
GYNAECOLOGY

Survival Outcomes Between Clear Cell and Non-Clear Cell Epithelial Ovarian Cancer

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ABSTRACT

Objective: To compare the 5-year survival rates of women with clear cell (CCC) versus those with non-clear cell (non-CCC) epithelial ovarian cancer.

Materials and Methods: Retrospective study was performed on patients with epithelial ovarian cancer who had undergone treatment at Rajavithi Hospital from January 1995 to December 2006. Five-year survival rate was compared between the clear cell (n=196) and non-clear cell (n= 304) epithelial ovarian cancer.

Result: The mean age of patients with CCC was 49.7 years compared to 49.1 years for non-CCC group. Of 196 patients with CCC, 99 patients (50.5%) were in stage I. Of 304 patients with non-CCC, 100 patients (32.9%) were in stage I. Most of patients with CCC had optimal surgery and received paclitaxel and platinum (PT) regimen whereas most of patients with non-CCC had optimal surgery and received chemotherapy other than PT regimen. Median follow up time was 46.0 months. The 5-year survival rates were 60.4% for patients with clear cell and 63.8% for patients with non-clear cell group ($p<0.001$).

Conclusion: The overall 5-year survival rate of patients with CCC was significantly poorer than non-CCC epithelial ovarian cancer (60.4% VS 63.8%).

Keywords: clear cell ovarian cancer, non-clear cell ovarian cancer, survival rate

Introduction

Epithelial ovarian cancer has the highest fatality-to-case ratio of all the gynecologic malignancies. Jemal, et al estimated that 21,550 women in the United States would be diagnosed with the ovarian cancer in 2009. Of these women, 14,600 would die due to this disease⁽¹⁾. The Surveillance Epidemiology and End Results Program Database (SEER) showed that the median age of the patients with ovarian cancer that

would be diagnosed was 63 years⁽²⁾. The age-adjusted incidence rate was 13.3 per 100,000 women per year. This could be estimated that 1.39% of women born today will be diagnosed with ovarian cancer at some point during their lifetime⁽²⁾.

Kosiyatrakul, et al showed that ovarian cancer was the third most common gynecologic cancer after cervical cancer and endometrial cancer in Thailand. Over 80% of ovarian cancer was epithelial type. The

age-standardized incidence rate (ASR) was 5.0 per 100,000 women per year and the age of Thai women diagnosed with ovarian cancer was around 55-60 years⁽³⁾.

Sugiyama et al showed that 15% of all epithelial ovarian cancer was clear cell ovarian cancer (CCC)⁽⁴⁾. The clinicopathologically characterized features of CCC were huge mass, unilateral, and usually associated with endometriosis. Moreover, it was also associated with deep vein thrombosis and hypercalcemia⁽⁴⁾. Although CCC is often found in an early stage, the response rate to adjuvant chemotherapy is worse than other type of epithelial ovarian cancer⁽⁴⁾. Many investigators still debate on the survival rate of CCC⁽⁴⁾.

The objective of the present study was to compare the 5-year survival rates of women with CCC versus those with non-CCC epithelial ovarian cancers at Rajavithi Hospital.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) of Rajavithi Hospital. The oncologic data records of the Rajavithi Hospital were used to identify all cases of ovarian cancers during 1995-2006. There were 775 cases diagnosed with epithelial ovarian cancer. Fig. 1 showed trial profiles of the study. Heintz, et al reported the overall 5-year survival rate of 40% in patients with serous type, 58.6% for clear cell type, 59.6% for endometrioid type and 62.8% for mucinous type⁽⁵⁾. The sample size was calculated from the study of Heintz et al⁽⁵⁾. The significant level was 0.05 and power of test was 80%. Thus, the sample sizes of this study were 125 cases for each group. However, since 125 cases were the lowest number of sample size for study, we collected 196 cases for CCC and 304 cases for non-CCC groups to give the better results. The inclusion criteria were patients who 1) had clear cell, serous, mucinous or endometrioid ovarian cancer 2) underwent complete surgical staging 3) received chemotherapy. Every case that met the inclusion criteria was selected. Exclusion criteria were 1) patients who had coincident with other cancer 2) incomplete therapeutic data.

