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# Correlation between Regression of Postoperative CA125 Level in Epithelial Ovarian Cancer and 3-Year Progression Free Survival

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## ABSTRACT

**Objectives:** To examine the relationship between regression of postoperative cancer antigen 125 (CA 125) level in epithelial ovarian cancer and 3-year progression free survival.

**Materials and Methods:** A retrospective study was conducted in patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I-IV epithelial ovarian cancer treated by complete surgical staging or primary debulking surgery between 2013 and 2017 at Prapokklao Hospital, Chanthaburi, Thailand. The study focused on pre-postoperative decline of serum CA 125 level. Three-year progression free survival analyses were conducted by the Kaplan-Meier method, log-rank test and multivariate Cox regression.

**Results:** A total of 125 epithelial ovarian cancer patients were enrolled as 38 patients with < 50% regression of CA 125, 41 patients with 50 - < 80% regression of CA 125 and 46 patients with ≥ 80% regression of CA 125. Survival analysis showed association between regression of CA 125 level and 3-year progression free survival ($p < 0.001$). Patients with ≥ 80% regression of CA 125 had better 3-year progression free survival than the 50 - < 80% and < 50% groups. [hazard ratio (HR) 50 - < 80% = 2.87 [95% confidence interval (CI): 0.90-9.13], HR < 50% = 5.34 [95%CI: 1.74-16.4] vs. ≥ 80% group].

**Conclusion:** Pre-postoperative regression of CA 125 had associated with 3-year progression free survival in patients who underwent primary surgery in epithelial ovarian cancer. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups.

**Keywords:** regression of postoperative CA125, epithelial ovarian cancer, progression free survival.

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# *ความสัมพันธ์ระหว่างค่า CA125 ที่ลดลงหลังผ่าตัดในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี*

***มานิตา รักตประจิต, นฤมล วิเชียรสมสกุล***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อหาความสัมพันธ์ของการลดลงของ CA 125 หลังการผ่าตัดกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี ในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว*

***วัสดุและวิธีการ:*** *รวบรวมข้อมูลจากแฟ้มเวชระเบียนและบันทึกการผ่าตัดของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งรังไข่ชนิดเยื่อบุผิวและได้รับการผ่าตัดระหว่างปีพ.ศ.2556 ถึง 2560 จำนวนทั้งสิ้น 125 คน เพื่อนำมาหาความสัมพันธ์ของค่า CA 125 ที่เปลี่ยนแปลงไปก่อนและหลังผ่าตัดกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี โดยใช้ Kaplan-Meier method, log-rank test, และ multivariate Cox regression analysis ในการวิเคราะห์*

***ผลการศึกษา:*** *จากการศึกษานี้มีผู้ป่วยเข้าเกณฑ์ทั้งหมด 125 คน แบ่งเป็นกลุ่มที่ CA 125 ลดลง ≥ ร้อยละ 80, ร้อยละ 50 ถึง < ร้อยละ 80, < ร้อยละ 50 จำนวน 46 คน, 41 คน, 38 คนตามลำดับ พบว่าค่า CA 125 ที่เปลี่ยนแปลงไปหลังการผ่าตัดมีความสัมพันธ์กับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี ($p < 0.001$) โดยกลุ่มที่ CA 125 ≥ ร้อยละ 80 จะมีระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรคนานมากกว่ากลุ่มร้อยละ 50 ถึง < ร้อยละ 80 และกลุ่ม < ร้อยละ 50 ตามลำดับด้วย hazard ratio (HR) ≥ 50 - < 80% = 2.87 ช่วงความเชื่อมั่น 0.90-9.12 และ HR < 50% = 5.34 ช่วงความเชื่อมั่น 1.74-16.42 เทียบกับกลุ่ม CA 125 ที่ลดลง ≥ ร้อยละ 80*

***สรุป:*** *การลดลงของระดับค่า CA 125 ก่อนและหลังผ่าตัดในกลุ่มผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่ได้รับการผ่าตัดมีความสัมพันธ์กับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี โดยกลุ่มที่ CA125 ≥ ร้อยละ 80 จะมีระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรคนานมากกว่ากลุ่มร้อยละ 50 ถึง < ร้อยละ 80 และกลุ่ม < ร้อยละ 50 ตามลำดับ*

***คำสำคัญ:*** *CA 125 ที่เปลี่ยนแปลงไปหลังการผ่าตัด, มะเร็งรังไข่ชนิดเยื่อบุผิว, ระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค*

## Introduction

Ovarian cancer is the second most common type of female reproductive cancer and the sixth most common type of cancer in Thai women. The most common type of ovarian cancer is epithelial ovarian cancer[1]. Ovarian cancer has a high mortality rate and 14,240 out of 22,280 women in a 2016 study in the United States died from ovarian cancer[2].

