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## GYNAECOLOGY

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# Clinical Course of Epithelial Ovarian Cancer Patients with Pleural Effusion in Siriraj Hospital

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### ABSTRACT

**Objective:** To evaluate the clinical course and determine the survival of epithelial ovarian cancer patients with pleural effusion.

**Study design:** Retrospective study

**Materials and methods:** Data from epithelial ovarian cancer patients who had pleural effusion were reviewed from medical records between January 1997 and December 2007 in Siriraj Hospital. Characteristics, clinical outcomes and survival analysis were reported.

**Results:** 95 cases of epithelial ovarian cancer patients who had pleural effusion with medical records were identified. The median age was 53.7 years. There were 38.9% of these patients who had been proven as malignant pleural effusion. Only 23 cases (24.2%) underwent optimal cytoreductive surgery. Most patients received platinum-taxane combination chemotherapy. The median survival for malignant pleural effusion patients was 16.8 months, while median survival in the group who had negative cytological diagnose as malignant effusion was 31 months. The pleural effusions were subsided after the third and the sixth course of chemotherapy in 23% and 58% of cases respectively. Pleural intervention needed mostly in the first course of chemotherapy to release patients' symptom.

**Conclusion:** Epithelial ovarian cancer patients with malignant pleural effusion had poor survival. Platinum base-chemotherapy can reduce the clinical symptom in more than half of pleural effusion patients with no need of surgical intervention.

**Keywords:** epithelial ovarian cancer patients, pleural effusion

## Introduction

Ovarian cancer is the second most common female reproductive cancer. Epithelial ovarian cancer comprised of more than 80 % of all ovarian cancer.<sup>(1-3)</sup> Until now, there is no effective screening test for ovarian cancer and most of these patients presented in advanced stage. In Siriraj Hospital, in

the year 2007, there were 143 new cases of epithelial ovarian cancer, of these; 70% presented in stage III/IV disease.<sup>(4)</sup> Standard treatment, according to NCI (National Cancer Institute) and TGCS (Thai Gynecologic Oncology Society) guideline was tumor debulking surgery together with surgical staging, classified by FIGO (International Federation of

Obstetrics and Gynecology). Maximum cytoreductive surgery, leaving very small or no residual tumor have been shown to improve response and survival.<sup>(5)</sup>

Previous studies reported 5 year-survival rate of stage III and IV epithelial ovarian cancer patients around 17-59%. They also reported that survival rate was not significantly different among patients with various metastasis sites.<sup>(6,7)</sup> However; patients with pleural effusion, which was the common clinical manifestation, had better prognosis.<sup>(8,9)</sup> However Bennefoi, et al.,<sup>(7)</sup> reported median overall survival of patients with positive pleural effusions was 13.4 months, which was not significantly different from 10.5 months in those who had visceral organ metastases. Prognosis of stage III- IV epithelial ovarian cancer patients with malignant pleural effusion, and with other visceral metastases was not consistent among previous studies.<sup>(9)</sup> This study, we aim to evaluate clinical course and survival outcomes of epithelial ovarian cancer patients with pleural effusion.

## Materials and methods

The study was performed at Siriraj Hospital after institutional ethical board approval, Medical record of 95 cases of epithelial ovarian cancer patients diagnosed with pleural effusions between January 1997 to December 2007 were reviewed. Data on patients' characteristics and clinical outcomes were collected. Histological types were defined according to World Health Organization's Classification while surgical staging was defined according to International Federation of Obstetrics and Gynecology (FIGO).

Data was analyzed using SPSS statistical software (SPSS version 11.5 for Microsoft Windows). Survival analysis and comparison were performed using Kaplan-Meier method. The COX regression model was used to identify independent variables associated with survival outcomes.

## Results

95 cases of epithelial ovarian cancer patients diagnosed in stage III, IV and other stages who had

pleural effusions diagnosed from plain film chest X-ray were reviewed. Patients' characteristics were described in table 1. Mean age was 53.7 years (range 32-77), 10.5% were younger than 40 years old, where as 6.3% were older than 70 years old. About half of patients with pleural effusion (54.7%) were found to be stage IV, others with pleural effusion which were not cytological proven as malignant effusion were classified as FIGO stage IIIC (36.8%), FIGO IIIB/ IIIA (4.2%) and FIGO IA/ IC/ IIC (4.2%), respectively. The most common histological type was serous cystadenocarcinoma. Malignant pleural effusion which was proven by positive cytology was found in 37 cases (38.9%). Almost all of 95 cases (95.8%) had ascites. More than half of the patients had extraperitoneal metastasis. Other metastasis sites were found in cervical lymph node 1 case, bone 1 case and liver 1 case. Pre-chemotherapy CA 125 levels ranged between 4 to 53,905 U/ml.

