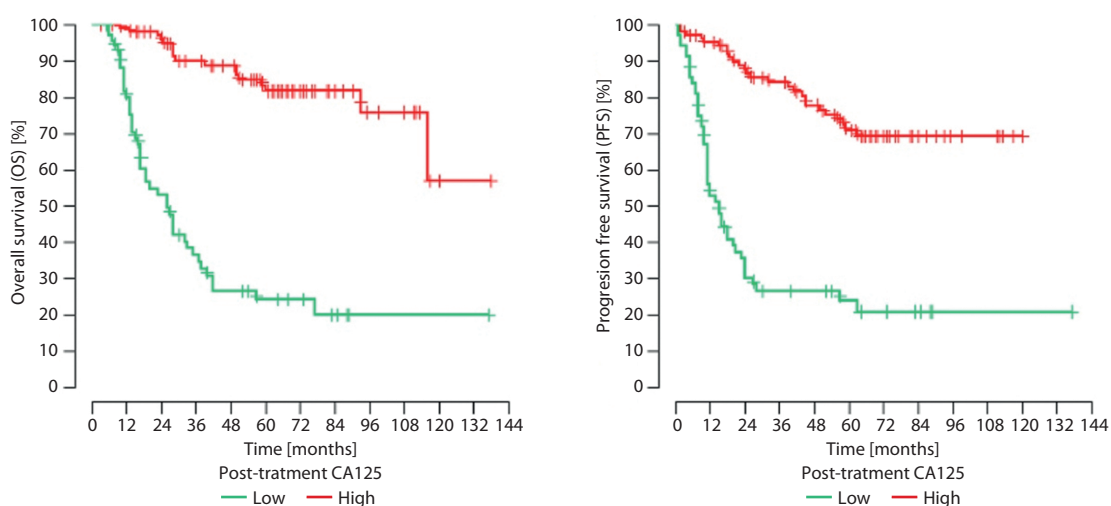
Figure 2. Kaplan-Meier overall survival and progression-free survival curves for the post-treatment serum CA125 level

35–40 U/mL. [4, 18] On the other hand, Hsieh and Chang emphasis that the decision not to perform lymphadenectomy cannot by based on a low serum CA 125 level, as more than 45% of results proved to be false negative. [8] There is also significant association between elevated preoperative CA 125 ≥ 21.2 U/mL and fibrinogen levels ≥ 2.58 mg/dL and lymphovascular space invasion (LVSI) as shown by Zhou and al. [9], whereas in a recent paper Shawn LyBarger and al. point that a pretreatment CA 125 level above 175 U/mL corelates significantly with LVSI and lymph node metastasis, with the effect peaking at levels above 222 U/mL. Researchers state that the increase in risk was the most prominent for patients having stage III/IV disease, reaching 1.67-fold. [10] Various prognostic models and algorithms based on CA 125 levels in compilation with HE4 and BMI [11], or immunohistochemical markers such as progesterone receptors

and Ki67 [12] are being developed as diagnostic tools to facilitate pretreatment stratification of EC patients.

There are very few studies on the significance of the serum CA 125 level in advanced endometrial cancer. The first was in 1989 concerning a series of 15 aEC cases treated with either chemo or hormonal therapy. The reported post-treatment reduction in the CA 125 level, which had initially been elevated, was considered to be an indicator of a response to treatment. [13] A much larger group of 185 newly diagnosed aEC patients who underwent chemotherapy (paclitaxel + + carboplatin in 6 cycles) with or without radiotherapy as adjuvant treatment was studied by Hoskins and al. Many EC prognostic factors were taken into consideration along with the serum CA 125 level prior to treatment as well as following 3 cycles of chemotherapy. The results of the univariate analyses showed that CA 125 levels above 35 U/mL