Many indicators are used to diagnose ovarian cancer including risk of malignancy index (RMI), risk of ovarian malignancy (ROMA), or cancer antigen 125 (CA 125). Cancer antigen 125 or CA 125 is a high molecular weight glycoprotein coded from the MUC16 gene, which is overexpressed in epithelial ovarian cancer, causing Mullerian duct differentiation[3]. The cut-off value of CA 125 is 35 U/ml. The sensitivity of CA 125 ranges from 61 to 90%, with specificity of 71% to 93%, positive predictive value of 35% to 90% and negative predictive value of 67% to 90%[4]. The CA 125 indicator is commonly used but has certain limitations and can show false-positive results for diseases such as endometriosis, pelvic inflammation and other cancers.

Many attributes affect the prognosis of epithelial ovarian cancer such as residual tumor volume, volume of ascites, histologic subtype, stage, patient age and performance status[1]. CA 125 levels are influenced by several variables[5, 6]. But the serum CA 125 is a tumor marker that is measurable and commonly used in diagnosing and following-up the disease. It is important to monitor serum CA 125 levels and the change pattern of CA 125 levels for predicting prognosis[7]. A few previous studies have examined the correlation between changes in pre-postoperative CA 125 levels and progression free survival of the disease in the Thai population. This study examined the correlation between regression of pre-postoperative CA 125 levels in epithelial ovarian cancer and 3-year progression free survival.

## Materials and Methods

Approval was given by the Ethics Committee of Prapokklao Hospital, Chanthaburi, Thailand to study the medical records and no informed consent was required.

This was a retrospective survival analysis study. Data were collected by reviewing medical records and operative notes of diagnosed 2014 the International Federation of Gynecology and Obstetrics (FIGO) stage I-IV epithelial ovarian cancer patients who underwent complete surgical staging or debulking surgery and received complete adjuvant management according to National Comprehensive Cancer Network (NCCN) guideline at the Department of Obstetrics and Gynecology, Prapokklao Hospital between January 2013 and December 2017. The data were reviewed along a 3-year clinical course from the date of surgery until imaging evidence of disease progression or event of disease-specific death. Exclusion criteria included inoperable patients, patients newly diagnosed ovarian cancer after recent surgical procedure without surgical staging, patients treated with neoadjuvant chemotherapy, patients diagnosed with endometriosis, patients diagnosed with other cell types of ovarian cancer (germ cell tumors, stromal tumors) and patients with no medical records regarding pre-postoperative CA 125, operative findings and pathological reports. The collected data included patients characteristics (age, body mass index, co-morbidities), tumor characteristics (histologic type, FIGO stage), specific data of primary surgery (presence of ascites, residual tumor after primary surgery, pre-postoperative serum CA 125 level) and follow-up data. The time from the date of primary cytoreductive surgery to the time of disease progression or cancer-related death in each patient was calculated follow-up time in months. Right censoring in this study concerned patients who lost to follow-up before recurrence or death during the 3-year clinical course.

The preoperative CA 125 levels were selected as closest to the date of surgery when more than one serum CA 125 level was documented. The postoperative CA 125 levels were obtained as close to the date of surgery as possible in early cancer stage patients who had observation and before the initiation of adjuvant therapy in advanced stage patients who had primary adjuvant chemotherapy. Pre-postoperative changes in

serum CA 125 levels were calculated as the absolute difference values. In addition, the percentage postoperative regression in CA 125 level was calculated for each patient. Based on previous studies[8], the study population was categorized into three groups as ≥ 80% reduction of CA 125, 50% - < 80% reduction of CA 125 and < 50% reduction of CA 125. Patients in whom the postoperative serum CA 125 level increased were included in the latter category. The outcome of primary surgery was categorized into three groups as complete (no residual tumor), optimal (residual tumor diameter ≤ 1 cm) and suboptimal (residual tumor diameter > 1 cm). The histology was categorized into four groups as serous, mucinous, endometrioid and clear cell.

