Diagnostic value of CA125 as a predictor of recurrence in advanced ovarian cancer

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Summary

Purpose: The aim of this study was to establish the guidelines for detecting early recurrences of advanced epithelial ovarian cancer by use of the CA-125 level. *Materials and Methods:* Eighty-five of the patients who met the inclusion criteria were enrolled in this study. The authors examined 25 incremental changes of CA125 from one to 25 IU/ml, and compared the CA-125 value with other prognostic factors. Increases in the CA-125 level from the nadir level were expressed as CA-125- increments. *Results*: Among the 25 increments, a CA-125-8 (eight IU/ml) was selected as the predictor that was the most efficient and time-effective. CA-125-8 had a sensitivity of 91.5%, a specificity of 84.6%, a positive predictive value of 93.1%, a negative predictive value of 81.5%, an efficiency of 89.4%. and a median lead-time of 68.5 days ($p < 0.0001$). *Conclusion:* The authors suggest the incremented CA-125-8 as a predictor of recurrent advanced ovarian cancer.

Key words: Advanced ovarian cancer, CA-125; Early detection of recurrence.

Introduction

Ovarian cancer has the highest mortality rate of all gynecologic cancers. The majority (nearly 75%) of patients with newly-discovered ovarian cancer have advanced disease at the time of diagnosis. Nevertheless, complete clinical remission can be achieved in 80% of advanced disease with the use of optimal cytoreductive surgery followed by adjuvant chemotherapy [1, 2]. However, advanced ovarian cancer ultimately recurs within the first two years after diagnosis in up to 80% of cases, consequently the expected five-year survival rate of advanced ovarian cancer does not exceed 30%-50% [3, 4]. Recently, one study group announced that early treatment for recurrent ovarian cancer based on a rising CA-125 does not appear to improve the overall survival compared with treatment that is commenced upon presentation of symptoms [5]. The clinical study was based on chemotherapy alone. However, it has also been reported that secondary cytoreductive surgery achieves survival benefits in the management of patients with recurrent ovarian cancer [6-11]. It is well-known that localized recurrent disease is more treatable with secondary cytoreductive surgery [12, 13]. Therefore, it is important to inspect the early state of recurrence in order to detect localized or small volume recurrence before dissemination [6, 9]. Currently, recurrence of ovarian cancer is diagnosed by consideration of several factors, including an increase in the level of CA-125, radiologic findings, and clinical symptoms. Generally, among these factors, the CA-125 level changes most rapidly and emerges two to six months earlier than the appearance of new lesions identified by imaging [14-16]. To date, the CA-125 level as a criterion for recurrence is considered to be a two-fold increase in the upper limit of normal (35 IU/ml) [17, 18]. The present study was undertaken to determine the early state of recurrence of advanced epithelial ovarian cancer by analysis of serially-measured CA-125 levels.

Materials and Methods

Patient population

Between January 1995 and May 2008, 571 patients were diagnosed with ovarian cancer at Seoul St. Mary's Hospital. The medical records of all patients were analyzed retrospectively. Eighty-five cases satisfied all of the following criteria: (1) FIGO Stage III-IV; (2) initial serum CA-125 level > 35 IU/ml at the time of diagnosis; (3) complete remission (CR) after proper primary treatment (cytoreductive surgery followed by adjuvant chemotherapy (platinum + taxane) and a normal CA-125 level (< 35 IU/ml); (4) recurrence confirmed with radiographic documentation or surgery; and (5) in patients with no recurrence, sustained CR for at least two years. After the completion of proper primary treatment, patients underwent follow-up every three months for the first two years, every six months thereafter for three years, then annually. A history, physical examination, CA-125, and a radiologic examination were performed in routine follow-up, and chest/abdominal/pelvic computed tomography (CT) or positron emission tomography (PET) scans and chest X-rays were ordered if determined to be clinically necessary. The Institutional Review Board approved this study.