The important data of this study were 1) age of the patients 2) stage of the disease 3) histology 4) operative procedures 5) first-line adjuvant chemotherapy 6) date of first diagnosis and 7) date of the last follow up or death.

All patients underwent exploratory laparotomy for either primary surgery or interval debulking surgery and received chemotherapy. FIGO nomenclature was used for staging⁽⁶⁾. Optimal surgery was defined as the maximum of residual tumor < 2 cm at any site⁽⁷⁾. Pelvic and/or para-aortic lymphadenectomy was done and numbers of nodes removed were collected. The chemotherapy regimens using in this study were paclitaxel and platinum (PT), single platinum or platinum-based combination regimen other than PT. The standard chemotherapeutic regimen for treatment of epithelial ovarian cancer at Rajavithi Hospital prior to 2002 was platinum with cyclophosphamide \pm doxorubicin, while it was platinum and paclitaxel after 2002. All patients were scheduled for surveillance every 3 months for the first 2 years, and then every 6 months until 5 years after completing treatment. The patients who had recurrent disease were treated with second line chemotherapy.

Descriptive data were presented as percentage, mean, and median. Characteristic data were evaluated using chi-square and Kruskal-Wallis tests. Survival rate was calculated from the date at first diagnosis to the date of death or the last follow up. The survival distributions were calculated by the Kaplan-Meier method. The significance of survival difference was compared by log-rank test. Multivariate analysis was performed using Cox proportional Hazard regression model. A probability value of less than 0.05 was considered statistically significant. The SPSS version 11.5 (SPSS Inc., Chicago, IL) was used for statistical analysis.