The sample size was calculated at 122 patients by Stata software package, version 13.0. Using statistical values from a previous study, the hazard ratio of ≥ 80% reduction of the CA 125 group was 0.35 and censoring was 0.6[9]. Statistical analyses were to 80% power with alpha at 0.05. Continuous variables were presented as mean with standard deviation and median with interquartile range, while categorical variables were presented as numbers and percentages. Survival analyses were conducted by the Kaplan-Meier method and log-rank test. The relationships of other variables to progression free survival were determined by Cox regression analysis. Statistical significance was set at p value < 0.05.

## Results

A total of 157 patients were diagnosed with epithelial ovarian cancer between January 2013 and December 2017. Two patients newly diagnosed ovarian cancer after recent surgical procedure without surgical staging and 17 treated by neoadjuvant chemotherapy were excluded. Patients with no medical records (operative note, preoperative CA 125, postoperative CA 125) were also excluded (Fig. 1).

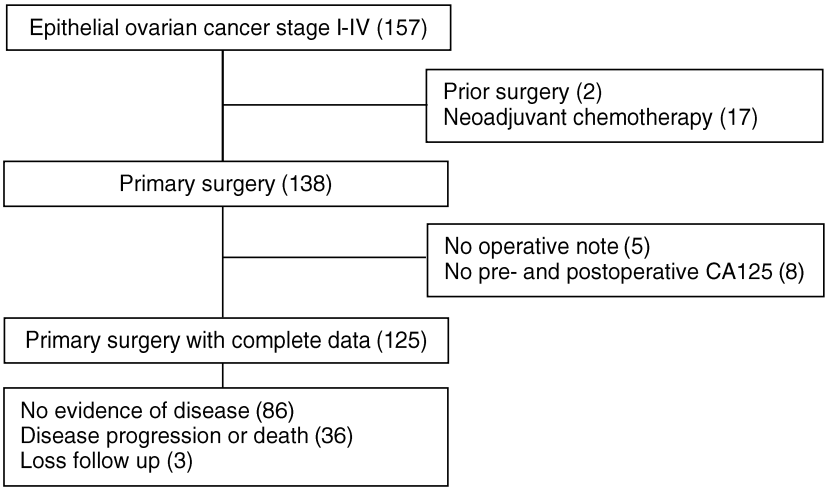



**Fig. 1.** Study flow.

Finally, 125 patients were enrolled and categorized into three groups according to percentage of CA 125 declination assessed in a previous study[5] as < 50%, 50 - < 80% and ≥ 80%. The 125 patients were enrolled as 38 patients with < 50% regression of CA 125, 41 patients with 50 - < 80% regression of CA 125 and 46 patients with ≥ 80% regression of CA 125. Four patients in whom the postoperative serum CA 125 level increased were included in the < 50% category. Most patients in the < 50% group (47.4%) and 50 - < 80% group (46.3%) were diagnosed with epithelial ovarian cancer FIGO stage III, while 50% of the ≥ 80% group were FIGO stage I. In all groups, most patients had optimal surgical outcome (50%, 43.9%, 45.7%) with no

ascites (55.3%, 61%, 56.5%). The most common cell type of the < 50% and 50 - < 80% groups was serous, whereas the ≥ 80% group was endometrioid. Median of preoperative CA 125 in each group were 251 U/ml, 86.80 U/ml and 420 U/ml, respectively. Median of absolute regression in CA 125 levels were 102.5 U/ml, 58 U/ml, 365 U/ml, respectively. Median times from serum preoperative CA 125 measurement to primary surgery were 27.5 days, 21 days and 29.5 days, respectively. Median times from surgery to serum postoperative CA 125 measurement were 30 days, 30 days and 32.5 days, respectively. The median follow-up time was 36 months. There were 5 of the 125 patients died from the ovarian cancer during the course of follow-up. Three patients lost to follow-up during the 3-year clinical course as right censoring in this study, including one patient from the 50 - < 80% group and two patients from the ≥ 80% group (Table 1).