CA-125 level

Serial CA-125 levels were determined during the interval from CR to recurrence or last day of follow-up. Increments of CA-125 levels were calculated by subtracting the baseline nadir

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from subsequently measured values, with the nadir defined as the level within the normal range (< 35 IU/ml) at the time of completion of primary chemotherapy and radiographic CR. In this study, the authors evaluated 25 one-unit increments from 1 - 25 IU/ml.

Statistical methods

The distribution of patient characteristics is presented as a frequency and percentage, and Fisher's exact test was used to compare the differences between patients with recurrence and patients with sustained CR. The median values of the disease-free interval, initial CA-125 level, and nadir were compared using the Wilcoxon rank-sum test. A two-sided *p* value of < 0.05 was considered to be statistically significant.

Results

Characteristics of patients

Table 1 shows the patient characteristics. Fifty-nine (69.4%) patients had an ovarian cancer recurrence and 26 patients had a sustained CR. The majority (71) of the patients (83.5%) had serous tumors and 40 patients (56.3%) had grade II tumors. Of the 85 patients, 63 (74.1%) underwent optimal surgery (no visible residual lesions), with 41 patients (69.5%) in the recurrent group and 22 patients (84.6%) in the sustained CR group (p = 0.1838). Fifty-five patients (64%) underwent second-look surgery, with negative results for 37 patients (67.3%). Specifically, 23 patients (60.5%) in the recurrent group and 14 (82.3%) patients in the sustained CR group had negative results on second-look surgery (p = 0.133). The CA-125 nadir level was similar for both groups (6.0 IU/ml in the recurrent group and 6.17 IU/ml in the sustained CR group; p = 0.973; Table 1). Ten of 85 patients had another pattern for the CA-125 level; specifically, the CA-125 level increased > 35 IU/ml at the time of diagnosis, but had not increased at the time of recurrence. The median disease-free interval for the recurrent group was < one year (362 days; range, 105 - 2,046 days), and the median duration of follow-up for the sustained CR group was 4.6 years (range, two - 12.4 years) after CR. The median frequency for measurement of the CA-125 level during the above follow-up period was six times in the recurrent group and 20 times in the sustained CR group.

Overall trends in diagnostic values and lead times based on the CA-125 level

As the increment of CA-125 increased (from one to 25 IU/ml), the sensitivities decreased from 94.9% to 79.7%; however, the specificities increased from 34.6% to 100% (Figure 1). The efficiencies between the CA-125-8 and CA-125-15 increments were 89.5% higher than the efficiencies of the other CA-125 increments. After calculating the diagnostic and prognostic abilities, the authors identified CA-125-8 as the best predictor of recurrence of advanced epithelial ovarian cancer. The CA-125-8 increment had a sensitivity of 91.5%, a specificity of 84.6%, a positive predictive value of 93.1%, a negative predictive value of 81.5%, and an efficiency of 89.4%.

Table 1. — *Patient characteristics and CA125 levels of recurrent and sustained CR groups.*

	Recurrent (n = 59)	CR sustained (n = 26)	Total- (n = 85)	*p* value*
Stage				0.0755
IIIa	3 (5.1)	3 (11.5)	6 (7.1)	
IIIb	2 (3.4)	3 (11.5)	5 (5.9)	
IIIc	47 (79.7)	20 (76.9)	67 (78.8)	
IV	7 (11.9)	0 (0.0)	7 (8.2)	
Grade	n = 56	n = 15	n = 71	0.1072
I	2 (3.6)	3 (20.0)	5 (7.0)	
II	32 (57.1)	8 (53.3)	40 (56.3)	
III	22 (39.3)	4 (26.7)	26 (36.6)	
Histology type				0.0347
Serous	53 (89.8)	18 (69.2)	71 (83.5)	
Endometrioid	4 (6.8)	4 (15.4)	8 (9.4)	
Clear	0 (0.0)	2 (7.7)	2 (2.4)	
Mucinous	1 (1.7)	0 (0.0)	1 (1.2)	
Others	1 (1.7)	2 (7.7)	3 (3.5)	
Surgery				0.1838
Optimal	41 (69.5)	22 (84.6)	63 (74.1)	
Non-optimal	18 (30.5)	4 (15.4)	22 (25.9)	
Second-look op	n = 38†	n = 17†	n = 55†	0.1330
Pathology (-)	23 (60.5)	14 (82.3)	37 (67.3)	
Pathology (+)	15 (39.5)	3 (17.7)	18 (32.7)	
CA125				
Initial	501 (69-7593)	345 (57-989)	487 (57-7593)	0.0099
Nadir	6.0 (1.2-31)	6.17 (0.59-21)	6.05 (0.59-31)	0.9734

