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Epithelial ovarian cancer in the young in Siriraj Hospital

Phakawan Thornprateepchot MD,*
Atthapon Jaishuen MD,*
Suwanit Therasakvichya MD,*
Wiboolphan Thitadilok MD,*
Suthipol Udompunturak **

*Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
**Department of Research Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

ABSTRACT

Objective: To access incidence, risk factors, 5-year progression free survival and overall survival in young patients equal or younger than 40 years old with epithelial ovarian cancer (EOC) in Siriraj Hospital.

Materials and Methods: Medical records of patients equal to or younger than 40 years of age diagnosed of EOC and treated in Siriraj Hospital from January 1998 to December 2007 were reviewed for clinical characteristics, treatments, and outcomes. Survival curves were generated using Kaplan-Meier method. Cox regression analysis to determine multivariate factor for recurrence and survival was performed.

Results: Incidence of patients equal to or younger than 40 years old diagnosed of EOC and treated in Siriraj Hospital was 5.8 %. Mean age was 33.4±5.4 years. Sixty five percents o f patients had abnormal high pretreatment CA-125 level. Majority of the patients were in stage I of EOC. Sixty five percents of patients underwent optimal surgery. Adjuvant chemotherapy was applied in 83.7%. Twenty two patients were dead with a median time to death of 3 months. Five-year progression survival was 84.8% and 5-year overall survival was 76% with the median follow up time of 20.5 months. Abnormal pretreatment CA-125 level and suboptimal surgery were the only two independent prognostic factors for survival .

Conclusion: The incidence of patients equal to or younger than 40 years of age diagnosed of EOC and treated in was 5.8% of all EOC. The 5-year overall survival rate was 76%. From multivariate analysis, the independent prognostic factors for overall survival were abnormal high pretreatment CA-125 level and suboptimal surgery with the hazard ratio of 6.69 (P<0.001) and 2.79 (P=0.033).

Keywords: epithelial ovarian cancer, women ≤ 40 years, survival rate

Introduction

Ovarian cancer was the second most common gynecologic cancer in United States after endometrium cancer, accounting for 3% of all female cancers and 27% of cancer of all female genital cancers.[1] In Thai women, ovarian cancer is the

second most common gynecologic cancer after cervical cancer. The age-standardized incidence rate of ovarian cancer is 5.2 per 100,000 women per year or 1,655 new cases were found.[2] Ovarian cancer was the most common cause of death from malignancy in women due to its rapid progression and lack of effective screening methods. Epithelial ovarian cancer (EOC) acquired about 80% of all ovarian cancers.[2,3] According to the International Federation of Gynecology and Obstetrics (FIGO) guideline, the current standard treatment of EOC consists of complete surgical staging, including hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, infracolic omentectomy, peritoneal washing, multiple peritoneal biopsy, and maximal cytoreductive surgery, followed by taxane/platinum-based adjuvant chemotherapy.[4]

EOC was predominantly a disease of postmenopausal women with the median age of diagnosis of 60 years, and a peak incidence in 75-79 year age group.[5] There were 3-17% of all EOC patients are aged less than 40.[6-10] Fertility is one of the most important issues related to quality of life in younger patients with EOC. Fertility sparing surgery, with preservation of ovarian tissue in one or both ovaries and uterus in young patient has been proposed in selected patients with EOC.[11] However, the results and limits of these treatments remain unclear. We therefore reviewed the incidence, prognostic factors, treatments, recurrence, and survival outcome in the EOC patients equal or younger than 40 year of age in Siriraj hospital in the last 10 years.(1998-2007)

Materials and Methods

After obtaining the ethical committee, faculty of Medicine, Siriraj Hospital Mahidol University approval, we searched an institutional database to retrospectively identify patients with EOC who had been treated at Siriraj Hospital from January 1998 to December 2007. Patients' medical records were reviewed to obtain demographic and clinical data, including presenting symptoms; pretreatment cancer antigen-125 (CA-125) level, histologic cell type, stage of disease; and grade of disease; operative procedure; type of adjuvant chemotherapy; date of recurrence; date of last follow-up or death.

