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Treatment outcome of stage Ic ovarian clear cell carcinoma compared to non-clear cell type

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Objective : *The aim was to evaluate the treatment outcome of stage Ic clear cell carcinoma of the ovary compared to that of non-clear cell carcinoma of the same stage.*

Methods : *Having searched the tumor registry database of the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital from June 1997-December 2002, we enrolled all patients with stage Ic (according to FIGO staging criteria) clear cell carcinoma who underwent complete surgical staging procedure. Patients with non-clear cell adenocarcinoma of the ovary were enrolled by the same criteria as control group. They all received post-operative adjuvant chemotherapy with single-agent platinum based regimen. The clinical characteristics, survival time, and recurrence free survival of both groups were compared.*

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Result : *A total of 56 patients with stage Ic carcinoma of the ovary were recruited into this study. The mean age was 50 years (36 - 86 years old) in both groups. The median follow-up duration in the clear cell and non-clear cell groups were 61 months (5 - 120 months) and 67 months (15 -103 months), respectively.*

The mean tumor diameter in the clear cell group was significantly larger than that of the control group (12.96 vs. 9.89 cm; P-value = 0.001). Other clinical characteristics of the two groups were similar.

The recurrence rate of the clear cell and non-clear cell groups were 46.4% vs. 14.2% (P = 0.004) and the median time to recurrence were 10.5 months (2 – 35 months) vs. 8 months (3 - 28 months), respectively. The estimated 5-year survival for the clear cell group was significantly lower than that of the non-clear cell (53.6% vs. 85.7%; P-value = 0.01).

Conclusion : *Clear cell carcinoma of the ovary stage Ic have lower 5-year survival rate and recurrence free survival than that of the patients with non-clear cell epithelial ovarian carcinoma in the same stage. Combined chemotherapy may be needed to improve the survival of patients in stage Ic clear cell ovarian cancer.*

Keywords : *Ovarian cancer, Clear cell carcinoma, Stage Ic.*

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ยุทธเดช ทวีกุล, เรืองศักดิ์ เลิศขจรสุข, นิพนธ์ เขมะเพชร, ธาริณี แม่นชนะ, นครินทร์ ศิริทรัพย์, พงษ์เกษม วรเศรษฐสิน, อภิชัย วสุรัตน์, ตุลย์ สิทธิสมวงศ์, วิชัย เตมรุ่งเรืองเลิศ, ดำรง ตรีสุโกศล. ผลการรักษาผู้ป่วยมะเร็งรังไข่ชนิด Clear cell carcinoma ระยะ 1C เปรียบเทียบกับชนิด Non clear cell. จุฬาลงกรณ์เวชสาร 2553 พ.ค. – มิ.ย.; 54(3): 213 – 23

วัตถุประสงค์ : *เพื่อศึกษาผลการรักษาในผู้ป่วยมะเร็งรังไข่ชนิด Clear cell carcinoma ระยะ 1C เปรียบเทียบกับชนิด Non clear cell carcinoma ที่ระยะเดียวกัน*

วิธีการศึกษา : *ได้ศึกษาข้อมูลของผู้ป่วยมะเร็งรังไข่กลุ่ม Clear cell carcinoma เปรียบเทียบกับชนิด Non clear cell ระยะ 1C ในโรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนมิถุนายน 2540 ถึงเดือนธันวาคม 2545 ผู้ป่วยทุกรายได้รับการผ่าตัด Complete surgical staging และได้รับเคมีบำบัดหลังการผ่าตัดเป็น Single-agent platinum based regimen ข้อมูลของผู้ป่วยทั้งสองกลุ่มได้นำมาเปรียบเทียบกันได้แก่ ข้อมูลทางคลินิก ระยะเวลาการอยู่รอด และระยะเวลาการปลอดโรค*

ผลการศึกษา : *จำนวนผู้ป่วยกลุ่มมะเร็งรังไข่ระยะ 1C ทั้งหมด 56 ราย อายุเฉลี่ยของผู้ป่วยทั้งสองกลุ่มคือ 50 ปี (36 - 86 ปี) ระยะเวลาการตรวจติดตามในกลุ่ม clear cell และ non clear cell มีค่ามัธยฐาน 61 เดือน (5 - 120 เดือน) และ 67 เดือน (15 -103 เดือน) ตามลำดับ*