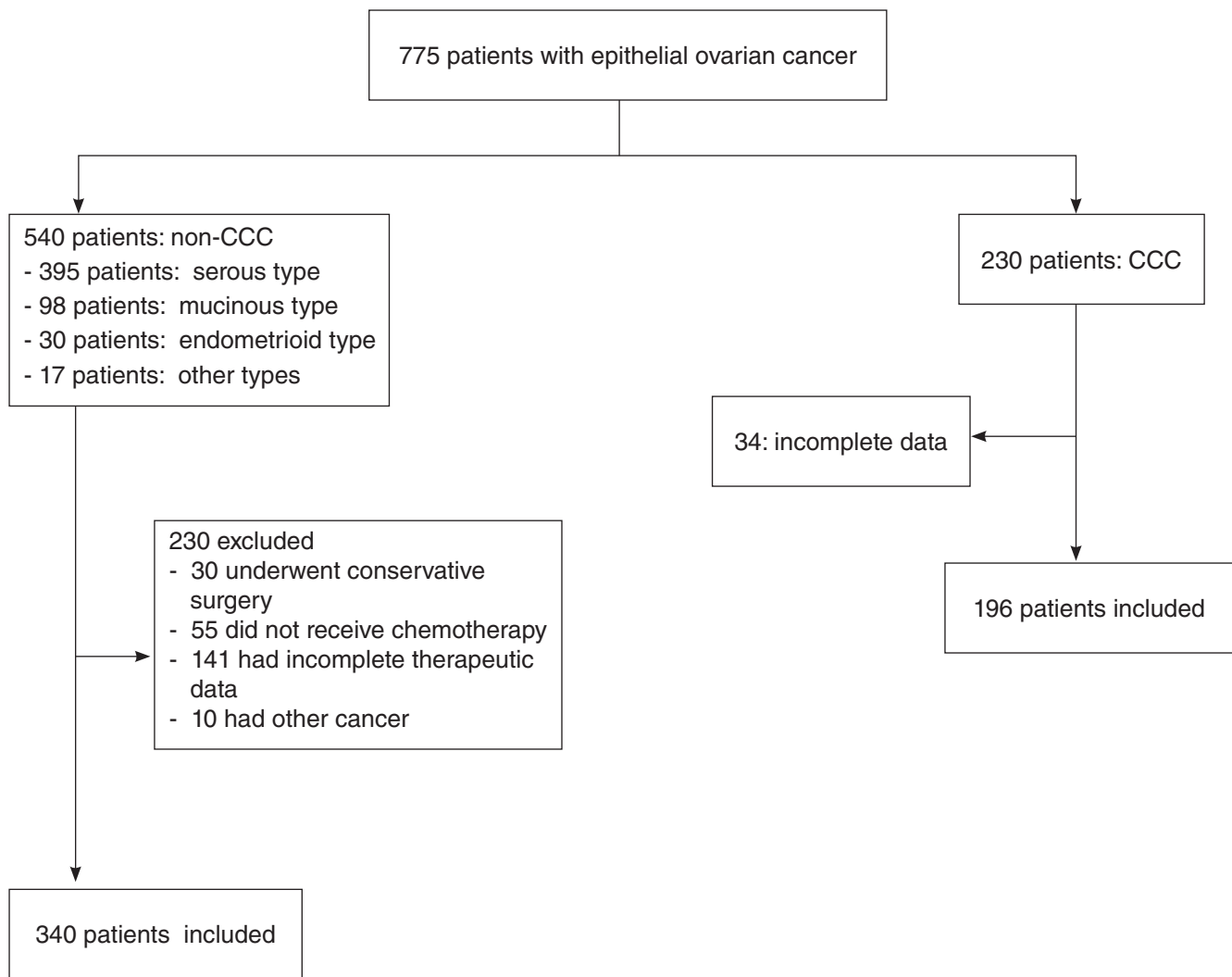


Fig. 1. Trial profile

Results

The mean age of the patients who were diagnosed with CCC was 49.7 years compared to 49.1 years for the non-CCC group. Most of them were diagnosed before the age of 60. Of 196 patients who had CCC, 99 patients (50.5%) were in stage I. Of 304 patients who had non-CCC, 100 patients (32.9%) were in stage I.

We organized all types of treatment into 3 groups. The first group was suboptimal surgery with post-operative adjuvant chemotherapy. The chemotherapeutic regimens that were used in the first group were single platinum, platinum-based combination regimen or

regimen other than PT. The second group was optimal surgery with PT regimen. This group was used as the reference. The last group was optimal surgery with post-operative single platinum or platinum-based combination regimen other than PT. The chemotherapeutic regimen was chosen on the gynecologic oncologist's preference. Table 1 showed the characteristics of the patients. Most patients received the treatments categorized in the third group. Twenty-nine patients with CCC (14.8%) had suboptimal surgery whereas 68 patients with non-CCC (22.4%) had suboptimal surgery. Ninety-two patients with CCC (46.9%) had optimal surgery and received

PT regimen. One hundred and sixty-five patients with non-CCC (54.3%) had optimal surgery and received chemotherapy other than PT regimen.

With regard to a number of removed nodes, Table 1 showed that the median number of nodes removed in CCC and non-CCC was 12 nodes (range 1-49 nodes). The number of positive nodes in CCC versus in non-CCC is not significantly different ($p=0.184$).

The median follow up time in this study was 46.0 months (range 0.4-169.3 months). Nearly half of the patients with CCC (45.9%) and 40.5% in non-clear cell group had recurrence ($p=0.228$). The most common site of recurrence is intra-abdomen in both groups. Moreover, we found that the status at last follow up of patients was not significantly different in both groups ($p=0.076$).

The 5-year overall survival rate of patients with CCC was 60.4% comparing to 63.8% of non-CCC group ($p<0.001$) (Table 2).