Table 6. Multivariate analysis results

Multivariate analysis results					
Feature		**HR**	**95% CI**		**p value**
OS					
Age	[years]	1.02	0.988	1.053	0.226
Grade	G1	1	ref.		
	G2	1.123	0.403	3.131	0.825
	G3	1.459	0.484	4.403	0.503
Bokhman type	I	1	ref.		
	II	1.433	0.662	3.102	0.361
Post-treatment CA 125	Low	1	ref.		
	High	9.909	4.224	23.244	< 0.001*
PFS					
Age	[years]	1.022	0.99	1.054	0.176
Grade	GI	1	ref.		
	GII	1.336	0.539	3.31	0.532
	GIII	1.924	0.701	5.276	0.204
Bokhman type	I	1	ref.		
	II	1.504	0.738	3.066	0.261
Post-treatment CA 125	Low	1	ref.		
	High	4.778	2.421	9.429	< 0.001 *

HR — hazard ratio; CI — confidence interval

pretreatment, and above 24 U/ml after 3 cycles of treatment were significant markers of poorer prognoses. The serum CA 125 level exceeding 24 U/mL after 3 cycles of chemotherapy was found to be an independent negative prognostic factor in the multivariate analysis. Among patients with endometrioid aEC and a CA 125 level above 24 U/mL midway through chemotherapy, 13 out of 14 suffered a relapse, compared to 24 out of 56 in the low CA 125 group. The disease also relapsed in all patients in the Bokhman type II group with a high serum CA 125 level. The authors concluded that the marker is an excellent predictor of aEC recurrence and a mediocre predictor of non-recurrent disease [14].

In our own study, our analysis considered the serum CA 125 level before treatment, and after adjuvant treatment, and the difference between these two values. A statistically significant correlation between OS and PFS and the serum CA 125 level after AT was shown in the Cox analysis. There was also a significant correlation in the differences between pre- and post-treatment levels, but not in cases of the pre-treatment level alone. Though research shows that CA 125 assays are strongly related to each other and are clinically reliable for the quantification of serum CA 125, it is also advised against interchanging results from different methods [15]. Due to the low quality and quantity of data we had on the pretreatment serum CA 125 levels we put focus on the analysis of the post-treatment levels.

Further analyses of post-adjuvant treatment CA 125 level were performed dividing the variable to low- and high-level groups at the optimal cut-off of 21.4 U/mL (sensitivity 86%, specificity 76%). The logistic regression test showed a statistically significant (p < 0.001) correlation between the dichotomised CA 125 parameter and 5-year OS and PFS. The difference in survival in low- and high-level marker groups was considerable, with 5-year OS in the low-level group reaching 82%, which is 13% more than in the complete remission group based on the RECIST criteria. In the high-level group, 5-year OS was only 24%. The multivariate analysis results indicated that the serum CA 125 level after adjuvant treatment is an independent prognostic factor of OS (HR = 9.5) and of PSF (HR = 4.7) in advanced endometrial cancer. Our results are consistent with Hoskins' observation of the significance of low CA 125 level halfway through systemic treatment [14].

Unfortunately, we did not collect data on the Ca 125 levels during follow up, but there is evidence showing that CA 125 elevation can be an early marker preceding clinically evident recurrence [19].

CONCLUSIONS

A low level of post-treatment serum CA 125, defined as below 21.4 U/mL, is a strong marker of good 5-year survival in advanced endometrial cancer patients, with 82%

of patients alive after 60 months, and nearly 71% without recurrence. At the time of the emerging role of TCGA classification there are new ways to determine the prognosis of EC patients, but the availability of the new classification is still low due to the high cost of implementation. CA 125 is a cheap and easily accessible marker that can play an important role in planning individual follow-up schedules for aEC patients and counseling them about expected treatment outcome.

Article information and declarations

Data availability statement
Source data is available from the corresponding author.

Ethics statement
Does not apply due to the retrospective nature of the study.

Author contributions
Konrad Muzykiewicz — 60%, Ewa Iwańska — 5%, Karolina Pniewska — 5%, Maja Janeczek — 5%, Małgorzata Nowak-Jastrząb — 5%, Andrzej Kałamacki — 5%, Kazimierz Karolewski — 5%, Paweł Blecharz — 10%.

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Supplementary material
None.

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