Incidence, Survival Rate and Prognostic Factors of Recurrent/ Refractory Epithelial Ovarian Cancer in Siriraj Hospital

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ABSTRACT

Objective: To assess the incidence, 5-year survival rate and identify the prognostic factors for survival in a cohort of patients with recurrent/ refractory epithelial ovarian cancer in Siriraj Hospital.

Methods: We performed a retrospective chart review of 140 patients with primary recurrent / refractory epithelial ovarian cancer who received their treatment at Siriraj Hospital between October 1998 and December 2006. Incidence, 5-year survival rate and potential prognostic factors for survival were identified. Statistical analysis was by SPSS for Windows version 11.5. Kaplan-Meier survival curves were computed and a multivariable proportional hazard model (Cox) was applied to assess the prognostic significance of the different covariates.

Results: The incidence of recurrent/refractory epithelial ovarian cancer when compared to total new cases of epithelial ovarian cancer during a 1-year period was 33.62%. The 5-year survival rate for the cohort was 47%, whereas the median overall survival was 4.91 years and the median survival post recurrence was 2.5 years. Of these patients, 64/140 (45.7%) have died of disease. Seventeen factors were evaluated for prognostic significance for survival, on multivariate analysis, only the tumor free interval (TFI) (P = 0.016) and CA 125 at the time of recurrence or refractory (P = 0.02) retained prognostic significance.

Conclusion: The incidence of recurrent/ refractory epithelial ovarian cancer when compared to total new cases of epithelial ovarian cancer is about one third. This cohort had a prolonged median overall survival and satisfied a 5-year survival rate. The significant prognostic factors for survival in a cohort of patients are the tumor free interval and CA 125 at time of recurrence or refractory.

Keywords: Epithelial ovarian cancer, prognosis, recurrence

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Ovarian cancer is the second most common gynecologic cancer in Thai women and over eighty percent of cases are epithelial types.[1,2] The currently accepted management of epithelial ovarian cancer is primary cytoreductive surgery with the goal of resecting as much macroscopic tumor as possible (largest residual tumor is not more than 1 cm) and followed by platinum based combination chemotherapy.

The natural biology of the disease and the absence of effective screening methods lead to the frequent presentation of ovarian cancer in advanced stages (stage III-IV) at the time of diagnosis and the relative risk of death was increased to 8 and 11.7 times when compared to stage I disease.[3] Seventy percent of women with advanced epithelial ovarian cancer respond to their primary chemotherapy,[4] and at least 60% of advanced stage epithelial ovarian cancer patients who are without clinical evidence of disease after completing primary therapy will ultimately develop recurrent disease, which will prove fatal in the great majority and the prognosis is very poor.[2] It may be reasonable to suggest that those patients with both a low likelihood of response and a dismal survival outlook should receive less toxic treatment and maximal supportive and palliative care only which would be reasonable options for a well-defined poor prognosis group.

There have been several reviews of prognostic factors in patients with recurrent epithelial ovarian cancer and many investigators have emphasized the importance of these factors for treatment planning and outcome, such as the stage at initial diagnosis, tumor histology, residual tumor after surgery, performance status, and time to relapse from completion of primary treatment.[5-8] At present, there are only two studies of Hoskins

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et al.[4] and Gronlund et al.[8] which have combined several prognostic factors (The Canadian prognostic index and the Copenhagen index) for the use of prognostication in recurrent ovarian cancer.

The aims of this study were (a) to assess the incidence and 5-year survival rate of recurrent epithelial ovarian cancer patients in Siriraj hospital, (b) to identify significant prognostic factors for survival, and if possible, (c) to incorporate the significant parameters in a novel improved prognostic model for clinical decision making.