In the patients with CCC, the 5-year survival rate was 82.3% in those with stage I disease, 70.3% in those with stage II disease, 31.0% in those with stage III disease and 0.09% in those with stage IV disease. Moreover, the results showed that the 5-year survival rate was 10.7% in patients who had suboptimal surgery and received chemotherapy other than PT regimens, 77.9% in patients with optimal surgery and received PT regimen and 62.0% in patients with optimal surgery and received chemotherapy other than PT.

In the patients with non-CCC, the 5-year survival rate was 90.0% in those with stage I disease, 83.5% in those with stage II disease, 40.3% in those with stage III disease and 13.2% in those with stage IV disease. We also found that the 5-year survival rate was 21.5% for patients with suboptimal surgery and received chemotherapy other than PT regimen, 67.7% for patients with optimal surgery and received PT regimen and 84.0% for patients with optimal surgery and received chemotherapy other than PT.

With regard to stage I and III disease, the 5-year survival rate was significantly better in the non-CCC group than in CCC group. When considered the type of treatment, we found that patients with non-CCC who

had suboptimal surgery and received chemotherapy other than PT regimen and patients who had optimal surgery and received chemotherapy other than PT regimen had significantly better 5-year survival rate than those in CCC group. Fig. 2 showed the comparison of survival functions between CCC and non-CCC.

The results showed that CCC, stage III, IV of disease, and the suboptimal surgery and received chemotherapy other than PT regimen were poor prognostic factors for epithelial ovarian cancers based on multivariate analysis. Patients who diagnosed with CCC had 1.95 times more likely to die ($p<0.001$) (Table 3).

We also compared the prognostic factor between CCC and non-CCC. The results showed that stage III, IV of disease, optimal surgery with adjuvant treatment other than PT regimen and the suboptimal surgery with chemotherapy other than PT regimen were poor prognostic factors (Table 4).

Discussion

In this study, we compared the characteristics of patients in CCC and non-CCC groups and found that the mean age of patients diagnosed with CCC versus with non-CCC was not significantly different ($p=0.096$). The mean age of patients with CCC at diagnosis was 49.7 years and 49.1 years for patients with non-CCC. This finding corresponds with data from Sugiyama, et al, who studied 101 patients with CCC and 235 patients with serous adenocarcinoma of the ovary⁽⁴⁾. They found that there was no significant difference of the median age at diagnosis between two groups (51 vs 54 years). In contrary, many previous studies showed that the mean age of patients at diagnosis with CCC was around 55 years and was younger than those with non-CCC⁽⁸⁻¹³⁾. Our results showed the lower mean age of patients at the diagnosis than those presented in other studies. Since all the patients in this study underwent surgery, this implied that the condition of the patients were good enough to have the operation. This could be further implied that the age of the patients in our studies was lower than those selected in other studies.

Table 1. Characteristics of patients with epithelial ovarian cancer according to histology

Characteristics	Total	Non-CCC n=500	CCC n=304	p-value n=196
Mean age at diagnosis	49.4 (10.5)	49.1 (11.2)	49.7 (9.4)	0.096
≤ 60 years	431 (86.2%)	257 (84.5%)	174 (88.8%)	0.18
> 60 years	69(13.8%)	47(15.5%)	22(11.2%)	
Stage at diagnosis				0.001*
Stage I	199 (39.8%)	100 (32.9%)	99 (50.5%)	
Stage II	96 (19.2%)	70 (23.0%)	26 (13.3%)	
Stage III	173 (34.6%)	113 (37.2%)	60 (30.6%)	
Stage IV	32 (6.4%)	21 (6.9%)	11 (5.6%)	
Type of treatment				<0.001*
Suboptimal Sx + adjuvant Rx other than PT	97 (19.4%)	68 (22.4%)	29 (14.8%)	
Optimal Sx +PT regimen	163 (32.6%)	71 (23.4%)	92 (46.9%)	
Optimal Sx +adjuvant Rx other than PT regimen	240 (48.0%)	165 (54.3%)	75 (38.3%)	
Lymphadenectomy	285 (57%)	162 (53.3%)	123 (62.8%)	0.037*
No. of node removed	12 (1-49)	12 (1-49)	12 (1-34)	0.393
Positive nodes	44 (15.4%)	21 (13.0%)	23 (18.7%)	0.184
Recurrence	214 (42.6%)	124 (40.5%)	90 (45.9%)	0.228
Site of recurrence				0.002*
Intra-abdomen	185 (86.4%)	114 (92.7%)	71 (78.0%)	
Distant metastasis	29 (13.6%)	9 (7.3%)	20 (22.0%)	
Status at last follow-up				0.076
Alive without disease	266 (53.2%)	170 (55.9%)	96 (49.0%)	
Alive with disease	26 (5.2%)	19 (6.3%)	7 (3.6%)	
Death from disease	187 (37.4%)	106 (34.9%)	81 (41.3%)	
Death from other diseases	21 (4.2%)	9 (3.0%)	12 (6.1%)	