ขนาดของก้อนมะเร็งรังไข่ในกลุ่ม Clear cell มีขนาดใหญ่กว่าอย่างมีนัยสำคัญ (12.96 ซม. vs 9.89 ซม. P-value = 0.001) อัตราการกลับเป็นซ้ำของโรคในกลุ่มผู้ป่วย Clear cell คิดเป็นร้อยละ 46.4 เปรียบเทียบกับกลุ่ม Non clear cell ที่ร้อยละ 14.2 (P = 0.004) ระยะเวลาการกลับเป็นซ้ำในกลุ่มผู้ป่วย Clear cell เท่ากับ 10.5 เดือน (2 - 35 เดือน) เปรียบเทียบกับกลุ่ม Non clear cell ที่ 8 เดือน (3 - 28 เดือน) อัตราการอยู่รอดที่ 5 ปีของผู้ป่วย Clear cell carcinoma ต่ำกว่าอย่างมีนัยสำคัญ (ร้อยละ 53.6 vs ร้อยละ 85.7, P-value = 0.01)

สรุป : *อัตราการอยู่รอดที่ 5 ปี และระยะเวลาการปลอดโรคของผู้ป่วยมะเร็งรังไข่ชนิด Clear cell carcinoma มีระยะเวลาสั้นกว่าชนิด Non clear cell อย่างมีนัยสำคัญ การให้เคมีบำบัดแบบหลายชนิดร่วมกัน Taxane อาจเพิ่มระยะเวลาการรอดชีวิตในผู้ป่วยกลุ่มนี้*

คำสำคัญ : *มะเร็งรังไข่, clear cell carcinoma, ระยะ 1c.*

Ovarian carcinoma is the sixth most frequently found cancer in Thai women. [1] The incidence of the cancer varies among races. Epithelial ovarian cancer is the most common type of ovarian carcinoma, accounting for 85% of all cases.[2] It is the leading cause of death among all gynecological cancers. The death rate from ovarian cancer exceeds those of the cervical and endometrial carcinomas combined. In the United States, there were estimated 24,400 new cases in year 2003, and approximately 14,300 women died from the disease in the same year.[3] Most patients in their early stages of the disease are asymptomatic; therefore, two-thirds of the diagnosed patients are in advanced stages and have grave prognoses. Rates of long-term survival among patients with early stages of the disease (stage I or II) can be as high as 80 to 95%, whereas patients with advanced disease (stage III or IV) have lower survival rates, 10 to 30 percent. [4,5]

Clear cell carcinoma has been recognized as having distinctly histological entity according to the World Health Organization's classification of ovarian tumor since 1973. [6] Clear cell carcinoma constitutes of 5 - 10% of the surface epithelial ovarian cancer. [7] Many data show that clear cell carcinoma of the ovary has a distinctly different clinical behavior from other epithelial ovarian carcinomas, namely: a) it frequently presents as a large pelvic mass, and up to 60% of the patients with clear cell carcinoma have stage I disease; b) it rarely occurs bilaterally; c) it is often associated with endometriosis; d) hypercalcemia is observed at a high frequency. [8 - 13] Patients with stage I ovarian cancer usually have favorable prognosis. However, patients with clear cell carcinoma have poorer prognoses than those with other pathological types of epithelial ovarian carcinoma especially in early stages.[10] A significant proportion of women (20 - 50%) with stage I clear cell ovarian carcinoma have recurrence and die of their malignancies. [10,14] Previous reports on the survival of patients with early stages of clear cell ovarian cancer were possibly biased by limited staging information, such as lymph node status, that affected the outcome of the treatment. Furthermore, there has not been any definite consensus on the adjuvant chemotherapy regimen in stage Ic ovarian cancer.

We conducted a study to evaluate the outcome of the treatment of clear cell carcinoma of the ovary stage Ic (based on the FIGO classification) compared to non-clear cell carcinoma at the same stage (control group) when all patients underwent complete surgical staging (total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and/or para-aortic lymphadenectomy and peritoneal washing for cytology).