MATERIALS AND METHODS

A retrospective descriptive study was conducted including 140 patients with primary recurrent or refractory epithelial ovarian cancer who had been treated in the Department of Obstetrics & Gynecology, Faculty of Medicine, Siriraj Hospital between October 1998 and December 2006. This study excluded patients who had co-malignancies, incomplete medical record and follow up and previous participants in other studies. The study was approved by the Ethics Committee, Faculty of Medicine Siriraj Hospital, Mahidol University.

Individual records for all patients were reviewed and potential prognostic factors in this study came from the outcomes of previous studies, such as age and date at diagnosis, stage, tumor grade, histology, residual tumor after primary surgery, initial performance status, initial Hb level and CA 125, response to first-line treatment, tumor free interval (TFI), number of recurrent sites, size of tumor at recurrence, performance status at recurrence, Hb level and CA 125 at recurrence, presence of ascites, liver, lung and lymph nodes involvement, current disease status and date of death or last follow up, were abstracted. Recurrent disease was identified by physical examination and/or tumor marker and/or radiological imaging and the term "*refractory*" in this study was used for partial response, stable disease or progression of disease after primary treatment. The tumor free interval (TFI) was defined as the time interval between the ends of first-line treatment to the diagnosis of the primary recurrence of disease.

Statistics analysis

The data were processed using SPSS for Windows (Statistical Package for the Social Science) version 11.5. Kaplan-Meier analysis was used to determine the overall survival, TFI, and survival after primary recurrence/ refractory of disease. The potential prognostic factors for survival in this study were based on the outcomes of previous studies that were tested univariately, using the log-rank test for categorical factors and Cox's proportional hazards model for continuous factors. A multivariable proportional hazards model (Cox) was applied to assess the prognostic significance of the different covariates. The P value of < 0.05 was considered statistically significant.

RESULTS

Using the database of the Gynecologic Oncology Division, Department of Obstetrics & Gynecology, Siriraj Hospital in 2007, 199 new cases of ovarian cancer were identified. From this group of patients, 142/199 (71.36%) were epithelial ovarian cancer and 52 cases of primary recurrent/ refractory epithelial ovarian cancer were met.

TABLE 1. Incidence of epithelial ovarian cancer patients in Gynecologic Oncology Division, Department of Obstetrics & Gynecology, Siriraj Hospital in 2007.

Cases	Year 2007
Total new cases OVC	199
Epithelial OVC	142
1^{O} recurrent/ refractory epithelial OVC	52

OVC = Ovarian cancer

140 cases of primary recurrent/ refractory epithelial ovarian cancer who qualified for this study were identified. Patient characteristics at initial diagnosis of epithelial ovarian cancer were shown in Table 2. Of these 140 patients, 7/140 (5%) received platinum- based neoadjuvant chemotherapy before primary surgery and after primary cytoreductive surgery, all received adjuvant chemotherapy. 62/140 (44.3%) received platinum combined with cyclophosphamide, 58/140 (41.4%) received a combination of platinum and paclitaxel regimen, and the remaining 20/140 cases (14.3%) received a single platinum or paclitaxel regimen.

At the end of primary treatment, the results of treatment were complete response (CR) in 112/140 (80.0%), partial response (PR) in 16/140 (11.4%), stable disease (SD) in 2/140 (1.4%), and the remaining 10/140 (7.2%) had progression of disease (PD). In the complete response group, 14/112 (12.5%) had a TFI < 6 months and the majority of the group 98/112 (87.5%) had a

TABLE 2. Patient characteristics at initial diagnosis.