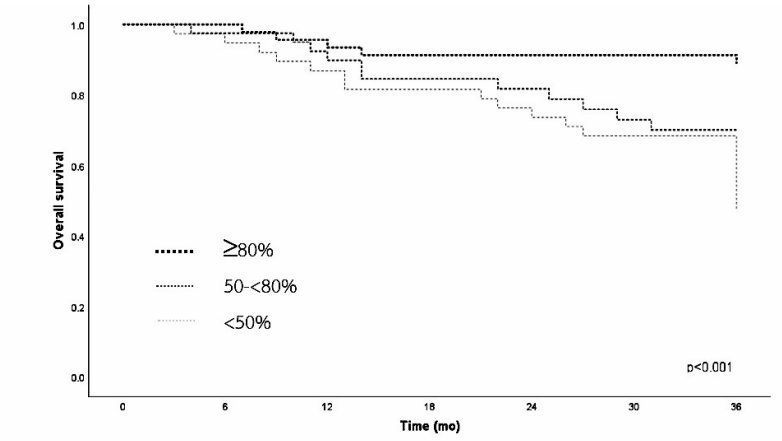
**Table 1.** Characteristic of the population.

| Variable | CA 125 declination | | | |
|---|---|---|---|---|
| | **< 50% (n = 38)** | **50 - < 80% (n = 41)** | **≥ 80% (n = 46)** | **p value** |
| Age (years)* | 53.61 ± 13.05 | 49.03 ± 14.27 | 51.78 ± 12.17 | 0.788 |
| BMI (kg/cm$^2$) * | 21.88 ± 3.65 | 21.74 ± 4.00 | 23.86 ± 4.92 | 0.763 |
| FIGO stage† | | | | 0.094 |
| I | 12 (31.6%) | 12 (29.3%) | 23 (50%) | |
| II | 0 (0%) | 3 (7.3%) | 5 (10.9%) | |
| III | 18 (47.4%) | 19 (46.3%) | 13 (28.3%) | |
| IV | **8 (21.1%)** | **7 (17.1%)** | 5 (10.9%) | |
| Surgical outcome† | | | | 0.819 |
| No residual tumor | 11 (28.9%) | 17 (41.5%) | 16 (34.8%) | |
| Optimal | 19 (50%) | 18 (43.9%) | 21 (45.7%) | |
| Suboptimal | 8 (21.1%) | 6 (14.6%) | 9 (19.6%) | |
| Histology† | | | | 0.074 |
| Serous | 17 (44.7%) | 17 (41.5%) | 10 (21.7%) | |
| Mucinous | 9 (23.7%) | 7 (17.1%) | 8 (17.4%) | |
| Endometrioid | 3 (7.9%) | 9 (22.0%) | 16 (34.8%) | |
| Clear cell | 9 (23.7%) | 8 (19.5%) | 12 (26.1%) | |
| Ascites† | | | | 0.862 |
| Negative | 21 (55.3%) | 25 (61%) | 26 (56.5%) | |
| Positive | 17 (44.7%) | 16 (39%) | 20 (43.5%) | |
| CA 125 (U/ml)‡ | | | | |
| Preoperative | 251 (59.6-520.3) | 86.8 (415-150.5) | 420 (137.8-1147.50) | 0.001 |
| Postoperative | 152.5 (62.8-314.0) | 27 (14.3-57.5) | 20.5 (10.0-44.28) | < 0.001 |
| CA 125 change | 102.5 (16.0-275.3) | 58 (29.1-91.0) | 365 (116.5-1044.0) | < 0.001 |
| Time from CA 125 surgery (day)‡ | | | | |
| Preoperative CA 125 | 27.5 (15.5-32.8) | 21 (14.0-32.0) | 29.5 (14.8-39) | 0.437 |
| Postoperative CA 125 | 30 (28.5-40.3) | 30 (29.0-58.0) | 32.5 (29.8-50.5) | 0.472 |
| Event† | | | | < 0.001 |
| No evidence of disease | 18 (47.4%) | 29 (70.8%) | 39 (84.8%) | |
| Disease progression or death | 20 (52.6%) | 11 (26.8%) | 5 (10.9%) | |
| Loss to follow-up | 0 (0%) | 1 (2.4%) | 2 (4.3%) | |

*mean ± standard deviation, †n (%), ‡median (interquartile range)

BMI: Body mass index, FIGO: International Federation of Gynecology and Obstetrics

The Kaplan-Meier survival curve showed that the ≥ 80% regression CA 125 group had better survival outcome than the 50 - < 80% and < 50% groups (p < 0.001 by log-rank test) (Fig. 2). Multivariate Cox regression analysis with full adjustment by other prognostic factors for survival as mentioned showed that the percentage of CA 125 declination for the < 50% and 80% groups was associated with 3-year progression free survival. The 3-year progression free survival of < 50% regression of CA 125 was 5.34 time worse than the 80% group [HR<50% = 5.34 [95%CI: 1.74-16.42], p = 0.003 vs. the ≥ 80% group, p = 0.011]. Whereas the 3-year progression free survival of 50 - < 80% group was 2.87 worse but this was not statistically significant [HR50-<80% = 2.87 [95%CI: 0.90-9.12], p = 0.075] (Table 2).