Materials and Methods

Having searched the tumor registry database of the Department of Obstetrics and Gynecology of King Chulalongkorn Memorial Hospital from June 1997 - December 2002, we recruited all patients with stage Ic clear cell carcinoma who underwent surgical staging procedure (i.e. total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and/or para-aortic lymphadenectomy and peritoneal washing for cytology). Stage Ic ovarian carcinoma was defined when the tumor is either stage Ia or Ib, with or without tumor on the surface of one or both ovaries, or with ruptured capsule, or with ascites containing malignant cells, or with positive peritoneal wash, according to

the FIGO staging criteria.

The exclusion criteria were as follows: a) the patient having undertaken incomplete surgical staging procedure; b) the patient had admixture of other histological types; c) the patient having undertaken any surgery from other hospitals. Patients with non-clear cell adenocarcinoma were enrolled under the same criteria as control group. They all received post-operative adjuvant chemotherapy with single-agent platinum based regimen (Carboplatin or Cisplatin). The dosage of Carboplatin in this regimen was calculated by Calvert's Formula [(GFR+25) x AUC; area under the curve (AUC) equals to 6]. Cisplatin dosage was 70 mg/m^2. All patients received six cycles of chemotherapy every 4 weeks.

The clinical characteristics of both groups were evaluated for age, occupation, marital status, parity, contraceptive methods, menopausal status, dysmenorrheal associated symptoms, presence or absence of endometriosis, maximum tumor diameter, grading and histological subtype.

Follow-up data were collected by reviewing medical records and tumor registry files or contacting the patients. Patients were monitored by physical examination, serum CA-125, pelvic ultrasound or CT scan only if they were clinically indicated. We conduct this study to evaluate the outcome (survival and recurrence free survival time) of stage Ic ovarian clear cell carcinoma as compared to non-clear cell carcinoma at the same stage.

Study design : Retrospective cohort study

Sample size

$$N = \frac{2\,pq\,(Z_\alpha + Z_\beta)^2}{(Pc - Pt)^2}$$

Z_α = 1.96 confidence interval of 95% (two-tailed)

Z_β = 0.84 (β= 0.2)

Pt = 0.54 (probability of **recurrence** in clear cell group)[13]

Pc = 0.17 (probability of **recurrence** in control group) [15]

p = (Pc+Pt) / 2 (0.35)

q = 1-p (0.65)

N = 25.7

Statistics

Patients' characteristics between both groups were compared using independent t-test and Chi-square test. Survival time was measured from the date of diagnosis to the date of death or until last contact. Recurrence free interval time was measured from the first date of treatment to the date of documented recurrence. Recurrence of disease was defined by clinical (physical and pelvic examination) or radiological evidence (CXR, pelvic ultrasound or CT scan) and/or rising in CA-125 level in patients with elevated level at the time of diagnosis. 5-year survival was percentage of patients that are alive at 5 years after treatment. Survival curves were generated using the method of Kaplan-Meier. Differences in the survival curves were calculated using log rank test. A P- value of < 0.05 was considered statistically significant. Statistical analyses were carried out with use of the SPSS version 13.

Results

From June 1997 - December 2002, there were 377 patients with epithelial ovarian cancer who underwent primary treatment at the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital. Among these patients, 83 (22%)

were diagnosed as clear cell carcinoma; 30 patients were stage Ic. After excluded 2 patients with incomplete surgical staging, 28 (93.3%) patients with stage Ic clear cell carcinoma were recruited into this study. Among the 294 patients (78%) in the non-clear cell group, there were 35 patients (11%) with stage Ic. After excluded 5 patients with incomplete staging and 2 patients with admixture of two histological types, 28 patients (80%) were also included for study as controls.

A total of 56 patients with stage Ic carcinoma of the ovary were enrolled in this study. The mean age was 50 years (36 - 86 years old) in both groups. The median follow-up durations in the clear cell and non-clear cell groups were 61 months (5 - 120 months) and 67 months (15 - 103 months), respectively. No patient was lost to follow up.