Inclusion criteria

1. Histologically confirmed EOC
2. Equal or younger than 40 year of age
3. Treatment with surgery, or chemotherapy at Siriraj Hospital

Exclusion criteria

1. Second primary malignancy
2. Borderline epithelial ovarian cancer

All of the patients underwent exploratory laparotomy. Using FIGO criteria for ovarian cancer, staging was assigned on the basis of surgical and pathological findings.[4] Optimal surgery was determined as the surgery that had the maximum diameter of residual tumor equal to or less than 1 cm.[12]

Most of the patients were scheduled for post-operative follow-up every 3 months for 2 years, and then every 6 months afterward. Descriptive statistics were presented as percentage. The time of diagnosis was considered the date of the primary surgical procedure. Progression free survival was calculated from the date of surgery/last chemotherapy (in adjuvant chemotherapy case) to the date of first recurrence. Overall survival was calculated from the date of surgery/last chemotherapy (in adjuvant chemotherapy case) to the date of death/last follow up. The time to recurrence and death or latest contact was determined.

We used Kaplan-Meier survival curves to evaluate survival durations by preoperative CA-125 level, histologic cell type, grade of disease, stage of disease, operative procedure, and adjuvant chemotherapy. We also used Cox regression analysis to determine the multivariate factors that affect recurrence and survival of EOC. The maximum p value that was considered statistically significant is 0.05.

Results

From January 1998 to December 2007, 1580

patients with EOC were treated at our institution; 92 (5.8%) of them were equal to or younger than 40 year of age. Mean age was 33.4 ± 5.4 years (13-40). Table 1 shows the characteristics of the 92 patients in the study population. Pelvic mass and pelvic pain are the two most common presenting symptoms. Sixty five percent (60/92) had abnormal pretreatment CA-125 level. Mucinous carcinoma was the most common histological cell type. Majority of the patients were in stage I of EOC. However, 65.2% of patients (60/92) underwent optimal operative procedure, including hysterectomy, bilateral salphingo-oophorectomy, with less than 1 cm of residual disease. Adjuvant chemotherapy was applied in 83.7 % of patients (77/92), including single platinum and platinum-based combination chemotherapy.

Fourteen patients had recurrence of disease with a median time to recurrence of 9.4 months (0-24.9). Twenty two patients were dead with a median time to death of 3 months (0.2-43.9).

Using Kaplan-Meier analysis, the median progression free survival and median overall survival were not reached. The 5-year progression free survival was 84.8% and 5-year overall survival was 76% with the median follow up time of 20.5 months (1-120 months). According to Table 2, stage of the disease, suboptimal surgery and type of adjuvant chemotherapy appeared to be the significant factors which associated with recurrence of ovarian cancer. When using multivariate analysis (Table 3), only suboptimal surgery was statistically significant.

Factors associated with survival were shown in the Table 4. Pretreatment CA-125, stage of the disease, suboptimal surgery and adjuvant chemotherapy were found to be affected (Fig. 1-4). However, stage of disease and type of adjuvant chemotherapy was not associated with the survival when using multivariate analysis (Table 5).

Table 1. Patients characteristics

Characteristics	No.	Percent
Age (year)		
≤ 20	2	2.2
21-30	24	26.1
31-40	66	71.7
Presenting symptoms		
Pelvic mass	55	59.8
Pelvic pain	23	25
Abdominal distension	13	14.1
Bleeding per vagina	1	1.1
Pretreatment CA-125 level (U/ml)		
≤ 35	21	22.8
> 35	60	65.2
No data	11	12
Histologic cell type		
Mucinous	33	35.9
Serous	20	21.7
Clear cell	18	19.6

Characteristics	No.	Percent
Endometrioid	12	13.
Mixed	9	9.8
Grade		
1	33	35.9
2	10	10.9
3	11	12
Unknown/missing	38	41.2
Stage		
I	52	56.5
II-IV	40	43.5
Operative procedure		
Suboptimal	32	34.8
Optimal	60	65.2
Adjuvant therapy		
Platinum alone	4	4.4
Platinum and cyclophosphamide	37	40.2
Platinum and taxane	36	39.1
None	15	16.3

Table 2. Recurrence by patients characteristics

Characteristics	No. of Patients	No. of Recurrence	Median progression free survival (months)	p value
Preoperative CA-125 (U/mL)				0.182
≤ 35	60	9	1880	
> 35	21	4	67.5	
Histologic cell type				0.069
Serous carcinoma	20	6	568.5	
Mucinous carcinoma	33	2	472	
Endometriod carcinoma	12	0	2178.5	
Clear cell carcinoma	18	4	394	
Mixed epithelial carcinoma	9	2	342	
Grade				0.983
1	33	3	1718.5	
2	10	1	548	
3	11	1	1381.5	