Characteristics		No.	%
Age	≤ 40 yr	24	17.1
	> 40 yr	116	82.9
mean (min-max) (yr)		49.8 (23-73)	
FIGO stage	I-II	42	30.0
	III-IV	98	70.0
Histology	Serous	60	42.9
	Mucinous	9	6.4
	Endometrioid	21	15.0
	Clear cell	27	19.3
	Other	23	16.4
Grade	I	17	12.1
	II	27	19.3
	III	65	46.4
	No data	31	22.2
Performance status	0-1	133	95.0
	≥ 2	7	5.0
Hb level	≤ 10 g/dl	25	17.9
	> 10 g/dl	115	82.1
CA 125	≤ 35 U/ml	23	16.4
	> 35 U/ml	117	83.6
Residual tumor	No	60	42.9
	≤ 2 cm	22	15.7
	> 2 cm	57	40.7
	No data	1	0.7
Response	CR	112	80.0
	PR	16	11.4
	SD	2	1.4
	PD	10	7.2

CR = complete response, PR = partial response, SD = stable disease, PD = progression of disease

TFI between 6 months and 14.3 years. Their data were illustrated in Figure 1.

The patient characteristics at recurrence or refractory of disease were shown in Table 3. Survival curves were estimated using the Kaplan- Meier method. The median overall survival of this cohort was 4.91 years and the 5-year survival after initial diagnosis of disease was 47% (Figure 2). After recurrence or refractory of disease, the median and mean survival times were 2.5 and 3.6 years, respectively. (Figure 3)

17 continuous and discrete variables were analyzed for prognostic significance. The results were shown in Table 4.

On Cox regression analysis, only a TFI ≥ 6 months (HR 0.43; 95% CI 0.21-0.85; P = 0.016) and CA 125 level at time of recurrence or progression of disease > 35 U/ml (HR 3.11; 95% CI 1.16-8.25; P = 0.02) retained prognostic significance, and the survival curves of these findings were shown in Figure 4 and 5, respectively.

Of the 140 patients, the median and mean overall survivals were 4.91 and 7.88 years, respectively. 64/140 died of disease and the remaining 76/140 (54.3%) were still alive at the time of analysis. In this group of the remaining, 21/76 (27.63%) have no evidence of disease, and 55/76 (72.37%) live with disease.

DISCUSSION

Epithelial ovarian cancer has been classified in various histological types. It is the most common type of ovarian cancer, so far. The results of this study revealed that the incidence of epithelial ovarian cancer compared to the other ovarian cancers is 71.36-82.42%. This incidence is similar to the previous studies.[1,2] From this study, it was found that the 5-year survival rate is 47%, which is slightly less than that it was in the USA in 1999.[6]

Nowadays, it has been widely accepted that the first line treatment of epithelial ovarian cancer is the maximum cytoreductive surgery follow by adjuvant combination chemotherapy. The Gynecologic Oncology Division, Department of Obstetrics & Gynecology, Faculty of Medicine Siriraj Hospital, has recommended that the clinical practice guideline of the adjuvant treatment for

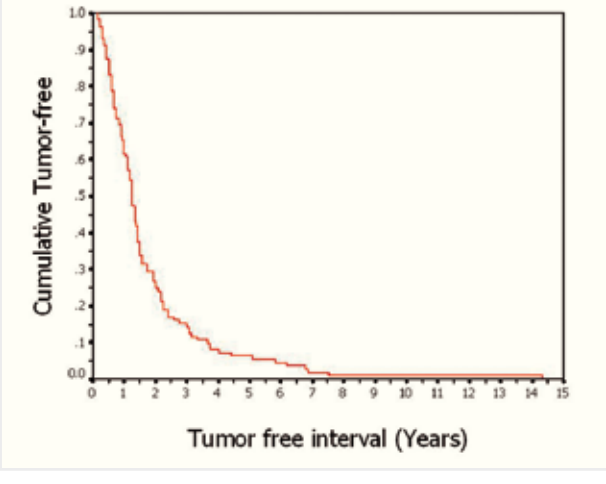


Fig 1. Tumor free interval after primary treatment of the 112 patients with CR.