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| <50% | 38 | 36 | 33 | 31 | 28 | 26 | 18 |
| 50-79% | 41 | 40 | 37 | 35 | 34 | 31 | 30 |
| ≥80% | 46 | 46 | 43 | 42 | 42 | 42 | 41 |

**Fig. 2.** Kaplan-Meier survival curves by categories of % postoperative regression in CA 125.

**Table 2.** Hazard ratio of % postoperative regression in CA 125.

| CA 125 declination | unadjusted | | | Fully adjusted | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p value | HR | 95%CI | p value |
| < 50% | 5.614 | 2.11-14.96 | 0.001 | 5.340 | 1.74-16.42 | 0.003 |
| 50 - < 80% | 3.100 | 1.08-8.93 | 0.036 | 2.866 | 0.90-9.12 | 0.075 |
| ≥ 80% | 1 | - | 0.002 | 1 | - | 0.011 |

Fully adjusted by age, BMI, FIGO stage, surgical outcome, histology, ascites

HR: hazard ratio, CI: confidence interval, BMI: body mass index, FIGO: International Federation of Gynecology and Obstetrics

## Discussion

This study focused on the relationship between regression of CA 125 level in epithelial ovarian cancer and 3-year progression free survival. Results showed that pre-postoperative CA 125 declination of ≥ 80% group and the < 50% group were associated with 3-year progression free survival. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups, respectively. The < 50% regression of postoperative CA 125 had 5.34 time worse of disease prognosis compared to the ≥ 80% regression group.

This associated relation between pre-postoperative CA 125 declination and 3-year progression free survival in our study concurred with Timmermans et al and Zwakman et al[8, 9]. They studied the prognostic value of perioperative change in CA 125, and reported that the decline in serum CA 125 significantly associated with better survival. The study suggested that the perioperative decline in serum CA125 was an early biomarker that predicts disease-specific survival. According to Yoo et al[10], a study of the relationship between perioperative changes in serum CA 125 levels and progression free survival, our findings were in agreement with the results. The decrease of serum CA 125 levels ≥ 80% after surgery was a prognostic factor for progression free survival.

A strong point of our study was the similarity in characteristics of our population, accuracy of CA 125 and the confounding factor adjustment process. Baseline characteristics of each CA 125 declination group in our study were similar for age, body mass index, FIGO stage, surgical outcome, histology and ascites. The fact that CA 125 measurements at different times affects on postoperative CA 125 because of peritoneal trauma from abdominal surgery procedure[11]. Times from serum preoperative CA 125 measurement to surgery and times from surgery to postoperative CA 125 measurement of each group were also similar. Serum CA 125 level of our study had only a small effect on accuracy. Other prognostic factor adjustment in multivariate Cox regression analysis included body mass index and histology, which were different from Zwakman et al[9].

According to NCCN guideline[12], patients have to visit every 2-4 months for first 2 years and 3-6 months for 3 years for surveillance, this study might be used to assist gynecologist to choose on minimum duration of follow-up periods to accurately assess the recurrence of the disease.

However, our study had some limitations. This was a retrospective study and only 125 patients were enrolled because data collection was performed at a single center, while most complete medical records were available only from 2013.

When correlating the regression of postoperative CA 125 levels and 3-year progression free survival, the more percentage of declination in CA 125 had the better survival outcome. Future studies should include details from multiple centers with a longer data collection period to get more population and study more in role of adjuvant chemotherapy treatment in population that had < 50% CA 125 regression. To improve reliability, a prospective study should be undertaken including date of pre-postoperative CA 125 measurement, onset date of adjuvant chemotherapy and all other essential parameters.

## Conclusion

Pre-postoperative regression of CA 125 had associated with 3-year progression free survival in patients who underwent primary surgery in epithelial ovarian cancer. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups. The < 50% regression of postoperative CA 125 had prognosis 5.34 times worse. To enable role of predicting 3-year progression free survival from regression of postoperative CA 125, more studies should be performed in large prospective studies.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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