All 56 patients were diagnosed as stage Ic due to ruptured ovarian capsule, either by accidental or spontaneous rupture. None had positive peritoneal cytology. The mean tumor diameter in the clear cell group was significantly larger than control group (12.96 *vs*. 9.89 cm; P-value = 0.001). The incidence of endometriosis between two groups were not significantly different (57.9% in the clear cell group *vs*. 42.1% in the non-clear cell group; P-value = 0.397). The other clinical characteristics of the two groups were similar (Table 1).

Table 1. Characteristics of clear cell and non-clear cell groups.

	Clear (N = 28)	**non-clear (N = 28)**	**P-Value**
Mean age (years)	50.12 ± 7.92	50.82 ± 8.79	
Mean BMI	22.79 ± 2.44	24.37 ± 4.59	
Para	0.82 ± 1.27	1.29 ± 1.86	
Marital status			
Single	11 (52.4%)	10 (47.6%)	
Couple	17 (48.6%)	18 (51.4%)	
Menopause			
menopause	16 (61.5%)	10 (38.5%)	
pre-menopause	12 (40%)	18 (60%)	
Mean operative time (min)	155.18 ± 37.57	155.36 ± 35.06	
Mean diameter of tumor (cm)	12.96 ± 3.90	9.89 ± 2.65	0.001 [a]
Intraabdominal Endometriosis			
present	11 (57.9%)	8 (42.1%)	
absent	17 (45.9%)	20 (54.1%)	0.397 [b]
Negative peritoneal cytology	28 (100%)	28 (100%)	
Ovarian rupture	28 (100%)	28 (100%)	

[a] based on independent t-test

[b] base on Chi-square test

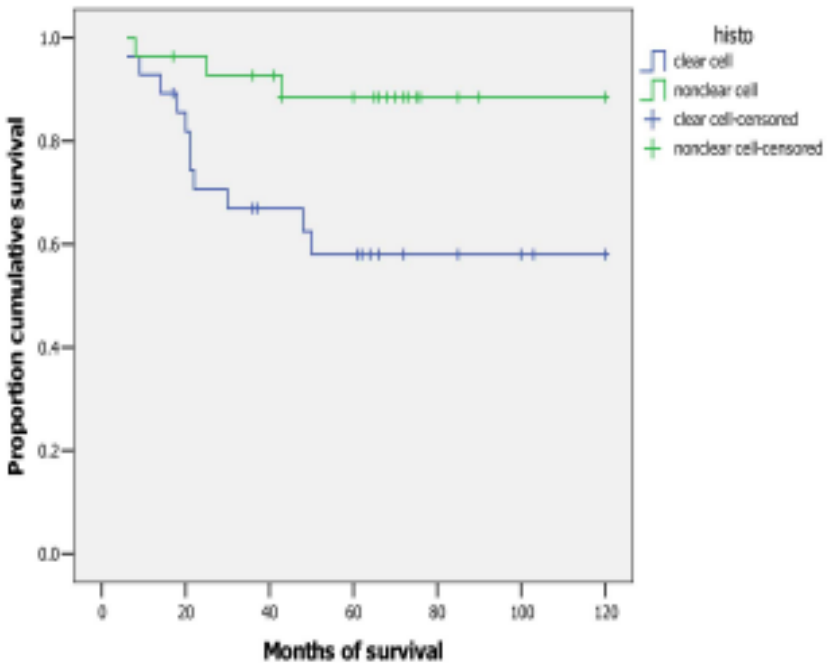
Among the control group, there were 23 patients with endometrioid adenocarcinoma (82.1%) and 5 with serous adenocarcinoma (17.9%). The tumor grading in this group consisted of well differentiated adenocarcinoma 13/28 (46.4%), moderately differentiated 7/28 (25%) and poorly differentiated 8/28 (28.6%). No patient had mucinous adenocarcinoma or other histological types. (Table 2)

The recurrence rate between the clear cell and non-clear cell groups were 46.4% *vs.* 14.2% (P = 0.004) and the median time to recurrence were 10.5 months (2-35 months) *vs.* 8 months (3-28 months), respectively. During this study, 53.5% of the patients in the clear cell group, and 85.7% in the non-clear cell group were still alive.