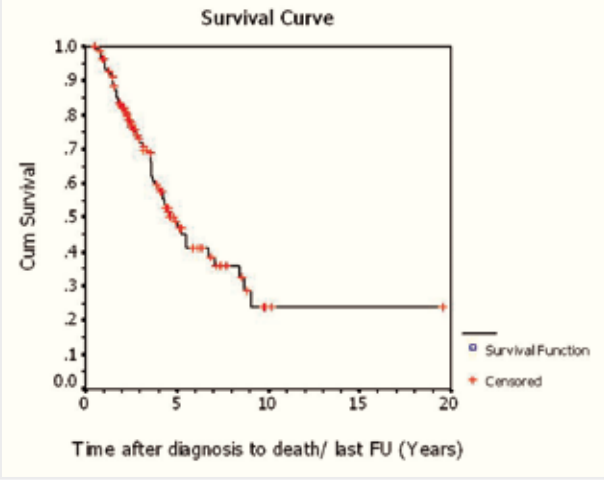


Fig 2. Survival curve after initial diagnosis to death/ last FU.

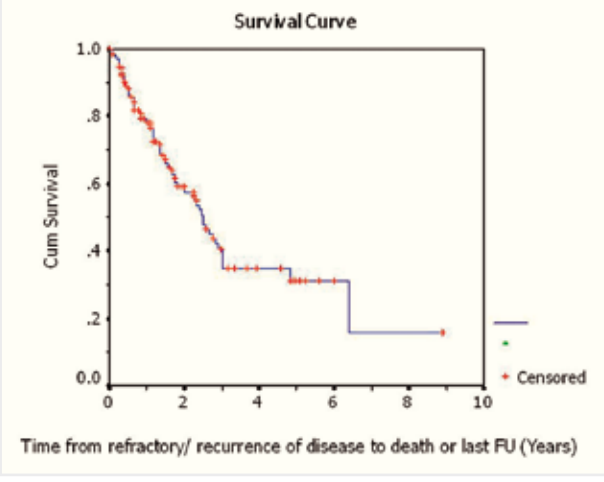


Fig 3. Survival curve after recurrence or refractory of disease.

TABLE 3. Patient characteristics at recurrence or refractory of disease.

Characteristics		No.	%
Tumor free interval	< 6 mo	37	26.4
	≥ 6 mo	103	73.6
No. of recurrent sites	Single	78	55.7
	Multiple	62	44.3
Size of largest tumor at recurrence			
	≤ 5 cm	89	63.6
	> 5 cm	51	36.4
Performance status	0-1	132	94.3
	≥ 2	8	5.7
Hb level	≤ 10 g/dl	37	26.4
	> 10 g/dl	103	73.6
CA 125	≤ 35 U/ml	22	15.7
	> 35 U/ml	118	84.3
Ascites	Positive	44	31.4
	Negative	96	68.6
Liver involvement	Positive	12	8.6
	Negative	128	91.4
Lung involvement	Positive	13	9.3
	Negative	127	90.7
LN involvement	Positive	28	20.0
	Negative	112	80.0

TABLE 4. Prognostic factors for survival after time of recurrence or refractory of disease.

Parameter		Hazard ratio	95%CI	*P*
At initial diagnosis				
Age	≤ 40 vs. > 40 yr	1.006	0.46-2.18	0.98
FIGO stage	I+II vs. III+IV	0.79	0.33-1.95	0.62
Histology	Serous	1.00	Reference	0.36
	Mucinous	1.55	0.34-6.90	0.56
	Endometrioid	0.59	0.23-1.51	0.27
	Clear cell	2.05	0.77-5.42	1.15
	Other	1.13	0.46-2.79	0.78
Performance status	0-1 vs. ≥ 2	1.03	0.28-3.71	0.96
Hb level	≤ 10 vs. > 10 g/dl	0.96	0.40-2.31	0.94
CA 125	≤ 35 vs. > 35 U/ml	1.95	0.74-5.09	0.17
Surgical status	optimal vs. suboptimal surgery*	0.70	0.36-1.34	0.28
At refractory or recurrence				
TFI	< 6 vs. ≥ 6 mo	0.43	0.21-0.85	0.016
No. of recurrent sites	single vs. multiple	1.26	0.66-2.39	0.47
Largest tumor size	≤ 5 vs. > 5 cm	1.46	0.79-2.68	0.21
Performance status	0-1 vs. ≥ 2	1.49	0.52-4.28	0.45
Hb level	≤ 10 vs. > 10 g/dl	1.31	0.60-2.88	0.49
CA 125	≤ 35 vs. > 35 U/ml	3.11	1.16-8.25	0.02
Ascites	present vs. absent	0.73	0.35-1.50	0.39
Liver involvement	present vs. absent	0.62	0.22-1.72	0.36
Lung involvement	present vs. absent	0.60	0.24-1.48	0.27
LN involvement	present vs. absent	1.80	0.91-3.64	0.08