Treatment modalities and response were shown in table 2. Only one fourth of cases underwent optimal surgery. After 6 courses of chemotherapy, 33 cases (34.8%) had complete response, while 35 cases (36.8%) suffered from progression of disease and 22 cases (23.2%) were dead of disease. Pleural effusion subsided in 96.5% after 6 courses of chemotherapy. Interventions for pleural effusion were provided in some cases, such as intercostal drainage (ICD), pleurodesis or pleural tapping for symptom release. Two patients refused adjuvant chemotherapy and was lost to follow up after suboptimal surgery. The patients with pleural effusion, who classified as other FIGO stages were shown in table 3.

**Table 1.** Characteristic of patients

Characteristics	n (%)
Total (cases)	95
Age (year)	
Mean $\pm$ SD	53.7 $\pm$ 9.9
Range	32 - 77
$\leq$ 40	10 (10.5)
$>$ 70	6 (6.3)
FIGO Stage	
IIIA and IIIB	4 (4.2)
IIIC	35 (36.8)
IV	52 (54.7)
Others (IA, IC, IIC)	4 (4.2)
Histology	
Serous	47 (49.5)
Endometrioid	13 (13.7)
Mucinous	10 (10)
Clear cell	7 (7.4)
Brenner	1 (1.1)
Mixed	12 (12.6)
Unclassified	5 (5.3)
Pleural effusion cytology	
Positive	37 (38.9)
Negative	12 (12.6)
No cytological study	46 (48.5)
Degree of pleural effusion *	
Degree = 1	39 (41.1)
Degree = 2	27 (28.4)
Degree = 3	27 (28.4)
No data available	2 (2.1)
Ascites	
Yes	91 (95.8)
No	2 (2.1)
No data available	2 (2.1)
Metastasis site	
Confined intraperitoneum	43 (45.3)
Lung	49 (51.6)
Others (liver, bone, cervical LN, skin)	3 (3.1)
CA 125 ** (U/ml) in 84 of 95 patients	
Mean $\pm$ SD	4,154.6 $\pm$ 9,145.0
Range	4 – 53,905

\* Degree of pleural effusion

degree = 1 (no symptom plus pleural effusion  $\leq$  1/3 of each lung field)

degree = 2 (symptom plus pleural effusion  $\leq$  1/3 of each lung field)

degree = 3 (symptom plus pleural effusion  $>$  1/3 of each lung field )