The estimated 5-year survival and 5-year recurrent free survival rate for clear cell group was significantly lower than that for non-clear cell (53.6% *vs.* 85.7%; P-value = 0.01; and, 50.0% *vs.* 85.7%; P-value = 0.005, based on the log rank test respectively) (Figure 1, 2).

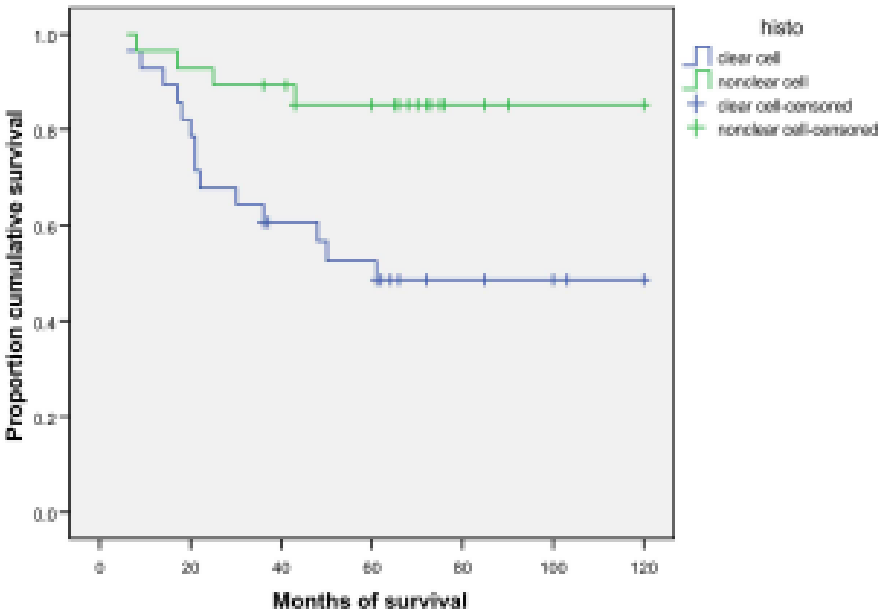
Table 2. Characteristic of non-clear cell group.

Cell type	
Serous adenocarcinoma	5/28 (17.9%)
Endometrioid carcinoma	23/28 (82.1%)
Grading	
Well differentiation	13 (46.4%)
Moderate differentiation	7(25%)
Poorly differentiation	8 (28.6%)



5-year survival for clear cell and non-clear cell group were 53.6% versus 85.7%, *P* -Value = 0.01

Figure 1. Kaplan-Meier estimated overall survival of stage Ic clear cell carcinoma.



5-year recurrence free survival rate for clear cell and non-clear cell group were 50.0% versus 85.7% respectively, P-value=0.005).

Figure 2. Kaplan-Meier estimated recurrence free survival of stage Ic clear cell carcinoma.

Among the clear cell group, divided into endometriosis-related and nonrelated clear cell carcinoma, subgroup analysis revealed no difference in the 5 -year survival times of the two groups (54.5% *vs*. 52.9%; P-value = 0.932, respectively).

Subgroup analysis was done between clear cell and poorly differentiated adenocarcinoma of non-clear group. There was no statistically significant difference in survival time of the two groups. The 5-year survival was 53.6% *vs*. 75.0%, respectively (P- value = 0.285).

Discussion

Clear cell carcinoma constitutes 5 - 10% of surface epithelial ovarian cancer [7], and up to 60% of the patients with clear cell carcinoma have stage I disease. However, many previous studies reported patients with clear cell carcinoma having poorer prognosis than do those with other pathological type of epithelial ovarian cancer. [10,14]

Behbakht *et al*. reported that clear cell tumors of ovary frequently present at early stage. There were 60% of patients in stage I (24% Ia, 7% Ib and 29% Ic) at the time of diagnosis. They observed a high recurrence rate (54%) of stage Ic patients at 35 months of follow up. Endometriosis was pathologically documented in 27% of the tumor but the presence of endometriosis had no impact on their survival. [15] In this study, 28 patients presented with stage Ic (33.7%). The recurrence rate was 13 (46.4%) in clear cell group as compare to 4 (14.2%) in non-clear cell group (P = 0.004). The presence of endometriosis in the clear cell and non-clear groups were 57.9% *vs*. 42.1%, respectively (P-value =0.397). There are two reasons for these indifferent results. Mostly, non-clear cell carcinoma were endometrioid subtype, that is

the second most common type related with endometriosis follow to clear cell type [16], and there maybe insufficient subjects to empower the result.