Optimal vs. suboptimal surgery* in this table defined optimal surgery by residual tumor ≤ 2 cm

early stage ovarian cancer, stage I-II, is a combination of platinum plus cyclophosphamide. In the case of an advanced stage, stage III-IV, which were the most common staging, or the early stage ovarian cancer with the aggressive histological cell type, such as clear cell type, will be given the combination of platinum plus paclitaxel, which is an international practical standard of treatment.[6,9-11] The recurrent ovarian cancer and the second line treatment are still rarely studied.[9,11,12] Moreover, currently, there still is no clinical practice guideline at Siriraj Hospital. However, we offer treatment by using the tumor free interval as a guideline. That is if it is more than 6 months of tumor free interval, we will offer the same chemotherapy regimen. If it is less than 6 months, the new chemotherapy regimen is offered. For surgical treatment, it is offered on an individual basis. In this study the researchers do not include some factors into the analysis, such as the regimen of chemotherapy, the type of surgery for recurrence of ovarian cancer. However, the results of some studies such as Vermorken JB, et al. in 1996[13] and Swenerton K, et al. in 1998[14] observed that the second line treatment had a very minimal effect to the survival of patients. However, the most prognostic effects were the patients themselves and the types of the ovarian cancer. The responsiveness of treatment will depend on histology, anemia, tumor size and chemotherapy free interval.

This study has interestingly revealed that the incidence of epithelial ovarian cancer in women less than or equal to 40 years old is 17.1%, where physicians should take into consideration the young age women who present with abdominal bloatness or pelvic mass. The epithelial ovarian cancer occurs more commonly among women over 50 years of age with the peak incidence at 56-60 years of age.[15,16] After the completion of the treatment we found that the median tumor free interval from the last chemotherapy to the recurrence of disease and the new chemotherapy initiated was 1.08 years. Therefore, it is essential to ask the patients to come back for the close follow-up. Within the first 2 years, the appointment should be at every 2-4 months, and then at every 6 months until 5 years after the completion of the treatment and a yearly check-up thereafter is recommended. Each follow-up visit should include the history taking, complete physical exam, vaginal exam and the combination of a blood test for tumor marker in the case of having a high level of tumor marker before.[17]

From this study, 94.3% of the patients with recurrence of disease had the performance status or ECOG score at the level of 0-1. This indicates that the patients were still in a general good health and there was no contraindication for additional chemotherapy. Maybe this is what made the median and mean survivals of these patients to be 2.5 and 3.6 years, respectively and 5-year survival of patients in this study was 47%. When compared to the results of a previous study by Hoskins,[4] it was found that the group of patients with good prognosis also had a median survival for only 1.5 years.

