Nadir CA-125 Is Prognostic for Recurrence, but Not for Survival in Patients With Ovarian Cancer

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Abstract

Objective of this study was to evaluate nadir CA-125 in patients with epithelial ovarian cancer**.** 168 patients, who achieved complete remission (no clinical and radiological signs, CA-125< 35 U/ml) after first line treatment were enrolled in the study. The relation between CA-125 and survival were examined using generalized additive models applied to the Cox proportional hazards model. The median CA-125 concentration after the treatment was 10 U/ml (2.7-35 U/ml). No correlation between CA-125 nadir and overall survival was found (p linear = 0.13; p nonlinear = 0.52). Patients with CA-125 serum concentrations of 11 - 25 U/ml and 26 - 35 U/ml had significantly higher risk of recurrence compared to patients with CA-125 concentration ≤ 10 U/ml with HR = 1.865 (P <0.0024) and HR = 2.17 (P <0.018), respectively. Nadir CA125 was not relevant for risk of recurrence in FIGO I and II (p=0.75 and p=0.99, respectively), neoadjuvant chemotherapy (p=0.49 and p=0.26 respectively) or bevacizumab (p=0.066 and p=0.26). Nadir CA-125 is not related to overall survival. Risk of ovarian cancer relapse increase with CA-125 nadir level. However in patients with early stage disease or those receiving neoadjuvant chemotherapy or bevacizumab may not be associated with recurrence risk.

Introduction

The reduction of CA-125 serum concentration to < 35 U/ml remains one of the goals of ovarian cancer (OC) treatment, however it is a poor predictor of complete remission during second look laparotomy (1). In advanced OC lowering CA-125 concentration < 20 U/ml was associated with microscopic remission (2, 3). Several authors found longer progression free survival (PFS) and overall survival (OS) in patients with low CA-125 nadir level; however different cut-off points (5–20 U/ml) were established (4–7) and they were set arbitrarily (4, 6), according to the median (8, 9) or quartile (9) CA125 concentration. On the other hand, the nadir of 5 U/ml is of little use in everyday practice (5). Therefore clinical usefulness of nadir CA-125 in patients with OC is not clear.

The main objective of this study was to evaluate CA-125 nadir as prognostic factor for survival regarding different subgroups of patients.

Results

The detailed characteristics of the study group was presented in our previous paper (10) and showed in Table 1. Almost 70% of women were diagnosed in advanced stage. Most cases were high grade (69.6%), serous type tumors (74%). The median CA-125 concentration at the end of treatment was 10 U/ml (2.7–35 U/ml).

Table 1
Patients' characteristics. The data in the table corresponds to those presented in the previous study (10).

Characteristics		Number (%) / Median (range)
Age		57 (19–86)
FIGO		
	I	42 (25%)
	II	10 (6%)
	III	103 (61.3%)
	IV	13 (7.7%)
Histology		
	Serous	124 (73.8%)
	Endometrioid	18 (10.7%)
	Clear cell	10 (6%)
	Mucinous	4 (2.4%)
	Nondifferentiated	4 (2.4%)
	Mixed	8 (4.8%)
Grade		
	1	16 (9.5%)
	2	35 (20.8%)
	3	117 (69.6%)
Cytoreduction		
	R0	116 (69.1%)
	R1 (≤ 1 cm)	29 (17.3%)
	R2 (> 1 cm)	23 (13.6%)
Neoadjuvant chemotherapy		26 (15.5%)
Bevacizumab		32 (19.1%)
CA-125 before therapy		229.2 U/ml (3.8–6000 U/ml)

Characteristics	Number (%) / Median (range)
Nadir CA-125 after therapy	10 U/ml (2.7–35 U/ml)

CA-125 nadir was not related to overall survival (OS) (p linear = 0.13, p nonlinear = 0.52; Fig. 1). Correlation between CA-125 nadir and recurrence was found (p linear = 0.014, p nonlinear = 0.2; Fig. 2). The plot for recurrence indicated nearly linear increase in risk to ~ 15 U/ml; then it reached plateau with slight increase in risk within the range 25–35 U/ml. According to the plot three groups of patients were determined with different CA-125 nadir level: ≤ 15 U/ml, 16–25 U/ml, 26–35 U/ml. In these groups nadir level was not related to progression free survival (PFS) (log rank test, p = 0.0742).