Characteristics	No. of Patients	No. of Recurrence	Median progression free survival (months)	p value
Stage				0.02
I	52	5	2261	
II-IV	30	9	570	
Operative procedure				0.014
Suboptimal	32	7	534	
Optimal	60	7	1935	
Adjuvant therapy				0.01
Platinum and cyclophosphamide	37	3	2190	
Platinum and taxane	36	8	253	

Table 3. Multivariate analysis of prognostic factors of recurrence

	Progression free survival		
Prognostic factor	**Hazard Ratio**	**95% Confident Interval**	**p value**
Stage			
I	Reference		
II-IV	1.373	N/A	0.241
Operative procedure			
Suboptimal	Reference		
Optimal	3.501	1.21-10.17	0.021

Table 4. Survival by patients characteristics

Characteristics	No. of Patients	No. of Deaths	Median survival duration (months)	p value
Preoperative CA-125 (U/mL)				<0.001
≤ 35	60	7	1935	
> 35	21	13	6805	
Histologic disease types				0.16
Serous carcinoma	20	5	669.5	
Mucinous carcinoma	33	7	709	
Endometrioid carcinoma	12	0	2178	
Clear cell carcinoma	18	7	417.5	
Mixed epithelial carcinoma	9	3	342	
Stages				<0.001

Characteristics	No. of Patients	No. of Deaths	Median survival duration (months)	p value
I	52	5	2261	
II-IV	30	17	591	
Grades				0.765
1	33	5	2190	
2	10	2	599	
3	11	2	1381.5	
Operative procedure				0.03
Suboptimal	32	14	649	
Optimal	60	8	1956	
Adjuvant therapy				0.04
Platinum and cyclophosphamide	37	5	2275.5	
Platinum and taxane	36	12	254	

Table 5. Multivariate analysis of prognostic factors of death

Prognostic factors	Overall survival		
	Hazard Ratio	95% Confident Interval	P value
Preoperative CA-125 (U/mL)			<0.001
≤ 35	Reference		
> 35	6.692	2.58-17.35	
Stage			0.217
I	Reference		
II-IV	1.521	N/A	
Operative procedure			0.033
Suboptimal	Reference		
Optimal	2.786	1.09-7.14	