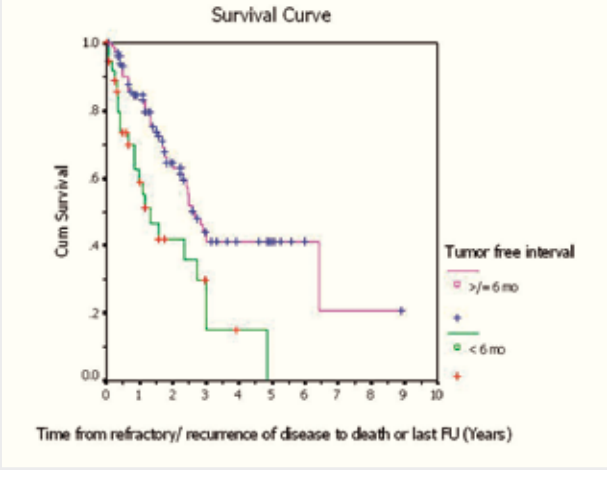


Fig 4.

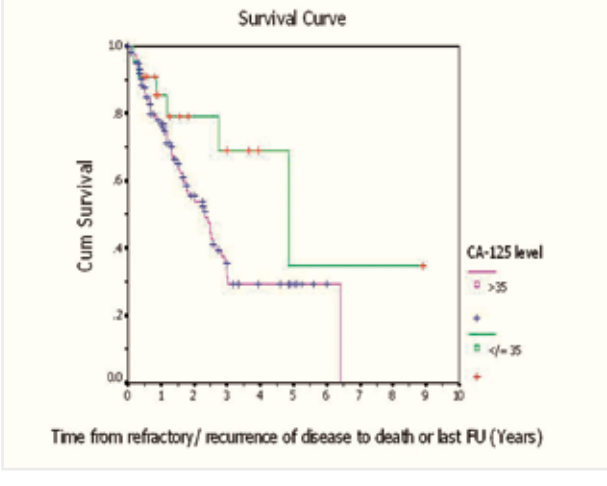


Fig 5.

However, the 5-year survival rate was only 21%. The difference between these two studies is probably due to the discrepancy between mean age and the regimen of second line chemotherapy, where the mean age of patients in this study was 49.8 years, whereas it was 60 years in Hoskins' study. This age difference probably affects the well-being of the patients. Moreover, in Hoskins' study, the study had been conducted during 1987-1993 and this had some effects on the regimens of the chemotherapy treatment. However, when we compared the results of this study with that of B. Gronlund[8] which had been conducted during 1994-2002, on the aspect of the recurrence of the disease, it was found that the median survival was similar, 28 months. Also another factor that made median and mean survival longer was the nature of the ovarian cancer, once it has recurred, it can recur often. However, at the present time, the various chemotherapy regimens have been available for this treatment.

The motivation for this study was from the previous studies of prognostic index of recurrent epithelial ovarian cancer such as the Canadian prognostic index, which was the study of Hoskins P, et al.[4] using 3 covariate prognostic indexes (tumor grade at diagnosis, initial performance status and time to relapse/primary progression). From this account, the diagram of prediction tree analysis has been created. The model from Gronlund B, et al.[8] had been modified by adding the variables such as TFI, number of recurrent disease sites, liver involvement, CA 125 at time of relapse/progression and performance status at the time of relapse/progression. The analysis from this study showed that these variables had a statistically significant prognostic index, $P < 0.05$. This was in line with the Canadian prognostic index, and that study created a new model called the Copenhagen index.

The limitations of this study were due to the retrospective design and incomplete data such as incidence of disease in the former years, grade of tumor, residual tumor or outcome after second line treatment and the reason for stopping treatment or changing of the regimens. These cannot be judged as prognostic variables in this study. However, this study still can provide some useful baseline information as well as counseling information to the patients and their relatives.

The suggestion from this study is to conduct a similar study with a prospective approach, which will yield more complete and accurate results, which in turn will be practically useful for patient practice guidelines.

CONCLUSION

The incidence of recurrent/ refractory epithelial ovarian cancer when compared to total new cases of epithelial ovarian cancer is about one third. This cohort had a prolonged median overall survival and satisfied a 5-year survival rate. The significant prognostic factors for survival in a cohort of patients are the tumor free interval and CA 125 at the time of recurrence or refractory.

The results from this study can be used as baseline information as well as counseling information to the patients and their relatives.

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