Considering the median CA-125 nadir and the linear relationship between CA-125 and the risk of recurrence, the cut-off level was changed to ≤ 10 U/ml, 11–25 U/ml, 26–35 U/ml. Figure 3 shows the Kaplan-Meier curves for cumulative PFS rates for patients according to nadir level. PFS was significantly longer for patients with nadir level ≤ 10 U/ml (Fig. 3, Table 2).

Table 2
Ovarian cancer recurrence risk related to CA-125 nadir level after first line treatment in patients with complete remission. A: HR – hazard ratio; B: Confidence interval.

CA-125 nadir	HR[a]	95% CI[b] min	95% CI max	*P*
≤ 10	1.00	-	-	-
11–25	1.87	1.25	2.8	< 0.0024
26–35	2.17	1.14	4.1	< 0.0178

Assessment of CA-125 nadir and recurrence risk was done in subgroups of patients (Table 3). Relationship between risk of recurrence and nadir was confirmed in patients with advanced disease (FIGO III,IV), serous neoplasm, high grade tumors (grade 2 and 3) and with optimal cytoreduction. In patients, who started treatment with neoadjuvant chemotherapy (NACT), received bevacizumab, with locally advanced tumors (FIGO I,II) or did not have elevated pretreatment CA-125 there was no correlation between CA-125 nadir and risk of relapse.

Table 3
Risk of relapse and CA-125 nadir after treatment in subgroups of patients.

Subgroup of patients		CA125 nadir after treatment		
		≤ 10	**11–25**	**26–35**
FIGO I, II (n = 52)	HR	1.00	0.83	0
	P	-	0.75	0.99
FIGO III, IV (n = 116)	HR	1.00	2.38	2.03
	P	-	< 0.001	< 0.037
Serous histology (n = 124)	HR	1.00	2.08	2.43
	P	-	< 0.002	< 0.009
Grade 2, 3 (n = 152)	HR	1.00	2.08	2.59
	P	-	< 0.001	< 0.005
NACT (n = 26)	HR	1.00	1.42	2.13
	P	-	0.49	0.26
Bevacizumab (n = 32)	HR	1.00	2.23	1.2
	P	-	0.066	0.78
Pre-treatment CA-125	HR	1.00	0	-
≤ 35 U/ml (n = 13)	*P*	-	0.99	-
Cytoreduction (R0 and R1) (n = 145)	HR	1.00	2.7	2.72
	P	-	< 0.02	< 0.05

Discussion

In contrast to previous studies, nadir was not related to overall survival. In most of these studies, CA-125 nadir was determined arbitrary (4, 6, 12) or based on median (8, 9, 13, 14) CA-125 or quartile (9). Riedinger et al. performed ROC curves and found nadir CA-125 of 20 U/ml predictive for PFS and OS (7). In our study, the relationship between nadir and the risk of recurrence was investigated using generalized additive models applied to the Cox proportional hazards method. Spline illustrating linear and non-linear effect between nadir and risk of death showed no relationship. Van Altena et al. found longer median OS in patients with nadir < = 5 U/ml, but likelihood ratio test in combination with Cox regression models showed nadir as independent predictor of tumor recurrence (not for OS) (5).

Linear correlation between the risk of recurrence and nadir CA-125 was found. Recurrence risk increased to ~ 15 U/ml, then it reached platau with a little change between 25 and 35 U/ml. Based on this splin, 15

U/ml and 25 U/ml were established as cut-off level. However log rank test was not significant (p = 0.0742) for these borders. The presence of relationship between the nadir and the risk of recurrence argued for setting new cut-off points. 10 U/ml instead of 15 U/ml was chosen for several reasons. As the risk increased to 15 U/ml, it was justified to change cut-off nadir towards lower values (shift to left side). Moreover, it reduced the disproportion in the numbers of patients between groups (~ 70% of patients had nadir < 15U/ml). Ease of application of the results in clinical practice also affected the choice of 10 U/ml as cut-off level.

Different survival was observed in patients with nadir as follow: <10 U/ml, 11–20 U/ml and 21–35 U/ml (20–30 U/ml) (5). In our study, a slightly different risk of recurrence was demonstrated for patients with nadir 11–25 and 26–35 compared to < 10. These results may be caused by a limited number (n = 15) of patients with nadir in the range of 26–35 U/ml. Direct comparison of patients with nadir level 11-25U/ml vs 26–35 U/ml showed no difference in risk of relapse. This is consistent with the publication of Markmann et al (6), who found increased recurrence risk in patients < 10 U/ml and no differences in the risk of relapse between 10–20 U/ml and 20–35 U/ml patients.