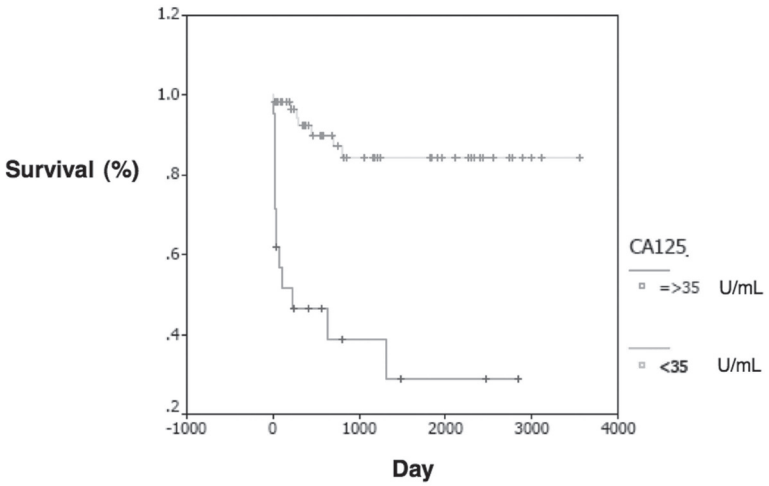

Fig. 1. Kaplan-Meier Survival Curves by pretreatment CA-125 level

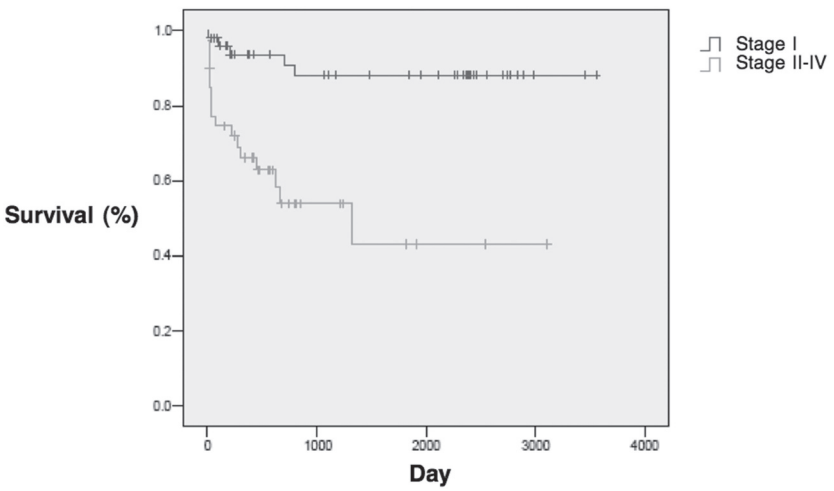

Fig. 2. Kaplan-Meier Survival Curves by stage of disease

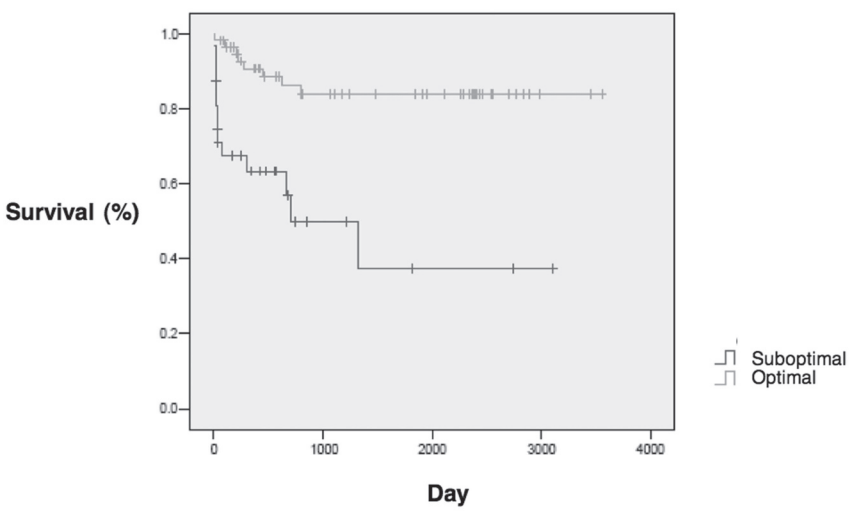

Fig. 3. Kaplan-Meier Survival Curves by operative procedure

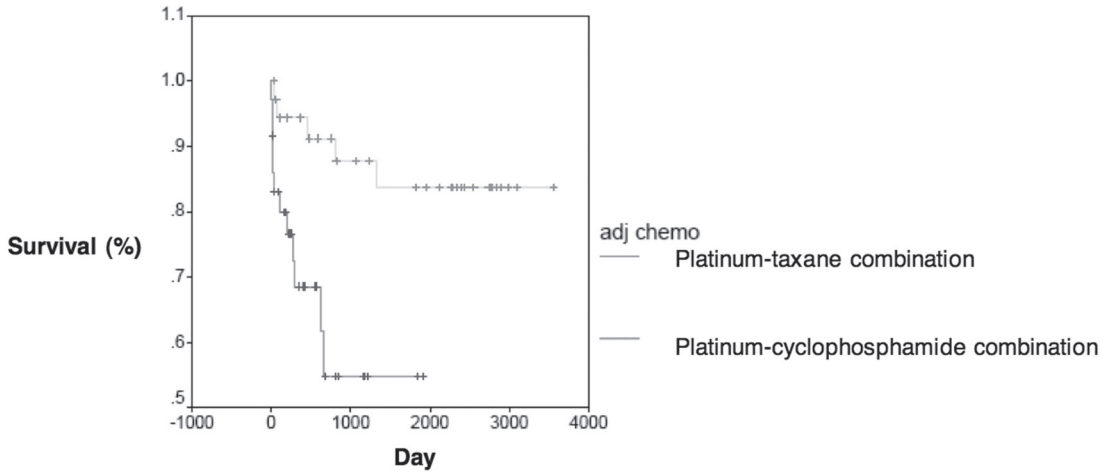

Fig. 4. Kaplan-Meier Survival Curves by type of adjuvant chemotherapy

Discussion

Ovarian cancer is the second most common gynecologic cancer in Thailand after cervical cancer. It is the most common cause of death from malignancy in women. About 80% of all ovarian cancers were epithelial type.[2,3] In younger patients with epithelial ovarian cancer, fertility-sparing surgery was not well defined.