Values are presented as number (percentage) and median (range).
* By Fisher's exact test or Wilcoxon rank sum test.
† Not all cases are included due to missing values.

Table 2. — *Multivariate logistic regression for recurrence.*

Factor	Crude Odd ratio	Crude 95% CI	Crude *p* value	Adjusted Odd ratio	Adjusted 95% CI	Adjusted *p* value
CA125-8	59.4	14.6-242.1	< .0001	127.9	17.1-955.9	< .0001
Stage (IIIc, IV)	3.24	0.89-11.81	0.0747	1.42	0.11-19.02	0.7932
Optimal surgery	0.41	0.13-1.38	0.1502	0.15	0.02-1.21	0.0751
Histology type (serous)	3.93	1.20-12.85	0.0238	4.55	0.46-44.71	0.1941
Initial CA125	1.002	1.00-1.003	0.0439	1.002	0.999-1.005	0.2324
Nadir	1.02	0.95-1.10	0.5965	1.131	0.989-1.294	0.0714

Multivariate logistic regression for recurrence

Table 2 shows the prognostic factors for the prediction of recurrence, CA-125-8, disease stage, optimal surgery, histologic type, initial CA-125 level, and nadir CA-125 level. Based on univariate analysis, CA-125-8, histologic type, and the initial CA-125 level were significant factors for recurrence; however, based on multivariate logistic regression analysis, CA-125-8 was statistically the most significant predictor of recurrence in advanced ovarian cancer (OR for recurrence = 127.9; 95% CI, 17.1-955.9; $p < 0.0001$).

Discussion

Recurrent ovarian cancer is a lethal disease. Furthermore, the optimal timing and modality of second-line therapy for recurrent disease is still a matter of debate. Systemic chemotherapy is generally offered to women with recurrent ovarian cancer and secondary surgical cytoreduc-

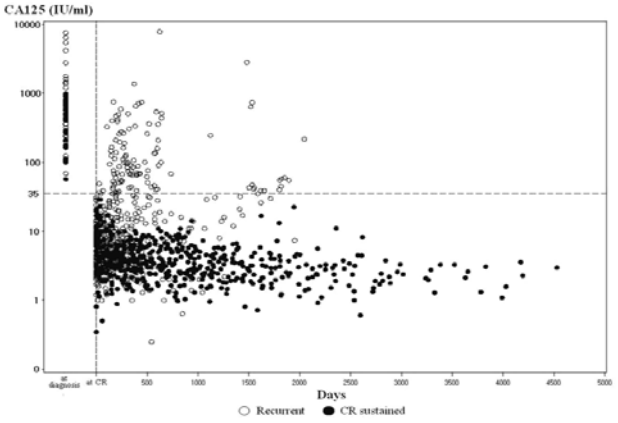

Figure 1. — Distributions of CA125 levels for both groups, recurrent and sustained CR. CA125 levels of the recurrent group were highly scattered within 5.6 years, but those of the sustained CR group were localized within normal levels, at the range of one to ten IU/ml. The axis showing CA125 values is a logarithmic scale.