Subgroups of patients were distinguished according to clinicopathological factors (Table 3). Not surprisingly there was no correlation between CA-125 nadir and recurrence risk in patients with normal pretreatment CA-125. Although elevated levels of CA-125 are found in 50% of early stage OC, our analysis included them (15). In these patients nadir CA-125 concentration was not helpful in predicting the relapse. Another group of patients with doubtful meaning of nadir are patients treated with bevacizumab. In 32 patients with bevacizumab therapy no correlation between nadir CA-125 and risk of recurrence was found. Gaducci et al.(9) included 11 patients, who received bevacizumab, but they did not calculate risk for this subgroup. Azad et al. showed that the efficacy of anti-angiogenic therapy in the treatment of ovarian cancer may not correspond to the serum CA-125 level (16). These authors concluded that caution should be exercised in using CA-125 among patients treated with molecular agents. Unexpected results were found in patients, who received NACT, because there was no correlation between nadir CA-125 and recurrence risk. Other authors also included patients with NACT (6, 12, 13) however they did not assess risk of recurrence in this subgroup separately. Our study contained only 26 patients, who began treatment with NACT and these observations need confirmation in numerous populations.

It was surprising that in patients with advanced disease the highest risk of relapse was observed in patients with nadir 11–25 U/ml. It was expected that recurrence risk increase with higher level of nadir. Possible explanation of this result is fact that some of these patients received bevacizumab, which may impair outcomes.

Our study had some limitations. As a retrospective analysis selection bias may appeared. Some subgroups of patients contained limited number of patients. Our results concerned only patients with complete radiological, biochemical and clinical remission.

Material And Methods

Study group was presented in details in previous paper (10). Briefly, 168 patients with epithelial ovarian cancer, who achieved complete response after first-line treatment were enrolled in the study. All patients underwent surgery and chemotherapy based on a combination of carbo-/cisplatin with paclitaxel. Complete response was confirmed clinically (no signs and symptoms of disease), radiologically (RECIST) and biochemically (CA-125 < 35 U/ml). The recurrence of the disease was diagnosed on the first appearance of symptoms: clinical or radiological or histopathological/cytological.

Nadir CA-125 concentration was measured in serum within one month after treatment. The CA125 was measured with electrochemoluminescence immunoassay (Roche Diagnostics). All biochemical tests were conducted in one laboratory.

Bioethical Committee of the Medical University of Warsaw approved the study (No AKBE/26/2018). All methods were performed in accordance with the relevant guidelines and regulations. Patients provided informed consent for using medical data in the study.

Statistical Analyses

The data were expressed as a percentage, means and medians. The percentage of women without recurrence during the 5-year observation was presented with the Kaplan-Meier (K-M) method and plotting relevant curves. The relationship between CA-125 and the risk of recurrence were examined using generalized additive models applied to the Cox proportional hazards model to determine curves illustrating both the linear and non-linear relationship of the examined parameter with the estimated recurrence risk. The emergence of a statistically significant non-linear effect was the basis for an approximate determination of limit values of CA125, which in turn were used to identify subgroups of patients for whom K-M curves were drawn. The methodological aspects of the study were based on the textbook by van Belle et al. (11), while SAS / STAT® 9.4 / 14.4, User's Guide, SAS Institute Inc., Cary, NC, USA, 2017 was used to solve the technical and methodological aspects.

Declarations

Acknowledgements: None

Author contributions: SP – study design, acquisition and interpretation of data, manuscript writing; GP – study design, manuscript writing, ZL – analysis of data; DP – manuscript writing; PK – manuscript writing; MB – manuscript revision, supervision

The authors declare no competing interests.