In our study, the incidence of EOC in patients under the age of 40 was 5.8 % (92/1580). EOC occurs more common among women over 50 years of age with the peak incidence at 75-79 years of age.[5] Most of the patients (66/92) were in 31-40 years old. The others were under the age of 30 and we found 2 cases having EOC under the age of 20 year. The youngest one was 13 years old, presenting with pelvic mass. She underwent unilateral salpingo-oophorectomy which revealed mucinous carcinoma. She was assumed to have stage IA without evidence of disease at 76 months of follow up. Another case was 18 year old with pelvic pain. She also underwent the same fertility-sparing surgery which revealed endometrioid carcinoma, stage IC. No evidence of disease was detected at 92 months.

The patients in this study were in the reproductive age. Only 17% (16/92) of patients underwent complete surgical staging, including hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, infracolic omentectomy, peritoneal washing, multiple peritoneal biopsy, and maximal cytoreductive surgery.[4] The reasons of incomplete surgical staging are advanced disease, surgery from the other hospital, and attempt fertility preservative surgery. However, the surgeons tried to remove as much disease as possible in order to reach the optimal surgery. Therefore, we assigned the stage for all patients using modified FIGO criteria for ovarian cancer on the basis of surgical and pathological findings.

The majority of women with epithelial ovarian cancer have vague and nonspecific symptoms.[13] Our study showed 60 % of the patients presented with pelvic mass and 56% of all patients were in stage I of disease. CA-125 levels are useful in predicting the presence of disease, but negative levels are insensitive determinant of the absence of disease.[13] Sixty five percent of the patient had pretreatment CA-125 level more than 35 U/mL which considered abnormal.[14] Our study showed that the abnormal high pretreatment CA-125 level was associated with shorter overall survival. The histologic cell types were consist of 5 majority subtypes, including mucinous, serous, endometrioid, clear cell, and mixed epithelial carcinoma. The progression free survival and overall survival had no

difference in each group of patient. The grade of disease was also showed no statistic significance to progression free survival.

Concerning type of adjuvant chemotherapy, single agent platinum was used in only 4.3%. Therefore, we excluded this group from survival analysis. Platinum-cyclophosphamide combination showed longer progression free survival and overall survival than platinum- taxane combination. However, currently accepted management of adjuvant chemotherapy for ovarian cancer is platinum-taxane combination. In our institute's guideline, we still used platinum-cyclophosphamide combination as a standard treatment for EOC stage I-II. This may be the confounding factor. Twenty two patients were dead, 17 (77.2%) were in stage IIc – IV, and the other 5 were in stage Ic. These data showed that most of the dead cases were in advanced stage which may cause the short median time to death in this study.

Most series reported the 5-year overall survival rates of 72-85%.[6,11,15,16] Our series also reported the 5-year survival rate of 76%. We found that pretreatment high CA-125 level and optimal surgery were the independent prognostic factors with the hazard ratio of 6.69 and 2.78, respectively. For the 5-year progression free survival, the prior studies reported the rate of 60-73%,[11,15] which was less than 84.8% from our study. The majority of our patients were in stage I disease may effected this result. The optimal surgery was only independent factor that associated with longer progression free survival. From multivariate analysis, the suboptimal surgery was the only significant hazard ratio for both progression free survival and overall survival. We recommend optimal cytoreductive surgery for all EOC patients. For the patient who still need fertility, the preservation of uterus and some part of ovary with removal of all visible tumors is optional. Pretreatment CA-125 level is also the option for prediction of survival of patients.

To our knowledge, this is the first study of EOC in the young in Thailand. However, our study has several limitations. Firstly, this study was retrospective and the pathology reports were not reviewed; as a result, some important information were not complete, such as data on CA-125 level, grade of disease. Secondly, not all patients underwent surgery by gynecologic oncologist. The extent of surgery may not reach the optimal operation. We reviewed ten years data, found the trend of increasing number of young patients with EOC (27 patients in 1998-2001, 22 patients in 2002-2004, and 44 patients in 2005-2007). This could be the result of different life style, including diet or the other factors. The further study may help us to solve this problem. The fertility outcome of the patients who had fertility sparing surgery with or without adjuvant chemotherapy is also interesting to study in the future.

In conclusion, the incidence of EOC in the patients equal to or younger than 40 years of age is 5.8% of all EOC. The 5-year overall survival rate was 76%. From multivariate analysis, the independent prognostic factors for overall survival were abnormal pretreatment CA-125 level and suboptimal surgery with the hazard ratio of 6.69 ($P<0.001$) and 2.79 ($P=0.33$), respectively.