\*\* CA 125 (U/ml) = before first chemotherapy

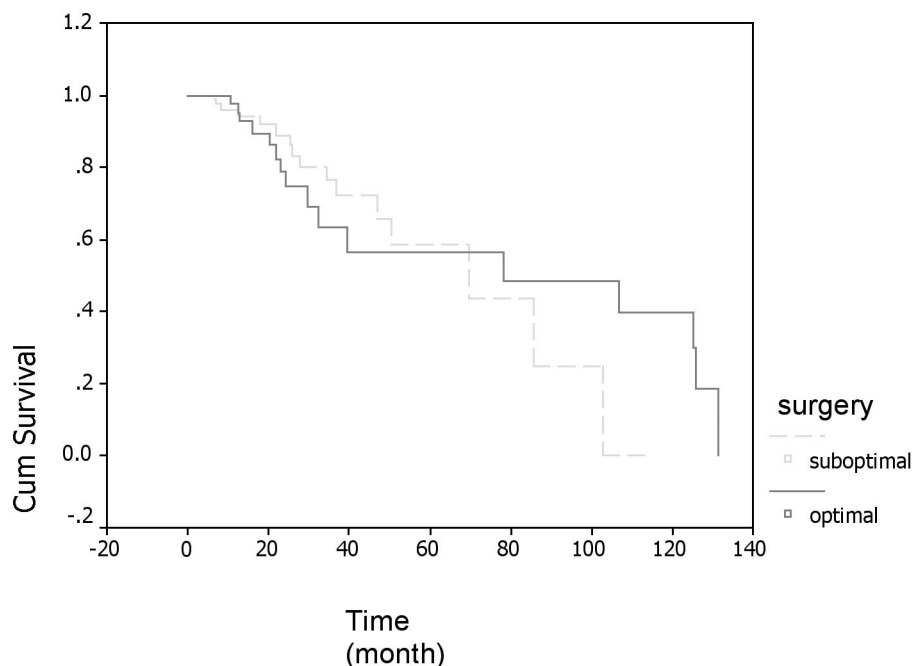
**Table 2.** Treatment and response

<b>Treatment and response</b>	<b>n (%)</b>
Surgical status	
Optimal cytoreductive	23 (24.2)
Suboptimal cytoreductive	67 (70.5)
No surgery	5 (5.3)
Neoadjuvant chemotherapy	
Yes	19 (20)
No	76 (80)
Chemotherapy regimens	
Carboplatin or Cisplatin plus Paclitaxel	43 (45.3)
Carboplatin or Cisplatin plus Cyclophosphamide	37 (38.9)
Carboplatin alone	12 (12.6)
Paclitaxel alone	1 (1.1)
No chemotherapy	2 (2.1)
Pleural effusion subside after chemotherapy course	
Course 3	22 (23)
Course 6	55 (58)
Intervention for pleural effusion	
Intercostal drainage (ICD)	6 (6.3)
Pleurodesis	4 (4.3)
Pleural tapping for symptom release during chemotherapy	
No	76 (80)
Course 1	13 (13.6)
Course 2	3 (3.1)
Course 5	1 (1.1)
Course 10	1 (1.1)
Course 11	1 (1.1)
Response	
Complete	32 (33.7)
Partial	1 (1.1)
Stable	1 (1.1)
Progressive	35 (36.8)
Dead	22 (23.2)
Loss follow up	4 (4.1)

**Table 3.** Characteristic of patients with pleural effusion in other FIGO Stages

No.	Stage	Age (year)	Characteristic of patients
1	IA	39	mucinous type, grade II, ascites but cytology negative, pleural effusion degree = 1, negative pleural effusion cytology, optimal surgery, CA125 = 23 U/ml, Cisplatin plus Cyclophosphamide regimen, complete response, pleural effusion subside after chemotherapy course 1.
2	IC	58	serous type, grade I, ascites, pleural effusion degree = 1, no data of pleural effusion cytology, optimal surgery, CA125 = 17 U/ml, Cisplatin plus Cyclophosphamide regimen, complete response, pleural effusion subside after chemotherapy course 6.
3	IIC	45	endometrioid type, grade III, ascites with positive cytology, pleural effusion degree = 1, no data of pleural effusion cytology, optimal surgery, CA125 = 403 U/ml, Cisplatin plus Cyclophosphamide regimen, complete response, pleural effusion subside after chemotherapy course 6.
4	IIC	51	clear cell type, grade III, ascites with positive cytology, pleural effusion degree = 2, negative pleural effusion cytology, optimal surgery, CA125 = 131 U/ml, Carboplatin regimen, complete response, pleural effusion subside after chemotherapy course 6.

Epithelial ovarian cancer patients with positive cytological diagnosed as malignant pleural effusion had median survival at 16.8 months (95% CI 11.1, 22.5), while median survival in the group who had negative cytological diagnose as malignant effusion was 31 months (95% CI 20.8, 41.3). Analysis with COX regression model showed that no independent variables were associated with overall survival ( $p > 0.05$ ).



**Fig. 1.** Survival function of the patients with pleural effusion, comparing between optimal and suboptimal cytoreductive surgery.

## Discussion

Patients with advanced epithelial ovarian cancer with pleural effusion had characteristics such as mean age, common histological type, CA 125 levels similar to previous studies.<sup>(9,10)</sup> Most of these patients presented with ascites and half of them had extraperitoneal spreading. Optimal or ultra-radical cytoreductive surgery is the suggested treatment for the better outcome.<sup>(11)</sup> However only one fourth of the patients in this study achieved these procedure due to multiple factors such as primary surgery at other institution, surgery not performed by gynecologic oncologist, frozen pelvis, very old age or poor performance status. This inadequate cytoreductive surgery may be an important factor for survival in these patients.

Cytological positive malignant effusion was found in 38.9%, which is nearly the same as Akahira's report.<sup>(12)</sup> Adjuvant treatment was given in 98% of cases, nearly all were platinum-base regimen, of which nearly half, had combination with paclitaxel. At our institute, platinum combination with cyclophosphamide was previously used, and only the last five years that almost all patients received platinum-taxane chemotherapy. Only one fifth of the patients received neoadjuvant chemotherapy, this is due to poor functional status of the patients, as we found that 6.3% of the patients were older than 70 years and more than half of the patients had symptom of dyspnea. And they were given platinum-taxane chemotherapy as the same report by Eisenhauer's, et al.<sup>(13)</sup> Nevertheless, the study of Le's, et al.<sup>(14)</sup> showed that neoadjuvant chemotherapy followed by cytoreductive surgery showed no significant difference in median overall survival compare with primary cytoreductive surgery followed by adjuvant chemotherapy. In case of optimal cytoreductive surgery, there were better survival outcome compared with suboptimal group as Winter's report.<sup>(11)</sup> Clinical complete response in our study was quite low compared with the same regimen in study of Eisenhauer's, et al.<sup>(13)</sup> Median survival of the patients with malignant pleural

effusion in this study was 16.8 months, which was similar to Akahira's, et al.<sup>(12)</sup> Pleural intervention was performed mostly in the first course of chemotherapy to relieve patient's symptom, other surgical interventions were quite in a small number that cannot be statistically compared. However, from the clinical course of the patients with pleural effusion during chemotherapy; 23% and 58 % of cases, pleural effusions subsided after the third course and the sixth course respectively.