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Figures

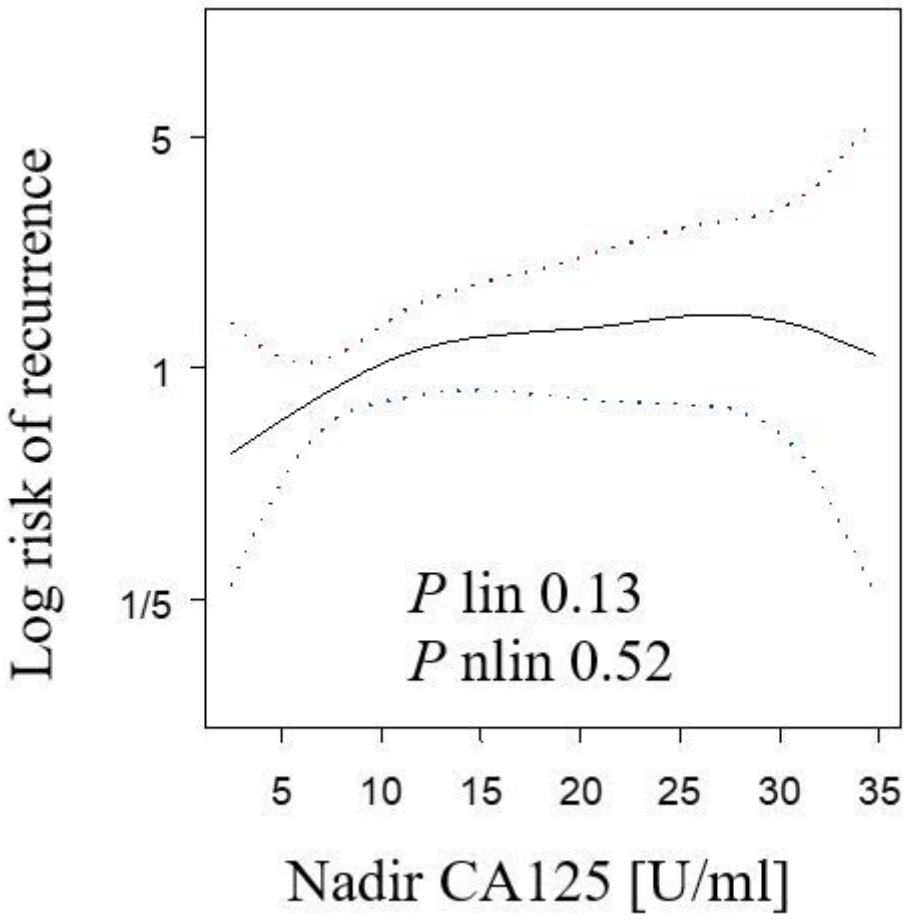


Figure 1

The risk of death and CA-125 nadir level within normal range after first-line treatment.