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มะเร็งรังไข่ชนิดเยื่อบุผิวในสตรีอายุน้อยกว่า 40 ปีของ รพ.ศิริราช

ผกาวรรณ ธรประทีปโชติ, อรรถพล ใจชื่น, สุวนิตย์ ธีระศักดิ์วิชยา, วิบูลพรรณ ฐิตะดิลก, สุทธิพล อุดมพันธุรัก

วัตถุประสงค์ *: เพื่อศึกษาอุบัติการณ์ ปัจจัยเสี่ยง อัตราการรอดชีวิตที่ 5 ปี และการพยากรณ์โรคของมะเร็งรังไข่ชนิดเยื่อบุผิวในสตรีที่มีอายุน้อยกว่าหรือเท่ากับ 40 ปีที่มารับการรักษาใน รพ. ศิริราช*

วัสดุและวิธีการ *: เป็นการศึกษาวิจัยข้อมูลแบบย้อนหลังจากแฟ้มประวัติของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งรังไข่ชนิดเยื่อบุผิวที่มีอายุน้อยกว่าหรือเท่ากับ 40 ปี และรับการรักษาตัวใน รพ. ศิริราช ตั้งแต่มกราคม 2541 ถึง ธันวาคม 2550 แล้วนำข้อมูลที่ได้มาวิเคราะห์ทางสถิติ (Kaplan-Meier method and Cox regression analysis)*

ผลการศึกษา *: อุบัติการณ์ของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งรังไข่ชนิดเยื่อบุผิวที่มีอายุน้อยกว่าหรือเท่ากับ 40 ปีและรับการรักษาตัวใน รพ. ศิริราช เท่ากับร้อยละ 5.8 อายุเฉลี่ยของกลุ่มผู้ป่วยที่ศึกษา เท่ากับ 33.4±5.4 ปี, ค่าซีรัมซีเอ 125 (CA125) ก่อนการรักษาอยู่ในระดับสูงพบร้อยละ 65 ของผู้ป่วยทั้งหมด ส่วนใหญ่ของผู้ป่วยอยู่ในระยะที่ 1 ของโรค ร้อยละ 65 ของผู้ป่วยได้รับการผ่าตัดอย่างเพียงพอ (optimal operative procedure) ร้อยละ 83.7 ได้รับการรักษาตามด้วยการให้ยาเคมีบำบัด การศึกษาพบผู้ป่วยเสียชีวิต 22 คน โดยมีค่าเฉลี่ยของเวลาการเสียชีวิต เท่ากับ 3 เดือน อัตราการเกิดซ้ำและอัตราการเสียชีวิตของโรคที่ 5 ปี เท่ากับร้อยละ 84.8 และ 76 ตามลำดับ โดยมีค่าเฉลี่ยของระยะเวลาการติดตามโรคเท่ากับ 20.5 เดือน จากการวิเคราะห์ข้อมูลทางสถิติ (multivariate analysis) พบว่าค่าซีรั่มซีเอ 125 (CA125) อยู่ในระดับสูงก่อนได้รับเคมีบำบัด การได้รับการผ่าตัดอย่างไม่เพียงพอ (suboptimal surgery) เป็นปัจจัยสำคัญที่มีผลต่ออัตราการเสียชีวิตของโรค*

สรุป *: อุบัติการณ์ของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งรังไข่ชนิดเยื่อบุผิวที่มีอายุน้อยกว่าหรือเท่ากับ 40 ปีและรับการรักษาตัวใน รพ.ศิริราช เท่ากับร้อยละ 5.8 ของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว อัตราการการรอดชีวิตของโรคที่ 5 ปี เท่ากับร้อยละ 76 จากการวิเคราะห์ข้อมูลทางสถิติ (multivariate analysis) พบว่ามีเพียงค่าซีรัมซีเอ 125 (CA125) อยู่ในระดับสูงก่อนได้รับเคมีบำบัดและ การได้รับการผ่าตัดอย่างไม่เพียงพอ (suboptimal surgery) มีความเสี่ยงต่อการเสียชีวิตของโรคอย่างมีนัยสำคัญทางสถิติ [hazard ratio of 6.69 (P<0.001) and 2.79 (P=0.033)] ตามลำดับ*