In this study, we found no significant difference in 5-year survival time among the clear cell with or without endometriosis (54.5% *vs.* 52.9%; P-value = 0.932 respectively). The contradictory result of Komiyama *et al*. showed that 5-year survival rate of stage Ic patients was significantly greater in ovarian clear cell carcinoma with pelvic endometriosis (100%) than in that without it (52.2%; P< 0.05). [17] However, they included 7 patients with different operation procedures in that study.

Subgroup analysis between clear cell and poorly differentiated adenocarcinoma revealed no significant difference in 5-year survival. This may also because of the small sample size to empower the result.

Sugiyama *et al*. also reported that patients with clear cell carcinoma were significantly more likely to have FIGO stage I disease than those with serous adenocarcinoma (48.5% *vs.* 16.6%). A high recurrence rate was noted in those with stage Ic clear cell carcinoma (37%). In the patients with stage Ic, the survival rate was lower than those with serous adenocarcinoma and the response rate to platinum based chemotherapy in the patients with clear-cell carcinoma was significantly lower than that those with serous adenocarcinoma.[18]

In this study, the clinical data of the two groups were homogeneous; these included stage of the disease, operative procedure and post - operative adjuvant chemotherapy (single agent platinum based). The mean diameter size of tumor in this study was 12cm. in clear cell group and 9 cm. in non-clear cell, this may resulted of ruptured tumor during operation . We found that 5-year survival and 5-year recurrence free survival rate in the clear cell group was significantly lower than that of the non-clear cell group (53.6% *vs.* 85.7%, P - value = 0.01 and 50.0% *vs.* 85.7%, P-value = 0.005). Our findings confirmed that patients with clear cell carcinoma have poorer outcome than those with non-clear cell epithelial carcinoma.

Ming *et al*. reported that the estimated 3-year recurrence-free survival and 4-year overall survival of stage I clear cell in patients who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic and/or para-aortic lymphadenectomy followed by post-operative chemotherapy, carboplatin and paclitaxel regimen, was significantly greater than those who underwent the same operation without pelvic lymphadenectomy followed by post-operative chemotherapy, cisplatin alone (91.7% *vs*. 33.3%; P - value = 0.014 and 100% *vs.* 50%; P - value = 0.014). [19] However, patients who had lymphadenectomy received post operative adjuvant chemotherapy regimen as a combination of platinum and paclitaxel compared to single agent cisplatin in the non-lymphadenectomy group.

Tammela *et al*. also reported the worse prognosis of clear cell carcinoma compared to serous adenocarcinoma. In the study, they compared the two groups, 22 patients each, matched for stages (stage I 18.2%, II 9.1%, III 63.1%, and IV 9.1%), age and levels of primary cytoreductive surgery. [20]

Itamochi *et al*. reported that clear cell carcinoma had lower response rate to chemotherapy than serous adenocarcinoma (14.6% *vs*. 72.2%); lower

proliferation of the tumor may be a behavior of clear cell carcinoma of the ovary that contributes its resistance to chemotherapy. [21]

Patients with early stages of ovarian cancer who are at high risk for relapse include stage Ic and stage II disease. Platinum based adjuvant treatment can reduce the risk of relapse in this group, resulting in disease-free survival of 80 %.[22] However, in stage Ic (high risk), it is still controversial in terms of regimen and the number of cycle of chemotherapy the patients should receive to achieve the optimal benefit.

Conclusion

The patients with stage Ic clear cell carcinoma of the ovary have lower 5-year survival rate and recurrence free survival than the patients with non-clear cell epithelial ovarian carcinoma in the same stage. Combined chemotherapy may be needed to improve the survival in stage Ic of clear cell ovarian cancer.

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