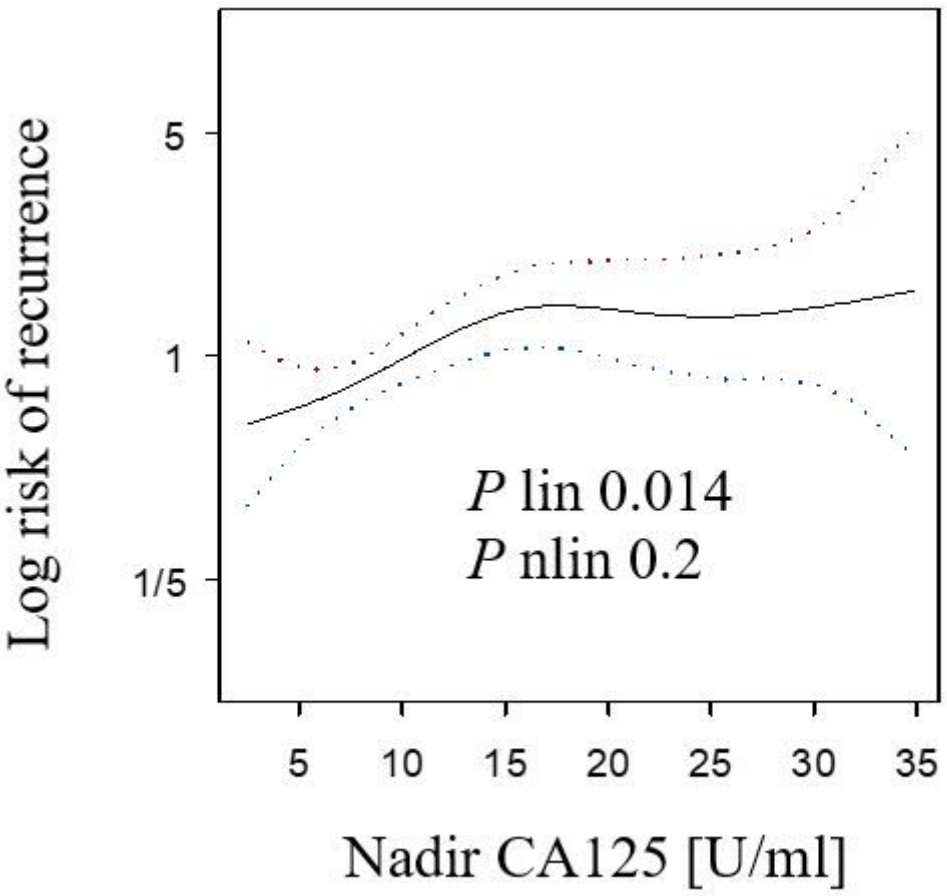
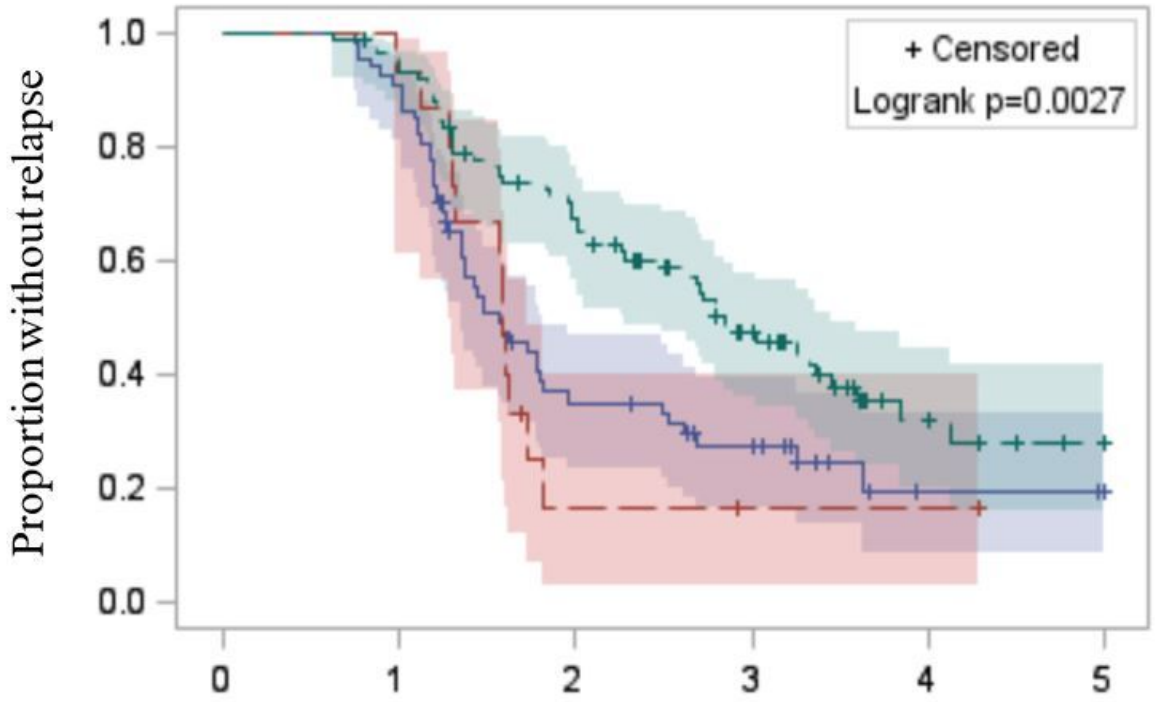


Figure 2

The risk of recurrence and CA-125 nadir level within normal range after first-line treatment. A splin indicated that risk of recurrence initially increased and around 15 U/ml it reached plateau (P linear = 0.014).



Percentage of patients without recurrence					
Time [y] / CA-125	1	2	3	4	5
≤ 10 U/ml	92.95	67.76	47.32	32.04	28.04
11-25 U/ml	91.04	35.23	27.55	19.59	19.59
26-35 U/ml	93.33	16.67	16.67	16.67	-

Figure 3

Kaplan-Meier curves of PFS for patients with different CA-125 nadir level - green ≤ 10 U/ml (n=86); blue 11-25 U/ml (n=67); red 26-35 U/ml (n=15). Significant difference in PFS was achieved with log-rank test ($p < 0.05$).