Data presented as mean +SD, n (%) or median (range)

Table 2. Univariate analysis between prognostic factors and survival rate

Variables	n	5-yr survival rate(n)		p-value
		Non-CCC	CCC	
Overall survival rate	500	63.8% (n=304)	60.4% (n=196)	<0.001*
Age				
≤60 years	431	65.9% (257)	60.7% (174)	0.293
>60 years	69	56.0% (47)	65.9% (22)	0.422

Table 2. Univariate analysis between prognostic factors and survival rate (Cont.)

Variables	n	5-yr survival rate(n)		p-value
		Non-CCC	CCC	
Stage				
Stage I	199	90.0% (100)	82.3% (99)	0.010*
Stage II	96	83.5% (70)	70.3% (26)	0.277
Stage III	173	40.3% (113)	31.0% (60)	0.031
Stage IV	32	13.2% (21)	0.09% (11)	0.177
Treatment				
Suboptimal Sx+adjuvant Treatment other than PT	97	21.5% (68)	10.7% (29)	0.023*
Optimal Sx with PT regimen	163	67.7% (71)	77.9% (92)	0.317
Optimal Sx +adjuvant treatment other than PT	240	84.0% (165)	62.0% (75)	0.003*

Abbreviation: CCC = clear cell carcinoma, Sx = surgery, PT = paclitaxel and platinum regimen, Rx = treatment

*significance at level $p < 0.05$

Table 3. Multivariate analysis of prognostic factors

Prognostic factors	n	HR	95% CI of HR		p-value
			Lower	Upper	
Type					
Non clear cell	304	1(Ref)	-	-	-
Clear cell	196	1.95	1.43	2.66	<0.001*
Stage					
Stage I	199	1(Ref)	-	-	-
Stage II	96	1.59	0.92	2.74	0.098
Stage III	173	4.89	3.15	7.62	<0.001*
Stage IV	32	6.53	3.41	12.48	<0.001*
Treatment					
Optimal Sx +PT	163	1(Ref)	-	-	-
Suboptimal Sx	97	2.90	1.89	4.45	<0.001*
Optimal Sx +others adjuvant	240	1.18	0.79	1.78	0.421
Age					
≤ 60 years	431	1(Ref)	-	-	-
> 60 years	69	0.88	0.58	1.32	0.536

Abbreviation: HR = hazard ratio, PT = platinum and paclitaxel regimen, Sx = surgery