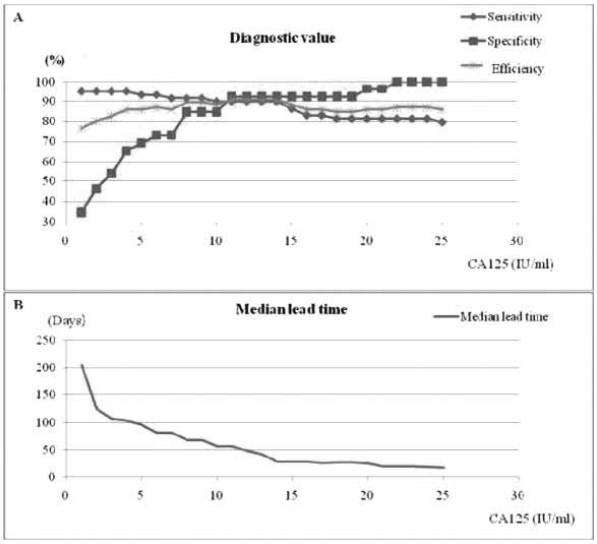

Figure 2. — Trend of diagnostic values (A) and median lead time (B) according to CA125 patterns.

tion is considered for patients with several good prognostic factors, such as an extended progression-free interval of at least 12 months, the potential to eradicate all gross residual disease, response to first-line therapy, and good performance status. There are many reports that optimal secondary cytoreductive surgery followed by chemotherapy provides a significant improvement in the median survival time for select patients [6, 9, 10, 17]. It was suggested that platinum-sensitive patients with seemingly resectable masses should be considered for surgery [6, 10, 17, 18]. CA-125 plays an important role in ovarian cancer, including screening, assessing the response to therapy, and follow-up after completion of initial therapy [19, 20]. A number of studies have attempted to define the CA-125 increment that can predict recurrence of ovarian cancer [15, 16]. A relative increment of 50% or 100% of the CA-125 level from the reference level (25 IU/ml) was introduced as a predictor of recurrence during follow-up after primary therapy [13]. Recent studies have analyzed the CA-125 levels at the time of follow-up after CR in patients with CA-125 levels that remained within the normal limit (< 35 IU/ml) at the time of recurrence. Patients with an absolute increment of five and ten IU/ml or relative increments of 100% from the nadir during follow-up experienced recurrences; thus, a small change in the CA-125 level could be a predictor of disease recurrence [21, 22]. These are notable results for clinicians, but there are several limitations to apply in the clinic. First, these studies enrolled the only patients with CA-125 levels that remained within a normal range after recurrence. It is impossible to predict whether or not a CA-125 level will be elevated after recurrence. Consequently, the studies have not proven useful to predict recurrences; rather a small increment in CA-125 can be a sign for recurrence. Furthermore, there is no rationale to define an absolute increment (five or ten IU/ml) or a relative increment (100%). For these reasons, the authors analyzed the CA-125 levels of all patients and compared diagnostic values and median lead times of 25 increments to define the most effective increment. As shown in Figure 2, the diagnostic values from CA-125-8 to CA-125-15 showed similar effective values. The authors considered median lead-times of each increment, and consequently CA-125-8, with the longest median lead time in this range (from CA-125-8 to CA-125-15), was selected as the best predictor. Furthermore, as compared with the other prognostic factors for recurrence, CA-125-8 was also statistically the most significant predictor, with an odds ratio of 127.9 (95% CI, 17.1 - 955.9) and a $p < 0.0001$. It is difficult to consider CA-125-8 as an early signal for recurrence due to the limited sample size and retrospective design of the study. In addition, most of clinicians may hesitate to accept the results that CA-125-8 is a very small increment. However, if it is considered that the CA-125 levels of the CR group were sustained in a fixed field without fluctuation, a small change of the CA-125 level could also be a significant indicator of a recurrence. Clinicians should only recognize the risk of recurrence and decide the next examination or follow-up date according to the change in the CA-125 level, such as CA-125-8. An early state of recurrence, such as a small volume or localized lesion, can yield options for treatment and a favorable prognostic factor. Therefore, the early detection of recurrence is important and an effort should be made to detect an early state of recurrence, which is a more curable state.

Conclusion

The current study has described the novel concept that an earlier indicator can be applied before the CA-125

level reaches an abnormal range (> 35 IU/ml) for recurrent disease. The authors suggest an increment of eight IU/ml for the CA-125 level among the assessed CA-125 increments as the best predictor. A larger study should be performed to evaluate the validity of these results in a prospective and controlled clinical setting.

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