Four patients with pleural effusion that were classified in early FIGO stages, had complete response after six courses of platinum-base chemotherapy. Hence, in epithelial ovarian cancer patients with pleural effusion, cytological study of pleural effusion should be considered to properly classified for FIGO staging, together with attention for optimal cytoreductive surgery which may result in good clinical outcomes.

## Acknowledgements

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## การศึกษาลักษณะทางคลินิกของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวที่มีภาวะน้ำในช่องเยื่อหุ้มปอดในโรงพยาบาลศิริราช

ภานพศ พันธุ์เมธาฤทธิ, สุวนิตย์ ธีระศักดิ์วิชยา

**วัตถุประสงค์ :** เพื่อศึกษาลักษณะทางคลินิกและประเมินระยะเวลาการรอดชีวิตของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวที่มีภาวะน้ำในช่องเยื่อหุ้มปอด

**ชนิดการวิจัย :** การศึกษาวิจัยแบบย้อนหลัง

**วัสดุและวิธีการ :** ศึกษาข้อมูลของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวในโรงพยาบาลศิริราช ที่ได้รับการวินิจฉัยว่ามีภาวะน้ำในช่องเยื่อหุ้มปอดร่วมด้วย จากการตรวจด้วยภาพรังสีวินิจฉัยของปอด จากบันทึกเวชระเบียนและทะเบียนผู้ป่วยมะเร็งรังไข่ ระหว่าง เดือนมกราคม พ.ศ. 2540 ถึง เดือนธันวาคม พ.ศ. 2550 รวบรวมข้อมูลลักษณะทั่วไปของผู้ป่วย การรักษารวมถึงผลการตอบสนองและการตรวจติดตาม นำมาวิเคราะห์และประเมินผลทางสถิติ

**ผลการศึกษา :** พบข้อมูลผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวจำนวน 95 รายที่มีภาวะน้ำในช่องเยื่อหุ้มปอด มีอายุเฉลี่ย 53.7 ปี ในจำนวนนี้เป็นกลุ่มที่ตรวจพบเซลล์มะเร็งจากน้ำในช่องเยื่อหุ้มปอด ร้อยละ 38.9 โดยมีผู้ป่วยร้อยละ 24.2 คิดเป็นจำนวน 23 รายได้รับการผ่าตัดแบบเหลือเนื้อออกน้อยกว่า 2 เซนติเมตร หลังการผ่าตัดผู้ป่วยส่วนใหญ่ได้รับการรักษาด้วยเคมีบำบัดสูตรพลาตินั่มร่วมกับแทกเซน พบว่ามีระยะเวลากการอยู่รอดของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวที่มีเซลล์มะเร็งในน้ำช่องเยื่อหุ้มปอด ประมาณ 16.8 เดือน เมื่อประเมินในกลุ่มผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิวที่ไม่พบเซลล์มะเร็งในน้ำช่องเยื่อหุ้มปอด มีค่าประมาณ 31 เดือน ในระหว่างการรักษาด้วยเคมีบำบัดพบว่าผู้ป่วยร้อยละ 23 มีอาการหายจากภาวะน้ำในช่องเยื่อหุ้มปอดหลังได้เคมีบำบัด 3 ครั้ง และเมื่อได้เคมีบำบัดครบ 6 ครั้งพบว่าผู้ป่วยร้อยละ 58 หายจากภาวะน้ำในช่องเยื่อหุ้มปอด การเจาะน้ำในช่องเยื่อหุ้มปอด เพื่อบรรเทาอาการหอบเหนื่อย ส่วนใหญ่ทำหัตถการนี้ ในช่วงการให้เคมีบำบัดครั้งแรก

**สรุป :** ในการดูแลรักษาผู้ป่วยมะเร็งรังไข่ชนิดเยื่อぶผิว พบว่าผู้ป่วยที่มีเซลล์มะเร็งในน้ำช่องเยื่อหุ้มปอดมีค่ามัธยฐานระยะเวลาการอยู่รอดน้อย อย่างไรก็ตามผู้ป่วยมากกว่าครึ่งหายจากภาวะน้ำในช่องเยื่อหุ้มปอดได้ภายหลังได้รับการรักษาด้วยเคมีบำบัดสูตรที่มีพลาตินั่ม โดยไม่มีความจำเป็นต้องทำหัตถการในช่องเยื่อหุ้มปอด