*significance at level $p < 0.05$

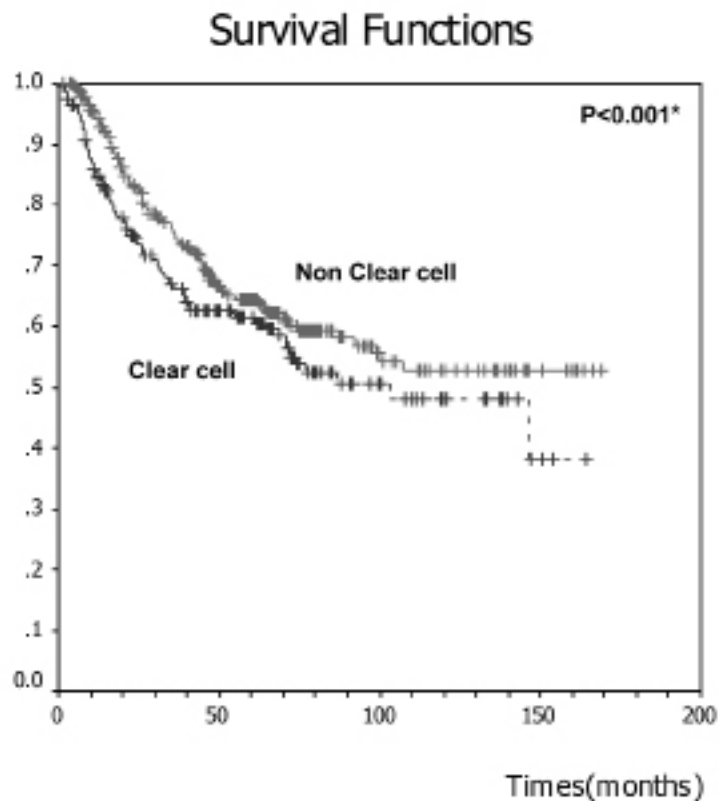


Fig. 2. Survival function between clear cell and non-clear cell ovarian cancer

When the relationship between the stage of the disease and histology was considered, Sugiyama, et al reported the higher number of patients who had stage I CCC than those who had stage I serous type (48.5% vs 16.6%)⁽⁴⁾. Kenedy, et al studied 64 patients with CCC and 163 patients with high grade serous tumor. They found that 50% of patients with CCC and 7% of non-clear cell were in stage I⁽⁸⁾. Pather, et al reported that about half of their patients with CCC were in stage I⁽⁹⁾. Our findings showed that 50.5% of patients with CCC and 32.9% of patients with non-CCC were in stage I.

In the present study, we found that the overall 5-year survival rate of CCC was significantly worse than those in non-CCC group (60.4% VS 63.8%, $p < 0.001$). The 5-year survival rate of patients with stage I, III disease was significantly poorer in the CCC group than those in non-CCC group. Sugiyama, et al reported no significant difference of 5-year survival rate between CCC and serous type in stage I, II and IV⁽⁴⁾. They also reported that survival rate of patients with stage III who diagnosed with CCC was significantly shorter than

those with serous type. Likewise, Goff, et al showed that the median survival rate of patients with stage III CCC was shorter than those with serous type⁽¹⁰⁾. In contrary, Kenedy, et al⁽⁸⁾ and Chan, et al⁽¹¹⁾ noted no statistical difference of survival rate in each stage between CCC and non-CCC. Pectasides, et al also reported no significant difference of median survival in the advanced stage patients between CCC and serous group⁽¹²⁾. These different outcomes may be due to high variation of number of studied patients, different of number and types of chemotherapeutic regimen and debulking status.

In the subgroup analysis, patients with CCC who had suboptimal surgery and received chemotherapy other than PT regimen revealed significantly shorter 5-year survival rate than those with non-CCC. This result was similar to the earlier study which revealed 5-year survival rate was 10.2% in patients who had suboptimal surgery (>2 cm) in CCC group compared to 23.9% in serous group ($p < 0.0005$)⁽⁴⁾.

Although platinum with or without paclitaxel was

the current standard chemotherapy regimen for epithelial ovarian cancer, the 5-year survival rate of patients with CCC was significant shorter than those in non-CCC group. This result may be suggested that CCC was chemoresistance. This finding was confirmed by Goff, et al who reported that 70% of patients with CCC had progressive disease while they were on platinum based chemotherapy compared to 23% of patients with serous type⁽¹⁰⁾. Likewise, Pectasides, et al reported the overall response rate of patients with CCC was significantly lower than those with serous type but no significantly shorter survival⁽¹²⁾.

Moreover, we also found that 5-year survival rate of patients with CCC who had suboptimal surgery and received chemotherapy other than PT regimen and patients who had optimal surgery and received chemotherapy other than PT regimen was shorter than those in non-CCC group (10.7% VS 21.5% and 62% VS 84%, respectively). However, the 5-year survival rate of patients who had optimal surgery and received PT regimen was not significantly different between two groups. We concluded that patients with CCC should receive chemotherapy with PT regimen for better survival rate.

In our study, all of patients underwent complete surgical staging so there was no selection bias. Limitation of our study is that the pathological specimens were not reviewed. There were different chemotherapeutic regimens among selected patients as described above. This may have impacts on the 5-year survival rate of the patients.

Conclusion

The overall 5-year survival rate of patients with CCC was significantly poorer than non-CCC epithelial ovarian cancer (60.4% VS 63.8%).

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อัตราการรอดชีวิตระหว่างผู้ป่วยมะเร็งรังไข่เนื้อเยื่อผิวหนังชนิด clear cell และ non-clear cell

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วัตถุประสงค์ : เพื่อเปรียบเทียบอัตราการรอดชีวิตที่ระยะ 5 ปี ระหว่างผู้ป่วยมะเร็งรังไข่เนื้อเยื่อผิวหนังชนิด clear cell (CCC) และ non-clear cell (non-CCC)

วัสดุและวิธีการ : การศึกษาย้อนหลังเก็บรวบรวมข้อมูลผู้ป่วยมะเร็งรังไข่เนื้อเยื่อผิวหนังที่มาับการรักษาที่โรงพยาบาลราชวิถี ตั้งแต่ มกราคม พ.ศ.2538 ถึง ธันวาคม พ.ศ.2549 ผู้ป่วยมะเร็งรังไข่ชนิด CCC 196 ราย และผู้ป่วยมะเร็งรังไข่ชนิด non-CCC 304 ราย

ผลการศึกษา : อายุเฉลี่ยของผู้ป่วยกลุ่มมะเร็งรังไข่ชนิด CCC เท่ากับ 49.7 ปี เปรียบเทียบกับผู้ป่วยมะเร็งรังไข่ชนิด non-CCC มีอายุเฉลี่ย 49.1 ปี ในกลุ่มผู้ป่วยชนิด CCC จำนวน 196 ราย ผู้ป่วย 99 ราย (ร้อยละ 50) ได้รับการวินิจฉัยระยะที่ 1 ส่วนผู้ป่วยชนิด non-CCC จำนวน 304 ราย มีผู้ป่วย 100 รายอยู่ในระยะที่ 1 การรักษาส่วนใหญ่ที่ผู้ป่วยในกลุ่ม CCC ได้รับความรอดชีวิตได้ optimal surgery และได้รับการรักษาด้วยยาเคมีบำบัดสูตร PT ขณะที่ผู้ป่วยในกลุ่ม non-CCC ส่วนใหญ่ได้รับการผ่าตัดได้ optimal surgery และรักษาด้วยยาเคมีบำบัดสูตรอื่นที่มีใช้ PT ระยะเวลาเฉลี่ยในการติดตามหลังการรักษาคือ 46 เดือน อัตราการรอดชีวิตที่ระยะ 5 ปี ของผู้ป่วยกลุ่ม CCC เท่ากับ ร้อยละ 60.4 ขณะที่ในกลุ่ม non-CCC เท่ากับร้อยละ 63.8 ($p < 0.001$)

สรุป : มะเร็งรังไข่เนื้อเยื่อผิวหนังชนิด CCC มีอัตราการรอดชีวิตที่ระยะ 5 ปีต่ำกว่ากลุ่ม non-CCC อย่างมีนัยสำคัญทางสถิติ
